

# SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

## FORM S-3

REGISTRATION STATEMENT  
Under  
THE SECURITIES ACT OF 1933

### ISIS PHARMACEUTICALS, INC.

(Exact name of Registrant as specified in its charter)

**Delaware**  
(State or other jurisdiction  
of incorporation or organization)

**33-0336973**  
(I.R.S. Employer  
Identification Number)

**2292 Faraday Avenue  
Carlsbad, California 92008  
(760) 931-9200**

(Address, including zip code, and telephone number, including  
area code, of Registrant's principal executive offices)

**B. Lynne Parshall, Esq.  
Executive Vice President  
Isis Pharmaceuticals, Inc.  
2292 Faraday Avenue  
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(Name, address, including zip code, and telephone number, including area code, of agent for service)

*Copies to:*  
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San Diego, CA 92121  
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**Approximate date of commencement of proposed sale to the public:  
From time to time after the effective date of this Registration Statement.**

If the only securities being registered on this Form are being offered pursuant to dividend or interest reinvestment plans, please check the following box.

If any of the securities being registered on this Form are to be offered on a delayed or continuous basis pursuant to Rule 415 under the Securities Act of 1933, other than securities offered only in connection with dividend or interest reinvestment plans, check the following box.

If this Form is filed to register additional securities for an offering pursuant to Rule 462(b) under the Securities Act, please check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering.

If this Form is a post-effective amendment filed pursuant to Rule 462(c) under the Securities Act, check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering.

If delivery of the prospectus is expected to be made pursuant to rule 434, please check the following box.

#### CALCULATION OF REGISTRATION FEE

Title of each class of securities to be registered	Amount to be registered	Proposed maximum offering price per unit(2)	Proposed maximum aggregate offering price	Amount of registration fee
5 <sup>1</sup> / <sub>2</sub> % Convertible Subordinated Notes due 2009(1)	\$125,000,000	100%	\$125,000,000	\$11,500
Common Stock, \$0.001 per share	7,518,800(2)	—	—	—(4)

- (1) The 5<sup>1</sup>/<sub>2</sub>% convertible subordinated notes due 2009 were issued by the Registrant on May 1, 2002 in an offering exempt from registration under the Securities Act of 1933. Under a Registration Rights Agreement dated May 1, 2002 among the Registrant and the initial purchasers of the notes who resold the notes in offerings exempt from registration under Rule 144A and Regulation S of the Securities Act of 1933, the Registrant is obligated to file this Registration Statement to permit registered resales by the selling security holders of the notes and the shares of common stock underlying the notes.
- (2) Estimated solely for the purpose of calculating the registration fee pursuant to Rule 457(i) of the Securities Act of 1933 based upon the offering price of the notes when the Registrant originally sold the notes on May 1, 2002 in an offering that was exempt from registration under the Securities Act of 1933.
- (3) Represents the number of shares of common stock issuable upon conversion of the 5<sup>1</sup>/<sub>2</sub>% convertible subordinated notes due 2009 registered hereby. The notes are convertible into 60,1504 shares of our common stock, par value \$0.001 per share, per \$1,000 principal amount of notes, subject to adjustment in certain circumstances. Pursuant to Rule 416 under the Securities Act, such number of shares shall include an indeterminate number of shares of common stock as may be issuable from time to time upon the conversion of the notes as a result of a stock split, stock dividend, capitalization or similar event, and the antidilution provisions thereof.
- (4) The shares of common stock issuable upon conversion of the notes will be issued for no additional consideration, and therefore no registration fee is required pursuant to Rule 457(i) of the Securities Act.

The Registrant hereby amends this Registration Statement on such date or dates as may be necessary to delay its effective date until the Registrant shall file a further amendment that specifically states that this Registration Statement shall thereafter become effective in accordance with Section 8(a) of the Securities Act of 1933 or until the Registration Statement shall become effective on such

**The information in this prospectus is not complete and may be changed. We may not sell these securities until the registration statement filed with the Securities and Exchange Commission is effective. This prospectus is not an offer to sell these securities and we are not soliciting offers to buy these securities in any state where the offer or sale is not permitted.**

**SUBJECT TO COMPLETION, DATED MAY 24, 2002**

**Isis Pharmaceuticals, Inc.**

**\$125,000,000 5<sup>1</sup>/<sub>2</sub>% Convertible Subordinated Notes Due 2009 and 7,518,800 Shares of Common Stock Issuable Upon Conversion of the Notes**

The notes and the common stock issuable upon conversion of the notes may be offered and sold from time to time pursuant to this prospectus by the holders of those securities. The selling security holders will receive all of the net proceeds from the sale of the securities and will pay any applicable discounts, commission or concessions. The selling security holders and any underwriters, broker-dealers or agents that participate in the sale of the securities may be "underwriters" within the meaning of the Securities Act, and any discounts, commissions, concessions or profit they earn on any resale of the securities may be underwriting discounts or commissions under the Securities Act.

On May 1, 2002, we issued and sold \$125,000,000 of 5<sup>1</sup>/<sub>2</sub>% convertible subordinated notes due 2009 in a private placement in reliance on an exemption from registration under the Securities Act. The initial purchasers of the notes in that offering resold the notes in offerings in reliance on an exemption from registration under Rule 144A and Regulation S of the Securities Act. The notes are convertible into 60,150,400 shares of our common stock, par value \$0.001 per share, per \$1,000 principal amount of notes and subject to adjustment in certain circumstances. This results in an initial conversion price of \$16.625 per share.

We will pay cash interest on the notes semiannually on May 1 and November 1 of each year, with the first payment to be made on November 1, 2002, at the rate of 5<sup>1</sup>/<sub>2</sub>% per annum. The notes will mature on May 1, 2009.

The notes are junior to all of our existing and future senior indebtedness and we structurally subordinated to all existing and future liabilities of our subsidiaries, including trade payables. As of March 31, 2002, we and our subsidiaries had approximately \$84.8 million of consolidated indebtedness and other liabilities effectively ranking senior to the convertible notes, assuming the extinguishment of our 14% senior subordinated debt which occurred on May 1, 2002.

We may redeem some or all of the notes at any time before May 3, 2005, at a redemption price of \$1,000 per \$1,000 principal amount of notes, if the price of our common stock reaches certain levels and certain other conditions are met. We will make an additional payment in cash or common stock or a combination thereof with respect to the notes called for provisional redemption in an amount equal to the aggregate amount of interest that would have been payable on the notes from the last day through which interest was paid on the notes (or May 1, 2002 if no interest was paid) through May 1, 2005 (or May 2, 2005, if redeemed on that date). On or after May 3, 2005, we may at our option redeem the convertible notes, in whole or in part, at the prices stated in this prospectus, plus any accrued and unpaid interest to the redemption date. Holders of the notes may require us to repurchase all or a portion of their convertible notes upon a change in control, as defined herein, at 100% of their principal amount, plus any accrued and unpaid interest to the repurchase date.

Our common stock is listed on the Nasdaq National Market under the symbol "ISIS." On May 22, 2002, the last reported bid price of our common stock was \$9.79 per share. The notes trade on the Private Offerings, Resales and Trading Through Automated Linkages, or "PORTAL," Market of the National Association of Securities Dealers, Inc.

**Investing in our common stock involves risks.  
See "Risk Factors" beginning on page 5**

**Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved of these securities or passed upon the adequacy or accuracy of this prospectus. Any representation to the contrary is a criminal offense.**

The date of this prospectus is \_\_\_\_\_, 2002

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## SUMMARY

*This summary highlights selected information appearing elsewhere in this prospectus and may not contain all of the information that is important to you. This prospectus includes information about the securities we are offering, as well as information regarding our business and detailed financial data. We encourage you to read this prospectus in its entirety, including the documents incorporated by reference. As used in this prospectus, unless otherwise specified or the context requires otherwise, the terms "Isis," "we," "our" and "us" refer to Isis Pharmaceuticals, Inc.*

### Our Business

We are a biopharmaceutical company pioneering RNA-based drug discovery technologies to identify and commercialize novel drugs to treat important diseases. RNA, or ribonucleic acid, is a molecule that provides to a cell the information that it needs to produce proteins, including those proteins that are involved in disease. Interference with RNA can keep the body from producing proteins that are involved in disease. We have a strong proprietary position in RNA-based drug discovery technologies. With our primary technology, antisense, we create inhibitors designed to bind with high specificity to their RNA target and modulate protein production. With our Ibis technology, we use our expertise in RNA to design small molecule therapeutics that bind to RNA. We also use our antisense technology in collaborations with pharmaceutical companies to identify and prioritize attractive gene targets for their drug discovery programs. We believe we have established a leadership position in exploiting RNA as a target for drugs.

We used our antisense technology to commercialize our first product, Vitravene. Vitravene demonstrates our ability to meet U.S. Food and Drug Administration, or FDA, regulatory requirements and to manufacture commercial antisense drugs. We have 13 products in our development pipeline with eight in human clinical trials designed to assess safety and efficacy. Our products in development address numerous therapeutic areas with major market potential, including cancer and inflammatory, viral, metabolic and dermatological diseases. We are expanding the therapeutic opportunities for antisense drugs by developing a variety of formulations to enhance patient convenience and compliance. Our second-generation drugs, which represent approximately half of our drugs in development, may be able to be dosed as infrequently as once per month. We are also making progress on oral formulations for our second-generation drugs.

Affinitac, formerly known as LY900003 or ISIS 3521, is our most advanced product in development. In August 2001, we licensed Affinitac to Eli Lilly and Company as part of a broad strategic collaboration. Affinitac is undergoing Phase III clinical trials in combination with traditional cancer chemotherapy drugs to treat non-small cell lung cancer, the most common form of lung cancer. In January 2002, we completed enrollment of a 600 patient Phase III trial that we initiated in late 2000. We initiated this trial based on promising results in a Phase II trial in patients with non-small cell lung cancer. Results from the Phase II study showed a median survival time of 15.9 months in patients using our drug in combination with standard chemotherapy. The typical median survival time of similar cancer patients receiving standard chemotherapy alone is approximately seven or eight months. In April 2002, Lilly launched a global Phase III trial of Affinitac in patients with non-small cell lung cancer. If the data from our Phase III trial are sufficiently positive to support a single study New Drug Application, or NDA, we and Lilly plan to file the NDA in 2003. If two Phase III studies are required, we and Lilly plan to file the NDA in 2004. In November 2000, the FDA granted Affinitac fast track review status. In November 2001, we initiated a Phase III clinical trial for another product, ISIS 2302, in an inflammatory bowel disease known as Crohn's disease. We have six additional products undergoing Phase II clinical trials.

Our GeneTrove division uses our antisense technology as a tool to provide pharmaceutical companies with important information about genes that these companies are interested in targeting for

their drug discovery programs. We provide this information rapidly and efficiently, using the same proprietary methods and systems that we developed to create antisense drugs. We are collaborating with nine major pharmaceutical partners for these services, which are Abbott Laboratories, Inc.; Amgen Inc.; Aventis (Rhône-Poulenc Rorer); Celera Genomics Group; Chiron Corporation; Eli Lilly and Company; Johnson & Johnson Pharmaceutical Research & Development, LLC; Merck & Co., Inc.; and Pharmacia Corporation. We supplemented our GeneTrove services business with the introduction in August 2001 of a subscription database product. This database will contain proprietary information about the function of thousands of genes, which we believe pharmaceutical companies will find valuable in designing and prioritizing their drug discovery programs. Our GeneTrove division is generating near-term revenues while enhancing our own antisense drug discovery efforts and our patent portfolio.

Our Ibis Therapeutics division designs small molecule drugs that work by binding to RNA, in contrast to traditional drugs, which bind to proteins. Our scientists have invented methods of identifying RNA targets and screening for drugs that bind to RNA. Beyond its therapeutic focus, Ibis has expanded the application of its technology to develop a new diagnostic platform to detect infectious agents. Since its inception, Ibis has received significant financial support from various federal government agencies to use its technology for the development of RNA-based countermeasures to biological warfare. In October 2001, Ibis received a two-year contract from the Defense Advanced Research Projects Agency, or DARPA, to develop a device to detect infectious agents used in biological warfare attacks. Under this two-year contract, for the research program Triangulation Identification Genetic Evaluation of biological Risks, or TIGER, we expect to receive up to \$8.9 million in funding. In June 2000, Ibis initiated its first collaboration with a pharmaceutical industry partner, Agouron Pharmaceuticals, Inc., a

Pfizer company. In May and October 2001, we received a \$2.5 million milestone payment and a \$1.5 million milestone payment, respectively, under this collaboration. This collaboration is scheduled to end in June 2002 in accordance with its terms.

We have a broad patent portfolio relating to our technologies. We have rights to more than 900 issued patents, which we believe represent the largest antisense and RNA-oriented patent estate in the pharmaceutical industry. In 2001, we continued to fortify our antisense technology portfolio by exclusively licensing Hybridon's antisense chemistry and delivery technology patents. Our intellectual property is a strategic asset that we are exploiting to generate near-term revenue and that we expect will also provide us with revenue in the future. The principal purpose of our intellectual property portfolio is to protect our inventions in RNA-based drug discovery. Our intellectual property estate also enables us to expand our pipeline by granting partners limited access to antisense technology. Licensing partnerships may include antisense and Ibis drug discovery alliances such as those we have with Lilly and Amgen, GeneTrove functional genomics collaborations such as those we have with Chiron, Amgen and Pharmacia or licenses to non-antisense patents for drug discovery such as our license to Eyetech Pharmaceuticals, Inc.

Isis was incorporated in California in January 1989 and in April 1991 changed its state of incorporation to Delaware. Our executive offices are located at 2292 Faraday Avenue, Carlsbad, California 92008, and our telephone number is (760) 931-9200.

Isis Pharmaceuticals™, GeneTrove™ and Ibis Therapeutics™ are our trademarks. Vitravene® is a registered trademark of Novartis AG. Affinitac™ is a trademark of Eli Lilly and Company. This prospectus also contains trademarks and servicemarks of other companies.

## NOTES AND COMMON STOCK ISSUABLE UPON CONVERSION OF THE NOTES

Issuer	Isis Pharmaceuticals, Inc.
Convertible notes	\$125,000,000 aggregate principal amount of 5 <sup>1</sup> / <sub>2</sub> % convertible subordinated notes due 2009.
Maturity	The convertible notes will mature on May 1, 2009.
Interest payment dates	We will pay interest on the convertible notes semi-annually in arrears on May 1 and November 1 of each year, starting on November 1, 2002.
Conversion rights	The convertible notes are convertible into 60.1504 shares of our common stock, par value \$0.001 per share, per \$1,000 principal amount of convertible notes, subject to adjustment in certain circumstances. This rate results in an initial conversion price of \$16.625 per share. See "Description of Notes—Conversion Rights."
Subordination	<p>The convertible notes are:</p> <ul style="list-style-type: none"> <li>• unsecured;</li> <li>• junior to all of our existing and future senior indebtedness; and</li> <li>• structurally subordinated to all existing and future liabilities of our subsidiaries, including trade payables.</li> </ul> <p>As of March 31, 2002 we and our subsidiaries had approximately \$84.8 million of consolidated indebtedness and other liabilities effectively ranking senior to the convertible notes, assuming the extinguishment of our 14% senior subordinated debt which occurred on May 1, 2002. The indenture under which the convertible notes were issued does not restrict our or our subsidiaries' ability to incur additional senior or other indebtedness or liabilities. See "Description of Notes—Subordination of Notes."</p>
Sinking fund	None.
Provisional Redemption	We may redeem the convertible notes, in whole or in part, at any time before May 3, 2005, at a redemption price equal to \$1,000 per note to be redeemed if (a) the closing price of our common stock has exceeded 150% of the conversion price then in effect for at least 20 trading days within a period of 30 consecutive trading days ending on the trading day before the date of the mailing of the provisional redemption notice and (b) the registration statement of which this prospectus is a part is effective and available for use and is expected to remain effective and available for use for the 30 days following the provisional redemption date, unless registration is no longer required. Upon any provisional redemption, we will make an additional payment with respect to the convertible notes called for redemption equal to the total value of the aggregate amount of interest that would have been payable on the convertible notes from the last day through which interest was paid on the convertible notes (or May 1, 2002 if no interest has been paid) through May 1, 2005 (or May 2, 2005, if redeemed on that date). We may make these additional payments, at our option, in cash or common stock or a combination thereof. We will be obligated to make this additional payment on all convertible notes called for provisional redemption, including any notes converted after the notice date and before the provisional redemption date. See "Description of Notes—Provisional Redemption."

Redemption of convertible notes at our option	On or after May 3, 2005, we may, at our option, redeem the convertible notes, in whole or in part, at the redemption prices described in this prospectus, plus any accrued and unpaid interest to the redemption date. See "Description of Notes—Redemption of Notes at Our Option."
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Change in control	If we experience a change in control, as defined in the indenture, each holder may require us to purchase all or a portion of the holder's convertible notes at 100% of the principal amount, plus any accrued and unpaid interest to the repurchase date. See "Description of Notes—Change in Control Permits Purchase of Convertible Notes by Us at the Option of the Holder."
Events of default	If an event of default on the convertible notes has occurred and is continuing, the principal amount of the convertible notes plus any accrued and unpaid interest may be declared immediately due and payable. These amounts automatically become due and payable upon certain events of default. See "Description Notes—Events of Default."
Use of proceeds	We will not receive any proceeds from the sale of the notes or common stock offered in this prospectus. See "Selling Security Holders."
Listing and trading	The convertible notes trade on The PORTAL Market. Our common stock is listed on the Nasdaq National Market under the symbol "ISIS."
Risk factors	In analyzing an investment in the convertible notes offered by this prospectus, prospective investors should carefully consider, along with other matters referred to in this prospectus, the information set forth under "Risk Factors."

For a more complete description of the terms of the convertible notes, see "Description of Notes." For a more complete description of the terms of our common stock, see "Description of Capital Stock," including the documents incorporated by reference in this prospectus that are referred to therein.

## RISK FACTORS

*Investing in our securities involves a high degree of risk. In addition to the other information in this prospectus, you should carefully consider the risks described below before purchasing our securities. If any of the following risks actually occur, our business could be materially harmed, and our financial condition and results of operations could be materially and adversely affected. As a result, the trading price of our securities could decline, and you might lose all or part of your investment.*

### RISKS RELATED TO OUR BUSINESS

#### **If we or our partners fail to obtain regulatory approval for our products, we will not be able to sell them.**

We and our partners must conduct time-consuming, extensive and costly clinical trials to show the safety and efficacy of each of our drug candidates, before a drug candidate can be approved for sale. We must conduct these trials in compliance with U.S. Food and Drug Administration regulations and with comparable regulations in other countries. If the FDA or another regulatory agency believes that we or our partners have not sufficiently demonstrated the safety or efficacy of our drug candidates, it will not approve them or will require additional studies, which can be time consuming and expensive and which will delay commercialization of a drug candidate. We and our partners may not be able to obtain necessary regulatory approvals on a timely basis, if at all, for any of our drug candidates. Failure to receive these approvals or delays in such receipt could prevent or delay commercial introduction of a product and, as a result, could negatively impact our ability to generate revenue from product sales. In addition, following approval of a drug candidate, we and our partners must comply with comprehensive government regulations regarding how we manufacture, market and distribute products. If we fail to comply with these regulations, regulators could force us to withdraw a drug candidate from the market or impose other penalties or requirements that could have a similar negative impact.

We have only introduced one commercial product, Vitravene. We cannot guarantee that any of our other drug candidates will be safe and effective, will be approved for commercialization or will be successfully commercialized by us or our partners.

#### **If the results of clinical testing indicate that any of our drugs under development are not suitable for commercial use, or if additional testing is required to demonstrate such suitability, we may need to abandon one or more of our drug development programs.**

Drug discovery and development has inherent risks, including the risk that molecular targets prove not to be important in a particular disease, the risk that compounds that demonstrate attractive activity in preclinical studies do not demonstrate similar activity in human beings, and the risk that a compound is not safe or effective for use in humans. Antisense technology in particular is relatively new and unproven. Most of our resources are being applied to create safe and effective drugs for human use. Any of the risks described above could prevent us from meeting this goal. In the past, we have invested in clinical studies of drug candidates, including some that remain in our pipeline, that have not resulted in proof of efficacy against targeted indications.

#### **If our products are not accepted by the market, we are not likely to generate significant revenues or become profitable.**

Our success will depend upon the medical community, patients and third-party payors accepting our products as medically useful, cost-effective and safe. We cannot guarantee that any of our products in development, if approved for commercialization, will be used by doctors to treat patients. We currently have one commercially available product, Vitravene, a treatment for cytomegalovirus, or CMV, retinitis in AIDS patients, which addresses a small market. We and our partners may not be successful in commercializing additional products.

The degree of market acceptance for any of our products depends upon a number of factors, including:

- the receipt and scope of regulatory approvals;
-

the establishment and demonstration in the medical and patient community of the efficacy and safety of our drug candidates and their potential advantages over competing products;

- the cost of our drug candidates compared to other available therapies;
- the patient convenience of the dosing regimen for our drug candidates; and
- reimbursement policies of government and third-party payors.

Based on the profile of our drug candidates, physicians, patients, patient advocates, payors or the medical community in general may not accept and use any products that we may develop.

**If any of our collaborative partners fail to fund our collaborative programs or develop or sell any of our products under development, or if we are unable to obtain additional partners, progress on our drug development programs could be delayed or stop.**

We have entered into collaborative arrangements with third parties to develop certain product candidates. We enter into these collaborations in order to:

- fund our research and development activities;
- access manufacturing by third parties;
- seek and obtain regulatory approvals; and
- successfully commercialize existing and future product candidates.

If any of our partners fails to develop or sell any drug in which we have retained a financial interest, our business may be negatively affected. These collaborations may not continue or result in commercialized drugs. Our collaborators can terminate their relationships with us under certain circumstances, some of which are outside of our control. Our most advanced drug candidate, Affinitac, is being developed collaboratively with Lilly, with the development funded by Lilly. Additional drug candidates in our development pipeline are being developed and/or funded by corporate partners, including Antisense Therapeutics Limited, Elan Corporation, plc, Merck & Co., Inc. and OncoGenex Technologies Inc. Failure by any of these pharmaceutical company partners to continue to fund and/or develop these drug candidates would have a material adverse effect on our business.

Certain of our partners are pursuing other technologies or developing other drug candidates either on their own or in collaboration with others, including our competitors, to develop treatments for the same diseases targeted by our own collaborative programs. Such competition may negatively impact the partners' focus on and commitment to our drug candidate and, as a result, could delay or otherwise negatively affect the commercialization of such drug candidate.

Historically, corporate partnering has played a key role in our strategy to fund our development programs and to add key development resources. We plan to continue to rely on additional collaborative arrangements to develop and commercialize our products. However, we may not be able to negotiate additional attractive collaborative arrangements, and, even if negotiated, the collaborative arrangements may not be successful.

**If our GeneTrove business is unable to market its products and services as planned, we could lose our investment in this technology.**

Our business could suffer if pharmaceutical companies do not use our GeneTrove target validation or gene functionalization services. We have invested in the development of a gene target validation and gene functionalization service business for validation and functionalization of gene targets for drug

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discovery. If pharmaceutical companies fail to use these services due to competition or other factors, our GeneTrove business could fail to make the planned contribution to our financial performance.

In addition, if customers do not subscribe to the database at the level we have planned, our GeneTrove business could fail to make the planned contribution to our financial performance.

**We have incurred losses, and our business will suffer if we fail to achieve profitability in the future.**

Because drug discovery and development and the development of database products and research services require substantial lead time and money prior to commercialization, our expenses have exceeded our revenues since we were founded in January 1989. As of March 31, 2002, our accumulated losses were approximately \$405 million. Most of the losses resulted from costs incurred in connection with our research and development programs and from general and administrative costs associated with our operations. Most of our revenue has come from collaborative arrangements, with additional revenue from interest income and research grants and the sale or licensing of patents. Our current product revenues are derived solely from sales of Vitravene. This product has limited sales potential. We expect to incur additional operating losses over the next several years, and these losses may increase if we cannot increase or sustain revenue. We may not successfully develop any additional products or services, or achieve or sustain future profitability.

**If we fail to obtain timely funding, we may need to curtail or abandon some of our programs.**

Most of our product candidates are still undergoing clinical trials or are in the early stages of research and development. All of our products under development will require significant additional research, development, preclinical and/or clinical testing, regulatory approval and a commitment of significant additional resources prior to their commercialization. Based on our current operating plan, we believe that our available cash, cash equivalents and short-term investments at March 31, 2002 combined with investment income, committed contractual cash payments and proceeds from our May 2002 offering of the notes, will be sufficient to meet our anticipated requirements for at least the next 36 months. If we fail to meet our goals regarding commercialization of our drug products, gene function database product and research services and licensing of our proprietary technologies, we may need additional funding in the future. Our future capital requirements will depend on many factors, such as the following:

the profile and launch timing of our drugs;

- continued scientific progress in our research, drug discovery and development programs;
- the size of these programs and progress with preclinical and clinical trials;
- the time and costs involved in obtaining regulatory approvals;
- competing technological and market developments, including the introduction by others of new therapies that address our markets;
- success in the marketing of our gene function database and research service products; and
- changes in existing collaborative relationships and our ability to establish and maintain additional collaborative arrangements.

If we need additional funds, we may need to raise them through public or private financing. Additional financing may not be available at all or on acceptable terms. If additional funds are raised by issuing equity securities, the shares of existing stockholders will be diluted and their price, as well as the price of our other securities, may decline. If adequate funds are not available, we may be required to cut back on one or more of our research, drug discovery or development programs or obtain funds through arrangements with collaborative partners or others. These arrangements may require us to give up rights to certain of our technologies, product candidates or products.

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**If we cannot manufacture our products or contract with a third party to manufacture our products at costs that allow us to charge competitive prices to buyers, we will not be able to market products profitably.**

If we successfully commercialize any of our drug candidates, we may be required to establish large-scale commercial manufacturing capabilities. In addition, as our drug development pipeline increases and matures, we will have a greater need for clinical trial and commercial manufacturing capacity. Pharmaceutical products of the chemical class represented by our drug candidates, called oligonucleotides, have never been manufactured on a large scale, and to our knowledge there is no commercial scale oligonucleotide manufacturer in business today. We have a limited number of suppliers for certain capital equipment and raw materials that we use to manufacture our drugs, and some of these suppliers will need to increase their scale of production to meet our projected needs for commercial manufacturing. Further, we must continue to improve our manufacturing processes to allow us to reduce our product costs. We may not be able to manufacture at a cost or in quantities necessary to make commercially successful products.

Also, manufacturers, including us, must adhere to the FDA's current Good Manufacturing Practices regulations, which are enforced by the FDA through its facilities inspection program. We and our contract manufacturers may not be able to comply or maintain compliance with Good Manufacturing Practices regulations. Non-compliance could significantly delay our receipt of marketing approval for potential products or result in FDA enforcement action.

**If we fail to compete effectively, our products will not contribute significant revenues.**

Our competitors are engaged in all areas of drug discovery throughout the world, are numerous, and include, among others, major pharmaceutical companies and specialized biopharmaceutical firms. Other companies are engaged in developing antisense technology. Our competitors may succeed in developing drug candidates that are more effective than any drug candidates that we are developing. These competitive developments could make our products obsolete or non-competitive.

Our GeneTrove division competes with others in the use of antisense technology for gene target validation and gene functionalization, as well as with other technologies useful for target validation and gene functionalization. Our competition may provide services having more value to potential customers or may market their services more effectively to potential customers. In either case, our gene functionalization and target validation businesses may not contribute to our financial performance as planned.

Many of our competitors have substantially greater financial, technical and human resources than we do. In addition, many of these competitors have significantly greater experience than we do in conducting preclinical testing and human clinical trials of new pharmaceutical products and in obtaining FDA and other regulatory approvals of products for use in health care. Accordingly, our competitors may succeed in obtaining regulatory approval for products earlier than we do. We will also compete with respect to marketing and sales capabilities, areas in which we have limited or no experience.

**If we are unable to protect our patents or our proprietary rights, others may be able to compete more directly against us.**

Our success depends to a significant degree upon our ability to develop and secure intellectual property rights to proprietary products and services. However, patents may not be granted on any of our pending patent applications in the United States or in other countries. In addition, the scope of any of our issued patents may not be sufficiently broad to provide us with a competitive advantage. Furthermore, our issued patents or patents licensed to us may be successfully challenged, invalidated or circumvented so that our patent rights would not create an effective competitive barrier.

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**Intellectual property litigation could be expensive and prevent us from pursuing our programs.**

It is possible that in the future we may have to defend our intellectual property rights. In the event of an intellectual property dispute, we may be forced to litigate to defend our rights or assert them against others. Disputes could involve litigation or proceedings declared by the U.S. Patent and Trademark Office or the International Trade Commission. Intellectual property litigation can be extremely expensive, and this expense, as well as the consequences should we not prevail, could seriously harm our business.

On July 9, 2001, we initiated litigation against Sequitur, Inc. alleging patent infringement. On December 12, 2001, we initiated a second action against Sequitur, Inc. alleging patent infringement. On May 2, 2002 we initiated a third action against Sequitur, Inc. alleging patent infringement. If we do not prevail in the defense of these patents, it could impact our ability to realize future licensing revenues.

If a third party claims that our products or technology infringe their patents or other intellectual property rights, we might be forced to discontinue an important product or product line, alter our products and processes, pay license fees or cease certain activities. We may not be able to obtain a license to such intellectual property on favorable terms, if at all. There are many patents issued or applied for in the biotechnology industry, and we may not be aware of patents or applications held by others that relate to our business. This is especially true since patent applications in the United States are filed confidentially. Moreover, the validity and breadth of biotechnology patents involve complex legal and factual questions for which important legal issues remain unresolved.

**If we do not progress in our programs as anticipated, the price of our securities could decrease.**

For planning purposes, we estimate the timing of a variety of clinical, regulatory and other milestones, such as when a certain product candidate will enter the clinic, when a clinical trial will be completed or when an application for marketing approval will be filed. Some of our estimates are included in this prospectus. Our estimates are based on present facts and a variety of assumptions. Many of the underlying assumptions are outside of our control. If milestones are not achieved when we expect them to be, investors could be disappointed and the price of our securities would likely decrease.

**The loss of key personnel, or the inability to attract and retain highly skilled personnel, could make it more difficult to run our business and reduce our likelihood of success.**

We are dependent on the principal members of our management and scientific staff. We do not have employment agreements with any of our management. The loss of our management and key scientific employees might slow the achievement of important research and development goals. It is also critical to our success that we recruit and retain qualified scientific personnel to perform research and development work. We may not be able to attract and retain skilled and experienced scientific personnel on acceptable terms because of intense competition for experienced scientists among many pharmaceutical and health care companies, universities and non-profit research institutions. Our collaboration with Lilly requires us to add a significant number of skilled scientific personnel. Our inability to add these employees may impact the success of our Lilly collaboration.

**If the price of our securities continues to be highly volatile, this could make it harder for you to liquidate your investment and could increase your risk of suffering a loss.**

The market price of our common stock, like that of the securities of many other biopharmaceutical companies, has been and is likely to continue to be highly volatile. These fluctuations in our common stock price may significantly affect the trading price of the convertible notes. During the 12 months preceding May 1, 2002, the market price of our common stock has ranged from \$7.88 to \$27.15 per share. The market price of our securities can be affected by many factors, including, for example, fluctuations in our operating results, announcements of collaborations, clinical trial results,

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technological innovations or new drug products being developed by us or our competitors, governmental regulation, regulatory approval, developments in patent or other proprietary rights, public concern regarding the safety of our drugs and general market conditions.

**Provisions in our certificate of incorporation, other agreements and Delaware law may prevent stockholders from receiving a premium for their shares.**

Our certificate of incorporation provides for classified terms for the members of our board of directors. Our certificate also includes a provision that requires at least 66<sup>2</sup>/3% of our voting stockholders to approve a merger or certain other business transactions with, or proposed by, any holder of 15% or more of our voting stock, except in cases where certain directors approve the transaction or certain minimum price criteria and other procedural requirements are met.

Our certificate of incorporation also requires that any action required or permitted to be taken by our stockholders must be taken at a duly called annual or special meeting of stockholders and may not be taken by written consent. In addition, special meetings of our stockholders may be called only by the board of directors, the chairman of the board or the chief executive officer. We also have implemented a stockholders' rights plan, also called a poison pill, which could make it uneconomical for a third party to acquire our company on a hostile basis. These provisions, as well as Delaware law and other of our agreements, may discourage certain types of transactions in which our stockholders might otherwise receive a premium for their shares over then current market prices, and may limit the ability of our stockholders to approve transactions that they think may be in their best interests. In addition, our board of directors has the authority to fix the rights and preferences of and issue shares of preferred stock, which may have the effect of delaying or preventing a change in control of our company without action by our stockholders.

**If registration rights that we have previously granted are exercised, then the price of our securities may be negatively affected.**

We have granted registration rights in connection with the issuance of our securities to Elan International Services, Ltd., Eli Lilly and Company, Hybridon, Inc. and Reliance Insurance Company. In the aggregate, these registration rights cover approximately 4,590,378 shares of our common stock which are currently outstanding, an additional \$4.5 million of our common stock we are obligated to issue to Hybridon, and additional shares of our common stock which may become outstanding upon the conversion of outstanding convertible securities. If these registration rights are exercised by the holders, it will bring additional shares of our common stock into the market, which may have an adverse effect on the price of our securities.

**RISKS RELATED TO THE CONVERTIBLE NOTES**

**The convertible notes are subordinated to our senior indebtedness and are structurally subordinated to all liabilities of our subsidiaries.**

The convertible notes are junior in right of payment to all of our existing and future senior indebtedness and are structurally subordinated to all liabilities of our subsidiaries, including trade payables. As of March 31, 2002, we and our subsidiaries had approximately \$84.8 million of consolidated liabilities effectively ranking senior to the convertible notes, assuming the extinguishment of our 14% senior subordinated debt which occurred on May 1, 2002. The indenture governing the convertible notes does not restrict the incurrence of additional senior indebtedness or other debt or liabilities by us or our subsidiaries. By reason of such subordination, in the event of the insolvency, bankruptcy, liquidation, reorganization, dissolution or winding up of our business, our assets will be available to pay the amounts due on the convertible notes only after all of our senior indebtedness has been paid in full, and, therefore, there may not be sufficient assets remaining to pay amounts due on any or all of the convertible notes then outstanding. See "Description of Notes—Subordination of Convertible Notes."



**We may not have the ability to raise the funds necessary to finance the change in control offer required by the indenture.**

If we undergo a change in control, as defined in the indenture, each holder of the convertible notes may require us to repurchase all or a portion of the holder's convertible notes. We cannot assure you that there will be sufficient funds available for any required repurchases of these securities if a change in control occurs. In addition, the terms of any agreements related to borrowing which we may enter from time to time may prohibit or limit our repurchase of the convertible notes or make our repurchase of convertible notes an event of default under those agreements. If we fail to repurchase the convertible notes in that circumstance, we will be in default under the indenture governing the convertible notes. See "Description Notes—Change in Control Permits Purchase of Convertible Notes by Us at the Option of the Holder."

**Absence of a public market for the convertible notes could cause purchasers of the convertible notes to be unable to resell them for an extended period of time.**

Although the notes trade on The PORTAL Market, there is not an established trading market for the notes and we cannot assure you that an active public market for the notes will develop, or if such a market develops, how liquid it will be. At the time of the initial offering and sale of the notes, the initial purchasers of the notes informed us that they intended to make a market in the notes. The initial purchasers may cease their market-making activities, if any, at any time without notice.

If a trading market does not develop or is not maintained, holders of the convertible notes may experience difficulty in reselling, or an inability to sell, the convertible notes. If a market for the convertible notes develops, it may be discontinued at any time. If a public trading market develops for the convertible notes, future trading prices of the convertible notes will depend on many factors, including, among other things, the price of our common stock into which the convertible notes are convertible, prevailing interest rates, our operating results and the market for similar securities. Depending on the price of our common stock into which the convertible notes are convertible, prevailing interest rates, the market for similar securities and other factors, including our financial condition, the convertible notes may trade at a discount from their principal amount.

**If the private placement of the notes prior to this registration statement violated securities laws, purchasers in the private offering would have the right to seek refunds or damages.**

On May 1, 2002, we issued and sold the notes in a private placement transaction. The initial purchasers of the notes in that offering resold the notes to persons reasonably believed to be qualified institutional buyers (as defined in Rule 144A under the Securities Act) and non-U.S. persons (as defined in Regulation S under the Securities Act). On April 24, 2002, an article appeared in a San Diego newspaper regarding this offering in which one of our officers was interviewed. The newspaper article could form the basis for a claim that, in connection with our private placement of the convertible notes, we engaged in an unregistered public offering of the convertible notes in violation of the securities laws. We would dispute any such claim. However, if such a claim were made and it prevailed, the initial purchasers of the notes and persons who purchased the convertible notes from the initial purchasers would have the right, for a period of one year, to obtain recovery of the consideration paid in connection with their purchase of the convertible notes or, if they have already sold the convertible notes, to recover any losses resulting from their purchase of the convertible notes.

**RATIO OF EARNINGS TO FIXED CHARGES**  
(in thousands, except ratio of earnings to fixed charges)

The following table sets forth our ratio of earnings to fixed charges for the years ended December 31, 1997, 1998, 1999, 2000, 2001, for the three months ended March 31, 2002, for the pro forma year ended December 31, 2001, and the pro forma three months ended March 31, 2002. As earnings were inadequate to cover the combined fixed charges, we have provided the average deficiency amounts. For purposes of this computation, earnings are defined as net loss excluding the preferred stock dividend requirement on our Series A and Series B preferred stock. Fixed charges are the sum of (i) interest costs including the amortization of deferred financing costs; and (ii) the portion of operating lease rental expense that is representative of the interest factor of 15%. On a pro forma basis, we have assumed as of January 1, 2001, the early extinguishment of our 14% senior subordinated debt, which occurred on May 1, 2002, and assumed the receipt of \$125 million in proceeds from the private placement of our 5<sup>1</sup>/<sub>2</sub>% convertible subordinated notes due 2009, which occurred on May 1, 2002. The pro forma results are representative of the reduction in interest expense for the payment of our 14% senior subordinated debt and the additional interest expense associated with the issuance of our 5<sup>1</sup>/<sub>2</sub>% convertible subordinated notes.

	Year ended December 31,					Three months ended March 31, 2002	Pro Forma Year ended December 31, 2001	Pro Forma Three months ended March 31, 2002
	1997	1998	1999	2000	2001			
Ratio of earnings to fixed charges	—	—	—	—	—	—	—	—
Coverage deficiency	\$ (31,066)	\$ (42,983)	\$ (59,225)	\$ (53,485)	\$ (73,832)	\$ (17,972)	\$ (73,832)	\$ (17,972)

**SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS**

This prospectus and the documents incorporated by reference contain forward-looking statements regarding our business and the therapeutic and commercial potential of our technologies and products in development. Such statements are subject to certain risks and uncertainties, particularly those inherent in discovering, developing and commercializing drugs that are safe and effective for use as human therapeutics, in the process of conducting gene functionalization and target validation services and in launching new products and services for or with collaborators, and the endeavor of building a business around such potential products.

Actual results could differ materially from those discussed in this prospectus. Factors that could cause or contribute to such differences include, but are not limited to, those discussed in the section entitled "Risk factors" in this prospectus. As a result, you are cautioned not to rely on these forward-looking statements.

## USE OF PROCEEDS

We will receive no proceeds from the resale by the selling security holders of the notes or the common stock issuable upon conversion of the notes. The selling security holders will receive all of the net proceeds from the resales.

## SELLING SECURITY HOLDERS

We initially issued the notes to the initial purchasers of the notes who then resold the notes in transactions exempt from the registration requirements of the Securities Act to persons reasonably believed to be "qualified institutional buyers" (as defined in Rule 144A under the Securities Act) and non-U.S. persons outside the U.S. pursuant to Regulation S under the Securities Act. The selling security holders (which term includes their transferees, pledgees, donees or their successors) may from time to time offer and sell pursuant to this prospectus or any applicable prospectus supplement any or all of the notes and common stock issuable upon conversion of the notes.

No offer or sale under this prospectus may be made by a selling security holder unless that holder is listed in the table in this prospectus or until that holder has notified us and a supplement to this prospectus has been filed or an amendment to the registration statement of which this prospectus is a part has become effective. We will supplement or amend this prospectus to include additional selling security holders upon request and upon provision of all required information to us. Information concerning the selling security holders may change from time to time and any changed information will be set forth in supplements to this prospectus if and when necessary.

The following table sets forth information about each selling security holder, including the name, the number and percentage of the notes beneficially owned and being offered by the selling security holder and the number and percentage of common stock beneficially owned and being offered by the selling security holder. The percentages of common stock beneficially owned and being offered are based on the number of shares of our common stock that were outstanding as of May 21, 2002. Unless otherwise indicated below, none of the selling security holders nor any of their affiliates, officers,

directors or principal equity holders has held any position or office or has had any material relationship with us within the past three years.

Name	Principal Amount of Notes Beneficially Owned and Offered Hereby (1)	Percentage of Notes Outstanding	Shares of Common Stock Beneficially Owned and Offered Hereby	Percentage of Common Stock Outstanding
American Samoa Government	18,000	*	1,082	*
Argent Classic Convertible	2,000,000	1.6%	120,300	*
Aristeria Trading LLC	1,533,000	1.2%	92,210	*
Aristeria International	5,197,000	4.2%	312,601	*
Baird, Patrick & Co	1,500,000	1.2%	90,225	*
BP Amoco PLC Master Trust	571,000	*	34,345	*
Context Convertible Arbitrage	3,000,000	*	180,451	*
DKR Fixed Income	1,000,000	*	60,150	*
Estate of James Campbell	146,000	*	8,781	*
First Union Securities	13,500,000	10.8%	812,030	1.5%
Highbridge International LLC	11,000,000	8.8%	661,654	1.2%
Hotel Union of Hawaii	193,000	*	11,609	*
James Campbell Corporation	121,000	*	7,278	*
Jefferies & Co.	4,000	*	240	*
KBC Financial	3,650,000	2.9%	219,548	*
KD Convertible Arbitrage	1,000,000	*	60,150	*
McMahan Securities	1,550,000	1.2%	93,233	*
Pacific Life Insurance	500,000	*	30,075	*
Robertson Stephens, Inc.	3,000,000	2.4%	180,451	*
TQA Master Fund	1,000,000	*	60,150	*
Tribeca Investments LLC	5,000,000	4.0%	300,752	*
Viacom Inc. Pension Plan	19,000	*	1,142	*
Victus Capital, LP	1,500,000	1.2%	90,225	*
UBS Warburg LLC	24,995,000	20.0%	1,503,459	2.8%
Wachovia Securities	5,000,000	4.0%	300,752	*
WPG Convertible Arbitrage	1,500,000	1.2%	90,225	*
Zurich Institutional Benchmark	928,000	*	55,819	*

\* Less than one percent

(1)

We prepared this table based on the information supplied to us by the selling security holders named in the table and we have not sought to verify such information. This table only reflects information regarding selling security holders who have provided us with such information. We expect that we will update this table as we receive more information from holders of the notes who have not yet provided us with their information.

The selling security holders listed in the above table may have sold or transferred, in transactions exempt from the registration requirements of the Securities Act, some or all of their notes since the date on which the information in the above table was provided to us. Information about the selling security holders may change over time.

Because the selling security holders may offer all or some of the notes or the shares of common stock issuable upon conversion of the notes from time to time, we cannot estimate the amount of the notes or shares of common stock that will be held by the selling security holders upon the termination of any particular offering by a selling security holder. See "Plan of Distribution."

## PLAN OF DISTRIBUTION

The selling security holders, which term includes their transferees, pledgees or donees or their successors, may from time to time sell the notes and the underlying common stock covered by this prospectus directly to purchasers or offer the notes and underlying common stock through underwriters, broker-dealers or agents, who may receive compensation in the form of underwriting discounts, concessions or commissions from the selling security holders and/or the purchasers of securities for whom they may act as agent, which discounts, concessions or commissions as to any particular underwriter, broker-dealer or agent may be in excess of those customary in the types of transactions involved.

The notes and the underlying common stock may be sold in one or more transactions.

- at fixed prices;
- at prevailing market prices at the time of sale;
- at varying prices determined at the time of sale; or
- at negotiated prices.

These sales may be effected in transactions, which may involve block transactions, in the following manner:

- on any national securities exchange or quotation service on which the notes or the common stock may be listed or quoted at the time of sale;
- in the over-the-counter-market;
- in transactions otherwise than on these exchanges or services or in the over-the-counter market; or
- through the writing and exercise of options, whether these options are listed on an options exchange or otherwise.

In connection with the sale of the notes and common stock, the selling security holders may enter into hedging transactions with broker-dealers or other financial institutions, which may in turn engage in short sales of the securities in the course of hedging positions they assume. The selling security holders may sell the notes or common stock and deliver notes or common stock to close out short positions, or loan or pledge the securities to broker-dealers that in turn may sell these securities.

The aggregate proceeds to the selling security holders from the sale of the securities offered by them hereby will be the purchase price of such securities less discounts and commissions, if any. The selling security holder reserves the right to accept and, together with its agent from time to time, to reject, in whole or in part, any proposed purchase of securities to be made directly or through agents. We will not receive any of the proceeds from the resale by the selling security holders of the notes or the common stock issuable upon conversion of the notes.

The notes are traded on The PORTAL Market. Our common stock is listed for trading on the Nasdaq National Market under the symbol "ISIS."

In order to comply with the securities laws of some states, if applicable, the securities may be sold in such jurisdictions only through registered or licensed brokers or dealers. In addition, in some states the securities may not be sold unless they have been registered or qualified for sale in the applicable state or an exemption from registration or qualification requirements is available and is complied with.

The selling security holders, and any underwriters, broker-dealers or agents that participate in the sale of the securities, may be "underwriters" within the meaning of Section 2(11) of the Securities Act. Any discounts, commissions, concessions or profit they earn on any resale of the securities may be

underwriting discounts and commissions under the Securities Act. The selling security holders have acknowledged that they understand their obligations to comply with the provisions of the Securities Exchange Act of 1934 and the rules thereunder relating to stock manipulation, particularly Regulation M.

At the time of a particular offering of securities by a selling security holder, a supplement to this prospectus, if required, will be circulated setting forth the aggregate amount and type of securities being offered and the terms of the offering, including the name or names of any underwriters, broker-dealers or agents, any discounts, commissions and other terms constituting compensation from the selling security holders and any discounts, commissions or concessions allowed or reallocated or paid to broker-dealers.

We entered into a registration rights agreement for the benefit of holders of the notes to register their notes and the underlying common stock under applicable federal and state securities laws under specific circumstances and at specific times. The registration rights agreements provides for cross indemnification of the selling security holders and us and their and our respective directors, officers and controlling person against specific liabilities in connection with the offer and sale of the notes and the underlying common stock, including liabilities under the Securities Act.

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## DESCRIPTION OF NOTES

On May 1, 2002, we issued and sold the notes in a private placement transaction. The initial purchasers of the notes in that offering resold the notes to persons reasonably believed to be qualified institutional buyers (as defined in Rule 144A under the Securities Act) and non-U.S. persons (as defined in Regulation S under the Securities Act). The convertible notes were issued under the indenture dated May 1, 2002 between us and Wells Fargo Bank Minnesota, National Association, as trustee. The following statements are subject to the detailed provisions of the indenture and are qualified in their entirety by reference to the indenture. The indenture has been filed as an exhibit to the registration statement of which this prospectus is a part. Particular provisions of the indenture which are referred to in this prospectus are incorporated by reference as a part of the statements made, and the statements are qualified in their entirety by the reference. For purposes of this summary, the terms "Isis," "we," "us" and "our" refer only to Isis Pharmaceuticals, Inc. and not to any of our subsidiaries. References to "interest" shall be deemed to include "liquidated damages" unless the context otherwise requires.

### GENERAL

The convertible notes represent our unsecured general obligations, subordinate in right of payment to our obligations as described under "—Subordination of Convertible Notes," and convertible into our common stock as described under "—Conversion Rights." The convertible notes are limited to \$125,000,000 aggregate principal amount. Interest on the convertible notes will be payable semi-annually on May 1 and November 1 of each year, with the first interest payment to be made on November 1, 2002, at the rate of 5<sup>1</sup>/<sub>2</sub>% per annum, to the persons who are registered holders of the convertible notes at the close of business on the preceding April 15 and October 15, respectively. Unless previously redeemed, repurchased or converted, the convertible notes will mature on May 1, 2009. The convertible notes will be payable at the office of the paying agent, which initially will be an office or agency of the trustee, or an office or agency maintained by us for such purpose, in the Borough of Manhattan, the City of New York. Payments in respect of the convertible notes may, at our option, be made by check and mailed to the holders of record as shown on the register for the convertible notes.

We issued the convertible notes without coupons in denominations of \$1,000 and integral multiples thereof.

Holders may present for conversion any convertible notes that are eligible for conversion at the office of the conversion agent, and may present convertible notes for registration of transfer at the office of the registrar for the convertible notes, which initially will be the trustee.

The indenture does not contain any financial covenants or any restrictions on the payment of dividends or on the repurchase of our securities. The indenture does not require us to maintain any sinking fund or other reserves for repayment of the convertible notes.

### CONVERSION RIGHTS

Before the close of business on the date of maturity of the convertible notes, subject to prior redemption or repurchase, holders of convertible notes may convert the convertible notes, or portions thereof (if the portions are \$1,000 or whole multiples thereof) into 60.1504 shares of common stock per \$1,000 of principal amount of convertible notes. This rate results in an initial conversion price of approximately \$16.625 per share. Except as described below, the number of shares into which a convertible note is convertible will not be adjusted for dividends on any common stock issued on conversion. We will not issue fractional shares of common stock upon conversion of convertible notes and instead will pay a cash adjustment based on the market price of the common stock on the last trading day prior to the conversion date. In the case of convertible notes called for redemption,

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conversion rights will expire at the close of business on the date one business day prior to the redemption date.

We are not obligated to pay accrued interest on convertible notes submitted for conversion. Accordingly, if a convertible note is converted between a record date for the payment of interest and the next succeeding interest payment date, convertible notes submitted for conversion must be accompanied by funds equal to the interest payable to the registered holder on the interest payment date on the principal amount of such notes submitted for conversion. We will then make the interest payment due on the interest payment date to the registered holder of the convertible note on the record date. Notwithstanding anything to the contrary in this paragraph, any convertible note submitted for conversion need not be accompanied by any payment if either (1) the convertible note has been called for redemption or (2) the convertible note is converted on an interest payment date.

As soon as practicable following the conversion date, we will deliver through the conversion agent a certificate for the full number of full shares of common stock into which any convertible note is converted, together with any cash payment for fractional shares. For a discussion of the tax treatment of a holder receiving common shares upon surrendering convertible notes for conversion, see "Certain United States Federal Income Tax Considerations—U.S. Holders—Conversion of the notes."

We will adjust the conversion rate for:

- dividends or distributions on shares of our common stock payable in common stock;
- subdivisions, combinations or certain reclassifications of our common stock;
- distributions to all holders of common stock of certain rights or warrants entitling them for a period of 60 days or less to purchase common stock at less than the current market price at the time;

- distributions to all holders of our common stock of our assets, debt securities, shares of our capital stock other than our common stock, or certain rights to purchase our securities, but excluding cash dividends from current or retained earnings;
- all-cash distributions to all or substantially all holders of our common stock in an aggregate amount that, together with
  - any cash and the fair market value of any other consideration payable in respect of any tender offer (within the meaning of the U.S. federal securities laws) by us or any of our subsidiaries for our common stock consummated within the preceding 12 months not triggering a conversion rate adjustment, and
  - all other all-cash distributions to all or substantially all holders of our common stock made within the preceding 12 months not triggering a conversion rate adjustment,
 exceeds an amount equal to 10% of the market capitalization of our common stock on the business day immediately preceding the day on which we declare the distribution;
- the purchase of our common stock pursuant to a tender offer made by us or any of our subsidiaries to the extent that the same involves aggregate consideration that, together with
  - any cash and the fair market value of any other consideration payable in respect of any tender offer by us or any of our subsidiaries for our common stock consummated within the preceding 12 months not triggering a conversion rate adjustment, and
  - all-cash distributions to all or substantially all holders of our common stock made within the preceding 12 months not triggering a conversion rate adjustment,

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exceeds an amount equal to 10% of the market capitalization of our common stock on the expiration date of the tender offer.

Each adjustment referred to above will be made upon conclusion of the applicable event. We will not adjust the conversion rate, however, if holders of convertible notes are to participate in the transaction without conversion, or in certain other cases.

To the extent that our stockholders rights plan is still in effect, upon conversion of the notes into common stock, the holders will receive, in addition to the common stock, the rights described in our stockholders rights plan, whether or not the rights have separated from the common stock at the time of conversion, subject to certain limited exceptions. If we implement a new stockholders rights plan, we will be required under the indenture to provide that the holders of notes will receive the rights upon conversion of the notes, whether or not these rights were separated from the common stock prior to conversion, subject to certain limited exceptions.

Except as stated above, the number of shares issuable on conversion will not be adjusted for the issuance of common stock or any securities convertible into or exchangeable for common stock, or carrying the right to purchase any of the foregoing. The terms of the convertible notes do not require any adjustment for rights to purchase common stock pursuant to our present or any future stockholder rights plan or pursuant to any plans we have for reinvestment of dividends or interest, or for a change in the par value of the common stock. To the extent that convertible notes become convertible into cash, no adjustment will be required thereafter as to cash.

No adjustment in the conversion rate will be required unless the adjustment would require a change of at least 1% in the conversion rate then in effect; provided that any adjustment that would otherwise be required to be made will be carried forward and taken into account in any subsequent adjustment. We reserve the right to make such increases in the conversion rate in addition to those required in the foregoing provisions as we in our discretion shall determine to be advisable in order that stock-related distributions hereafter made by us to our stockholders shall not be taxable or for any other appropriate reason.

If we are party to a consolidation, merger or binding share exchange pursuant to which the common stock is converted into cash, securities or other property, at the effective time of the transaction, the right to convert a convertible note into common stock will be changed into a right to convert it into the kind and amount of cash, securities or other property which the holder would have received if the holder had converted its convertible note immediately prior to the transaction.

In the event of:

- a taxable distribution to holders of shares of common stock which results in an adjustment of the conversion rate; or
- an increase in the conversion rate at our discretion,

the holders of the convertible notes may, in certain circumstances, be deemed to have received a distribution subject to federal income tax as a dividend. See "Certain United States Federal Income Tax Considerations—U.S. Holders—Constructive dividends on the notes."

## **PROVISIONAL REDEMPTION**

We may redeem in cash any portion of the notes at any time prior to May 3, 2005 upon at least 30 and not more than 60 days notice by mail to the holders of the notes, at a redemption price equal to \$1,000 per note plus the "make whole" payment described below, if (1) the closing price of our common stock on the Nasdaq National Market (or other primary exchange where our common stock is traded) has exceeded 150% of the conversion price for at least 20 trading days in any consecutive 30-day trading period ending on the trading day prior to the mailing of the notice of redemption and

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(2) the shelf registration statement covering resales of the notes and the common stock issuable upon conversion of the notes is effective and available for use and is expected to remain effective and available for use for the 30 days following the redemption date, unless registration is no longer required. Notes will be redeemed only in integral multiples of \$1,000 principal amount.

If we redeem notes under these circumstances, we will make a "make whole" payment on the redeemed notes equal to the total value of the aggregate amount of interest that would have been payable on the notes from the last day through which interest was paid on the notes (or May 1, 2002 if no interest has been paid) through May 1, 2005 (or May 2, 2005, if redeemed on that date). We must make these "make whole" payments on all notes called for redemption prior to May 3, 2005, including notes converted after the date we mailed the notice. The "make whole" payment for notes converted shall not be reduced by accrued and unpaid interest. We may make these "make whole" payments, at our option, either in cash or in our common stock or a combination thereof. We will specify the type of consideration for the "make whole" payment in the redemption notice. Payments made in our common stock will be valued at 95% of the average of the closing sales prices of our common stock on the Nasdaq National Market (or other U.S. national securities exchange where our common stock is then traded) for the five trading days ending on the day prior to the redemption date.

Because the sale price of the common stock will be determined before the redemption date, if we specify that we will make payment of the redemption price in our common stock, holders of notes bear the market risk that our common stock will decline in value between the date the sale price is calculated and the redemption date.

#### REDEMPTION OF CONVERTIBLE NOTES AT OUR OPTION

No sinking fund is provided for the convertible notes. The convertible notes are redeemable at our option, in whole or in part, at any time on or after May 3, 2005, on any date not less than 30 nor more than 60 days after the mailing of a redemption notice to each holder of convertible notes to be redeemed at the address of the holder appearing in the security register. The redemption price for the convertible notes, expressed as a percentage of principal amount, is as follows for the periods set forth below:

Period	Redemption Price
May 3, 2005 to April 30, 2006	103.143%
May 1, 2006 to April 30, 2007	102.357%
May 1, 2007 to April 30, 2008	101.571%
May 1, 2008 to April 30, 2009	100.786%

Accrued and unpaid interest will also be paid to the redemption date.

If we will redeem less than all of the outstanding convertible notes, the trustee will select the convertible notes to be redeemed on a pro rata basis in principal amounts of \$1,000 or integral multiples of \$1,000. If a portion of a holder's convertible notes is selected for partial redemption and the holder converts a portion of the convertible notes, the converted portion shall be deemed to be the portion selected for redemption.

#### CHANGE IN CONTROL PERMITS PURCHASE OF CONVERTIBLE NOTES BY US AT THE OPTION OF THE HOLDER

In the event of a change in control, as defined below, with respect to us, each holder will have the right, at its option, subject to the terms and conditions of the indenture, to require us to purchase for cash all or any portion of the holder's convertible notes in integral multiples of \$1,000 principal amount, at a price for each \$1,000 principal amount of such convertible notes equal to 100% of the principal amount of such convertible notes tendered, plus any accrued and unpaid interest to the

purchase date. We will be required to purchase the convertible notes no later than 30 business days after notice of a change in control has been mailed as described below. We refer to this date in this prospectus as the "change in control purchase date."

Within 30 business days after the occurrence of a change in control, we must mail to the trustee and to all holders of convertible notes at their addresses shown in the register of the registrar and to beneficial owners as required by applicable law a notice regarding the change in control, which notice must state, among other things:

- the events causing a change in control;
- the date of such change in control;
- the last date on which a holder may exercise the purchase right;
- the change in control purchase price;
- the change in control purchase date;
- the name and address of the paying agent and the conversion agent;
- the conversion price, the conversion rate and any adjustments to the conversion rate;
- that convertible notes with respect to which a change in control purchase notice is given by the holder may be converted, if otherwise convertible, only if the change in control purchase notice has been withdrawn in accordance with the terms of the indenture; and
- the procedures that holders must follow to exercise these rights.

To exercise this right, the holder must deliver a written notice so as to be received by the paying agent no later than the close of business on the third business day prior to the change in control purchase date. The required purchase notice upon a change in control must state:

- the certificate numbers of the convertible notes to be delivered by the holder, if applicable;
- the portion of the principal amount of convertible notes to be purchased, which portion must be \$1,000 or an integral multiple of \$1,000; and
- that we are to purchase such convertible notes pursuant to the applicable provisions of the convertible notes.

A holder may withdraw any change in control purchase notice by delivering to the paying agent a written notice of withdrawal prior to the close of business on the second business day prior to the change in control purchase date. The notice of withdrawal must state:

- the principal amount of the convertible notes being withdrawn;
- the certificate numbers of the convertible notes being withdrawn, if applicable; and
- the principal amount, if any, of the convertible notes that remain subject to a change in control purchase notice.

Our obligation to pay the change in control purchase price for a convertible note for which a change in control purchase notice has been delivered and not validly withdrawn is conditioned upon delivery of the convertible note, together with necessary endorsements, to the paying agent at any time after the delivery of such change in control purchase notice. We will cause the change in control purchase price for such convertible note to be paid promptly following the later of the change in control purchase date or the time of delivery of such convertible note.

If the paying agent holds money sufficient to pay the change in control purchase price of the convertible note on the change in control purchase date in accordance with the terms of the indenture,

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then, immediately after the change in control purchase date, interest on such convertible note will cease to accrue, whether or not the convertible note is delivered to the paying agent. Thereafter, all other rights of the holder shall terminate, other than the right to receive the change in control purchase price upon delivery of the convertible note.

Under the indenture, a "change in control" is deemed to have occurred at such time as:

- any "person" or "group" (as such terms are used for purposes of Sections 13(d) and 14(d) of the Exchange Act), other than us, our subsidiaries or their employee benefit plans, is or becomes the "beneficial owner" (as such term is used in Rule 13d-3 under the Exchange Act), directly or indirectly, of 50% or more of the voting power of our common stock or other capital stock into which our common stock is reclassified or changed;
- at any time the following persons cease for any reason to constitute a majority of our board of directors:
  - individuals who on the issue date of the convertible notes constituted our board of directors, and
  - any new directors whose election by our board of directors or whose nomination for election by our stockholders was approved by at least a majority of the directors then still in office who were either directors on the issue date of the convertible notes or whose election or nomination for election was previously so approved; or
- the sale, lease or transfer of all or substantially all of our assets and property to any "person" or "group" (as such terms are used in Sections 13(d) and 14(d) of the Exchange Act), including any group acting for the purpose of acquiring, holding or disposing of securities within the meaning of Rule 13d-5(b)(1) under the Exchange Act.

However, a change in control will be deemed not to have occurred if either:

- the last sale price of our common stock for any five trading days during the ten trading days immediately preceding the change in control is at least equal to 105% of the conversion price in effect on such trading day; or
- in the case of a merger or consolidation, all or substantially all of the consideration for our outstanding common stock (excluding cash payments for fractional shares and cash payments pursuant to dissenters' appraisal rights) in the merger or consolidation constituting the change in control consists of common stock traded on a U.S. national securities exchange or quoted on the Nasdaq National Market (or which will be so traded or quoted when issued or exchanged in connection with such change in control) and as a result of such transaction or transactions the convertible notes become convertible solely into such common stock.

In connection with any purchase offer in the event of a change in control, we will to the extent applicable:

- comply with the provisions of Rule 13e-4, Rule 14e-1 and any other tender offer rules under the Exchange Act which may then be applicable; and
- file Schedule TO or any other required schedule under the Exchange Act.

The phrase "all or substantially all" of our assets will likely be interpreted under applicable law and will be dependent upon particular facts and circumstances. As a result, there may be a degree of uncertainty in ascertaining whether a sale, lease or transfer of "all or substantially all" of our assets has occurred, in which case a holder's ability to require us to purchase the holder's convertible notes upon a change in control may be impaired. In addition, we can give no assurance that we will be able to acquire the convertible notes tendered upon a change in control.

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The change in control purchase feature of the convertible notes may in certain circumstances make more difficult or discourage a takeover of our company.

We could, in the future, enter into certain transactions, including certain recapitalizations, that would not constitute a change in control with respect to the change in control purchase feature of the convertible notes but that would increase the amount of our, or our subsidiaries', indebtedness.

We may not purchase convertible notes at the option of holders upon a change in control if there has occurred and is continuing an event of default with respect to the convertible notes, other than a default in the payment of the change in control purchase price with respect to the convertible notes.

## **SUBORDINATION OF CONVERTIBLE NOTES**

Upon any distribution to our creditors in our liquidation, winding up or dissolution or in a bankruptcy, reorganization, insolvency, receivership or similar proceeding relating to us or our property, the payment of all amounts due on the convertible notes (other than cash payments due upon conversion in lieu of fractional shares) will be subordinated, to the extent provided in the indenture, in right of payment to the prior payment in full of all senior indebtedness and all indebtedness of our subsidiaries.

We will not pay, directly or indirectly, any amount due on the convertible notes (including any repurchase price pursuant to the exercise of the repurchase right), or acquire any of the convertible notes, in the following circumstances:

- if any default in payment of principal, premium, if any, or interest on senior indebtedness (as defined below) exists, unless and until the default has been cured or waived or has ceased to exist;
- if any default, other than a default in payment of principal, premium, if any, or interest, has occurred with respect to senior indebtedness, and that default permits the holders of the senior indebtedness to accelerate its maturity, until the expiration of the "payment blockage period" described below unless and until the default has been cured or waived or has ceased to exist; or
- if the maturity of senior indebtedness has been accelerated, until the senior indebtedness has been paid or the acceleration has been cured or waived.

A "payment blockage period" is a period that begins on the date that we receive a written notice from any holder of senior indebtedness or a holder's representative, or from a trustee under an indenture under which senior indebtedness has been issued, that an event of default with respect to and as defined under any senior indebtedness (other than default in payment of the principal of, or premium, if any, or interest on any senior indebtedness), which event of default permits the holders of senior indebtedness to accelerate its maturity, has occurred and is continuing and ends on the earlier of (1) the date on which such event of default has been cured or waived or (2) 180 days from the date notice is received. Notwithstanding the foregoing, only one payment blockage notice with respect to the same event of default may be given during any period of 360 consecutive days unless such event of default has been cured or waived for a period of not less than 90 consecutive days; provided that in no event shall more than one interest payment be blocked during any such 360-day period. No new payment blockage notice may be commenced by the holders of senior indebtedness during any period of 360 consecutive days unless all events of default which triggered the preceding payment blockage period have been cured or waived. However, if the maturity of such senior indebtedness is accelerated, no payment may be made on the convertible notes until such senior indebtedness that has matured has been paid or such acceleration has been cured or waived.

Senior indebtedness is defined in the indenture as all indebtedness (as defined below) of ours outstanding at any time except indebtedness that by its terms is subordinate in right of payment to the

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convertible notes or indebtedness that is not otherwise senior in right of payment to the convertible notes. Senior indebtedness does not include our indebtedness to any of our subsidiaries.

Indebtedness is defined with respect to any person as the principal of, and premium, if any, and interest on (a) all indebtedness of such person for borrowed money (including all indebtedness evidenced by notes, bonds, debentures or other securities sold by such person for money), (b) all obligations incurred by such person in the acquisition (whether by way of purchase, merger, consolidation or otherwise and whether by such person or another person) of any business, real property or other assets (except inventory and related items acquired in the ordinary course of the conduct of the acquiror's usual business), (c) direct or indirect guarantees or similar agreements by such person of indebtedness described in clause (a), (b), (e), (f), (g) or (h) of another person, (d) all renewals, extensions, refundings, deferrals, restructurings, amendments, supplements and modifications of any indebtedness, obligation or guarantee, (e) all reimbursement obligations and other liabilities, contingent or otherwise, of such person with respect to letters of credit, bankers' acceptances or similar facilities issued for the account of such person, (f) all capital lease obligations of such person, (g) all net obligations of such person under interest rate swap, currency exchange or similar agreements of such person and (h) all obligations and other liabilities, contingent or otherwise, under any lease or related document, including a purchase agreement, conditional sale or other title retention agreement, in connection with the lease of real property or improvements thereon (or any personal property included as part of any such lease) which provides that such person is contractually obligated to purchase or cause a third party to purchase the leased property or pay an agreed upon residual value of the leased property, including such person's obligations under such lease or related document to purchase or cause a third party to purchase such leased property or pay an agreed upon residual value of the leased property to the lessor.

By reason of the subordination provisions described above, in the event of insolvency, funds which would otherwise be payable to noteholders will be paid to the holders of senior indebtedness to the extent necessary to pay senior indebtedness in full. As a result of these payments, our general creditors may recover less, ratably, than holders of senior indebtedness and such general creditors may recover more, ratably, than holders of convertible notes or other subordinated indebtedness of ours.

We have subsidiaries which are separate and distinct legal entities and which have no obligation, contingent or otherwise, to pay any amounts due on the convertible notes or to make any funds available therefor, whether by dividends, loans or other payments. The payment of dividends and loans and advances to us by our subsidiaries may be subject to statutory or contractual restrictions, are contingent upon the earnings of our subsidiaries and are subject to various business considerations.



The convertible notes are effectively subordinated to all indebtedness and other liabilities and commitments (including trade payables) of our subsidiaries. Any right that we have to receive assets of any of our subsidiaries upon its liquidation or reorganization (and the consequent right of the holders of the convertible notes to participate in those assets) will be effectively subordinated to the claims of that subsidiary's creditors (including trade creditors), except to the extent that we ourselves are recognized as a creditor of that subsidiary, in which case our claims would still be subordinate to any security interests in the assets of that subsidiary and any indebtedness of that subsidiary senior to that held by us.

There are no restrictions in the indenture upon the creation of additional senior indebtedness by us, or on the creation of any indebtedness by us or any of our subsidiaries. As of March 31, 2002, we had approximately \$84.8 million of consolidated indebtedness and other obligations effectively ranking senior to the convertible notes, assuming the extinguishment of our 14% senior subordinated debt which occurred on May 1, 2002.

## **MERGER OR CONSOLIDATION, OR CONVEYANCE, TRANSFER OR LEASE OF PROPERTIES AND ASSETS**

The indenture provides that we may not consolidate with or merge with or into any other person or convey, transfer or lease our properties and assets substantially as an entirety to another person, unless:

- the resulting, surviving or transferee person is a corporation, limited liability company or other limited liability entity organized and existing under the laws of the United States, any state thereof or the District of Columbia; provided that this condition will not apply if independent tax counsel experienced in such matters delivers an opinion to us stating that, under then existing laws, there would be no adverse tax consequences to the holders of the convertible notes in the event this condition were not satisfied;
- such person assumes all our obligations under the convertible notes and the indenture; and
- we or such successor person shall not immediately thereafter be in default under the indenture.

Upon the assumption of our obligations by such a person in such circumstances, subject to certain exceptions, we shall be discharged from all obligations under the convertible notes and the indenture.

Although such transactions are permitted under the indenture, certain of the foregoing transactions could constitute a change in control permitting each holder to require us to purchase the convertible notes of such holder as described in "—Change in Control Permits Purchase of Convertible Notes by Us at the Option of the Holder."

## **EVENTS OF DEFAULT**

The following will be events of default for the convertible notes:

- default in the payment of the principal amount, redemption price or change in control purchase price with respect to any convertible note when such amount becomes due and payable;
- default in the payment of accrued and unpaid interest, if any (including liquidated damages), on the convertible notes for 30 days;
- failure by us to comply with any of our other covenants in the convertible notes or the indenture upon receipt by us of notice of such default by the trustee or by holders of not less than 25% in aggregate principal amount of the convertible notes then outstanding and our failure to cure (or obtain a waiver of) such default within 60 days after receipt of such notice; or
- certain events of bankruptcy, insolvency or reorganization affecting us.

If an event of default shall have occurred and be continuing, either the trustee or the holders of not less than 25% in aggregate principal amount of convertible notes then outstanding may declare the principal amount of the convertible notes plus accrued and unpaid interest, if any, on the convertible notes accrued through the date of such declaration to be immediately due and payable. In the case of certain events of our bankruptcy, insolvency or reorganization, the principal amount of the convertible notes plus accrued and unpaid interest, if any, accrued thereon through the occurrence of such event shall automatically become and be immediately due and payable.

## **MODIFICATIONS OF THE INDENTURE**

We and the trustee may enter into supplemental indentures that add, change or eliminate provisions of the indenture or modify the rights of the holders of the convertible notes with the consent

of the holders of at least a majority in principal amount of the convertible notes then outstanding. However, without the consent of each holder, no supplemental indenture may:

- reduce the rate or change the time of payment of interest (including any liquidated damages) on any convertible note;
- make any convertible note payable in money or securities other than that stated in the convertible note;
- change the stated maturity of any convertible note;
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reduce the principal amount, redemption price or change in control purchase price with respect to any convertible note;

- make any change that adversely affects the right of a holder to require us to purchase a convertible note;
- change the right to convert, or receive payment with respect to, a convertible note, or the right to institute suit for the enforcement of any payment with respect to, or conversion of, the convertible notes; or
- change the provisions in the indenture that relate to modifying or amending the indenture.

Without the consent of any holder of convertible notes, we and the trustee may enter into supplemental indentures for any of the following purposes:

- to evidence a successor to us and the assumption by that successor of our obligations under the indenture and the convertible notes;
- to add to our covenants for the benefit of the holders of the convertible notes or to surrender any right or power conferred upon us;
- to secure our obligations in respect of the convertible notes;
- to make any changes or modifications to the indenture necessary in connection with the registration of the convertible notes under the Securities Act and the qualification of the indenture under the Trust Indenture Act;
- to cure any ambiguity, defect, omission or inconsistency in the indenture in a manner that does not adversely affect the rights of any holder;
- to provide for uncertificated convertible notes; or
- to make any change that does not adversely affect the rights of any holder.

The holders of a majority in principal amount of the outstanding convertible notes may, on behalf of the holders of all convertible notes:

- waive compliance by us with restrictive provisions of the indenture, as detailed in the indenture; and
- waive any past default under the indenture and its consequences, except a default in the payment of the principal amount, accrued and unpaid interest, if any (including liquidated damages), redemption price or change in control purchase price or obligation to deliver common shares upon conversion with respect to any convertible note or in respect of any provision which under the indenture cannot be modified or amended without the consent of the holder of each outstanding convertible note affected.

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## **NO PERSONAL LIABILITY OF DIRECTORS, OFFICERS, EMPLOYEES, INCORPORATORS AND SHAREHOLDERS**

No director, officer, employee, incorporator or shareholder of ours, as such, shall have any liability for any of our obligations under the convertible notes or the indenture or for any claim based on, in respect of, or by reason of, such obligations or their creation. Each holder of convertible notes by accepting a convertible note waives and releases all such liability. The waiver and release are part of the consideration for issuance of the convertible notes. The waiver may not be effective to waive liabilities under the federal securities laws, and it is the view of the SEC that a waiver of such liabilities is against public policy.

## **SATISFACTION AND DISCHARGE**

We may discharge our obligations under the indenture while notes remain outstanding if (1) all outstanding notes have or will become due and payable at their scheduled maturity within one year or (2) all outstanding notes are scheduled for redemption within one year, and in either case, we have deposited with the trustee an amount sufficient to pay and discharge all outstanding notes on the date of their scheduled maturity or the scheduled date of redemption.

## **UNCLAIMED MONEY; PRESCRIPTION**

If money deposited with the trustee or paying agent for the payment of principal or interest or for redemption of the convertible notes remains unclaimed for two years or such shorter period under applicable state escheat laws, the trustee and paying agent shall notify us and shall pay the money back to us at our written request. Thereafter, holders of convertible notes entitled to the money must look to us for payment, subject to applicable law, and all liability of the trustee and the paying agent shall cease. Other than as described in this paragraph, the indenture does not provide for any prescription period for the payment of interest and principal on the convertible notes.

## **REPORTS TO TRUSTEE**

We will regularly furnish to the trustee copies of our annual report to stockholders, containing audited financial statements, and any other financial reports which we furnish to our stockholders.

## **RULE 144A INFORMATION REQUIREMENTS**

We agreed in the indenture to furnish to the holders or beneficial holders of the convertible notes and prospective purchasers of the convertible notes designated by the holders of the convertible notes, upon their request, the information required to be delivered pursuant to Rule 144A(d)(4) under the Securities Act at any time while the convertible notes or the common stock issuable upon conversion of the convertible notes are restricted securities within the meaning of the Securities Act, if we are not subject to the informational requirements of the Exchange Act.

## **TRUSTEE AND TRANSFER AGENT**

The trustee for the convertible notes is Wells Fargo Bank Minnesota, N.A. The holders of a majority in principal amount of the then outstanding convertible notes will have the right to direct the time, method and place of conducting any proceeding for any remedy available to the trustee, subject to certain exceptions. If an uncured event of default occurs, the trustee must exercise its rights and powers under the indenture using the same degree of care and skill as a prudent person

would use under the circumstances in the conduct of his or her own affairs. The trustee may refuse to perform any duty or exercise any right or power unless it receives indemnity reasonably satisfactory to the trustee against any loss, liability or expense.

The transfer agent for our common stock is American Stock Transfer and Trust.

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## LISTING AND TRADING

The convertible notes trade on The PORTAL Market. Our common stock is listed on the Nasdaq National Market under the symbol "ISIS."

## BOOK ENTRY, DELIVERY AND FORM

Notes resold under the registration statement of which this prospectus forms a part will be represented by one or more permanent global securities in definitive, fully registered form, which will be deposited with the trustee as custodian for DTC and registered in the name of DTC or a nominee of DTC in New York, New York for the accounts of participants in DTC. We initially issued the notes in the form of two global securities, bearing a legend relating to restrictions on transfer, which was deposited with the trustee as custodian for DTC and registered in the name of a nominee of DTC. Except as set forth below, the global securities may be transferred, in whole and not in part, only to DTC or another nominee of DTC. You may hold your beneficial interests in the global securities directly through DTC if you have an account with DTC or indirectly through organizations that have accounts with DTC. Notes in definitive certificated form (referred to as certificated securities) will be issued only in certain limited circumstances described below.

DTC has advised us that it is:

- a limited purpose trust company organized under the laws of the State of New York;
- a member of the Federal Reserve System;
- a "clearing corporation" within the meaning of the New York Uniform Commercial Code; and
- a "clearing agency" registered pursuant to the provisions of Section 17A of the Exchange Act.

DTC was created to hold securities of institutions that have accounts with DTC (referred to as participants) and to facilitate the clearance and settlement of securities transactions among its participants in such securities through electronic book-entry changes in accounts of the participants, thereby eliminating the need for physical movement of securities certificates. DTC's participants include securities brokers and dealers, which may include the initial purchasers, banks, trust companies, clearing corporations and certain other organizations. Access to DTC's book-entry system is also available to others such as banks, brokers, dealers and trust companies (referred to as indirect participants) that clear through or maintain a custodial relationship with a participant, whether directly or indirectly.

Pursuant to procedures established by DTC, upon the deposit of the global securities with DTC, DTC credited, on its book-entry registration and transfer system, the principal amount of notes represented by such global securities to the accounts of participants. The accounts to be credited were designated by the initial purchasers. Ownership of beneficial interests in the global securities will be limited to participants or persons that may hold interests through participants. Ownership of beneficial interests in the global securities will be shown on, and the transfer of those beneficial interests will be effected only through, records maintained by DTC (with respect to participants' interests), the participants and the indirect participants. The laws of some jurisdictions may require that certain purchasers of securities take physical delivery of such securities in definitive form. These limits and laws may impair the ability to transfer or pledge beneficial interests in the global securities.

Owners of beneficial interests in global securities who desire to convert their interests into common stock should contact their brokers or other participants or indirect participants through whom they hold such beneficial interests to obtain information on procedures, including proper forms and cut-off times, for submitting requests for conversion.

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So long as DTC, or its nominee, is the registered owner or holder of a global security, DTC or its nominee, as the case may be, will be considered the sole owner or holder of the notes represented by the global security for all purposes under the indenture and the notes. In addition, no owner of a beneficial interest in a global security will be able to transfer that interest except in accordance with the applicable procedures of DTC. Except as set forth below, as an owner of a beneficial interest in the global security, you will not be entitled to have the notes represented by the global security registered in your name, will not receive or be entitled to receive physical delivery of certificated securities, except as described below, and will not be considered to be the owner or holder of any notes under the global securities. We understand that under existing industry practice, if an owner of a beneficial interest in the global securities desires to take any action that DTC, as the holder of the global securities, is entitled to take, DTC would authorize the participants to take such action, and the participants would authorize beneficial owners owning through such participants to take such action or would otherwise act upon the instructions of beneficial owners owning through them.

We will make payments of principal of, premium, if any, and interest (including any additional interest) on the notes represented by the global securities registered in the name of and held by DTC or its nominee to DTC or its nominee, as the case may be, as the registered owner and holder of the global securities. Neither the trustee, any paying agent nor we will have any responsibility or liability for any aspect of the records relating to or payments made on account of beneficial interests in the global securities or for maintaining, supervising or reviewing any records relating to such beneficial interests.

We expect that DTC or its nominee, upon receipt of any payment of principal of, premium, if any, or interest (including liquidated damages) on the global securities, will credit participants' accounts with payments in amounts proportionate to their respective beneficial interests in the principal amount of the global securities, as shown on the records of DTC or its nominee. We also expect that payments by participants or indirect participants to owners of beneficial interests in the global securities held through such participants or indirect participants will be governed by standing instructions and customary practices and will be the responsibility of such participants or indirect participants. We will not have any responsibility or liability for any aspect of the records relating to, or payments made on account of, beneficial interests in the global securities for any note or for maintaining, supervising or reviewing any records relating to such beneficial interests or for any other aspect of the relationship between DTC and its participants or indirect participants or the relationship between such participants or indirect participants and the owners of beneficial interests in the global securities owning through such participants.

Transfers between participants in DTC will be effected in the ordinary way in accordance with DTC rules and will be settled in same-day funds.

DTC has advised us that it will take any action permitted to be taken by a holder of notes only at the direction of one or more participants to whose account DTC's interests in the global securities is credited and only in respect of that portion of the aggregate principal amount of notes as to which the participant or participants have given such direction. However, if DTC notifies us that it is unwilling to be a depository for the global securities or ceases to be a clearing agency or there is a continuing event of default under the notes, DTC will exchange the global securities for certificated securities which it will distribute to its participants and which will be appropriately legended, if required.

Although DTC is expected to follow the foregoing procedures in order to facilitate transfers of interests in the global securities among participants of DTC, it is under no obligation to perform or continue to perform these procedures, and these procedures may be discontinued at any time. Neither the trustee nor we will have any responsibility or liability for the performance by DTC or the participants or indirect participants of their respective obligations under the rules and procedures governing their respective operations.

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## **PAYMENTS OF PRINCIPAL AND INTEREST**

The indenture requires that payments in respect of the notes held of record by DTC or its nominee (including notes evidenced by the global securities) be made in same day funds. Payments in respect of the notes held of record by holders other than DTC may, at our option, be made by check and mailed to such holders of record as shown on the register for the notes.

## **REGISTRATION RIGHTS; LIQUIDATED DAMAGES**

We and the initial purchasers of the notes entered into a registration rights agreement dated May 1, 2002. Under the registration rights agreement, we agreed with the initial purchasers of the notes to file a shelf registration statement, of which this prospectus is a part, covering the resales of the notes and the common stock issuable upon the conversion of the notes in accordance with Rule 415 under the Securities Act.

We will use our commercially reasonable best efforts to cause a shelf registration statement to be declared effective and, subject to certain rights to suspend use of the shelf registration statement, to keep it effective until the earliest of (i) the date on which the notes or underlying shares of common stock have been effectively registered under the Securities Act and disposed of, whether or not in accordance with the shelf registration statement, and (ii) the date which is two years after the later of the date of original issue of the notes and the last date that we or any of our affiliates was the owner of such notes (or any predecessor thereto) or such shorter period of time as permitted by Rule 144(k) under the Securities Act or any successor provision thereunder. There can be no assurance that we will be able to maintain an effective and current registration statement as required. The absence of such a registration statement may limit a holder's ability to sell the securities offered hereby or adversely affect the price at which the securities can be sold.

We have agreed to pay predetermined liquidated damages as described herein to holders of the notes and the holders of common stock issued upon conversion of the notes if the shelf registration statement is not filed with the SEC by July 30, 2002 (90 days from the date the notes were originally issued), the shelf registration statement is not declared effective by October 28, 2002 (180 days from the date on which the notes were originally issued) or the shelf registration statement ceases to be effective (without being succeeded immediately by an additional registration statement filed and declared effective) or usable for the sale of the notes or the common stock underlying the notes for a period of time (including any period of time where we suspend use of the shelf registration statement) which shall exceed 30 days in the aggregate in any 3-month period or 60 days in the aggregate in any 12-month period. The liquidated damages shall accrue at a rate of 0.25% per year per \$1,000 principal amount of the notes and, if applicable, on an equivalent basis per share of common stock (valued on the basis of the conversion price then in effect and subject to adjustment in the event of stock splits, stock recombinations, stock dividends and the like) for each 90-day period until the shelf registration statement is declared effective or again becomes effective or usable, as the case may be, up to a maximum amount of liquidated damages of 0.75% per year per \$1,000 principal amount of the notes and, if applicable, on an equivalent basis per share of common stock (subject to adjustment as set forth above).

The foregoing summary does not purport to be complete and is subject to, and is qualified in its entirety by references to, the provisions of the registration rights agreement. A copy of the registration rights agreement has been filed as an exhibit to the registration statement of which this prospectus is a part.

## **GOVERNING LAW**

The indenture and the convertible notes are governed by and construed in accordance with the laws of the State of New York, without giving effect to such state's conflicts of laws principles.

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## **DESCRIPTION OF CAPITAL STOCK**

Our authorized capital stock consists of

- Series A Convertible Exchangeable 5% Preferred Stock, 120,150 shares of which were authorized, issued and outstanding at March 31, 2002;
- Series B Convertible Exchangeable 5% Preferred Stock, 16,620 shares of which were authorized and 12,015 shares of which were issued and outstanding at March 31, 2002;
- Series C Junior Participating Preferred Stock, 1,000,000 shares of which were authorized and none of which was issued and outstanding at March 31, 2002; and
- common stock, 100,000,000 shares of which are authorized and 53,974,109 shares of which were outstanding as of March 31, 2002.

## DIVIDEND POLICY

We have never declared or paid any cash dividends on our capital stock. We intend to retain any future earnings to support operations and to finance the growth and development of our business and we do not anticipate paying cash dividends for the foreseeable future.

## CERTAIN UNITED STATES FEDERAL INCOME TAX CONSIDERATIONS

The following discusses the material U.S. federal income tax consequences to holders of the notes or our common stock into which the notes may be converted. This discussion is for general information only and does not address all aspects of U.S. federal income taxation that may be relevant to you in light of your personal circumstances. This summary is based on the provisions of the Internal Revenue Code of 1986, as amended, applicable existing and proposed U.S. Treasury regulations, and judicial authority and current administrative rulings and practice, all of which are subject to change, possibly on a retroactive basis, or to differing interpretation. Except as otherwise noted, this summary applies only to holders, as defined below, that hold the notes and our common stock into which the notes may be converted as capital assets within the meaning of Section 1221 of the Internal Revenue Code (generally, for investment). It does not address tax consequences applicable to those U.S. holders that may be subject to special tax rules, such as:

- financial institutions;
- regulated investment companies;
- tax-exempt organizations;
- expatriates;
- persons subject to the alternative minimum tax provisions of the Internal Revenue Code;
- pension funds;
- insurance companies;
- dealers in securities or foreign currencies;
- persons that will hold notes as a position in a hedging transaction, straddle, conversion transaction or other risk reduction transaction for tax purposes;
- persons deemed to sell notes or common stock under the constructive sale provisions of the Internal Revenue Code;

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- persons who hold notes through a partnership or other pass through entity; or
  - persons that have a primary form of currency other than the U.S. dollar (except as disclosed below under "—Non-U.S. Holders").

We have not sought any ruling from the Internal Revenue Service, or IRS, with respect to the statements made and the conclusions reached in the following summary, and there can be no assurance that the IRS will agree with our statements and conclusions. Moreover, this discussion does not address the effect of any applicable state, local or foreign tax laws. INVESTORS CONSIDERING THE PURCHASE OF NOTES SHOULD CONSULT THEIR OWN TAX ADVISORS WITH RESPECT TO THE APPLICATION OF THE U.S. FEDERAL INCOME, GIFT AND ESTATE TAX LAWS TO THEIR PARTICULAR SITUATIONS AS WELL AS ANY TAX CONSEQUENCES ARISING UNDER THE LAWS OF ANY STATE, LOCAL OR FOREIGN TAXING JURISDICTION OR UNDER ANY APPLICABLE TAX TREATY.

For purposes of this discussion, the term U.S. holder means a beneficial owner of a note or common stock that is for U.S. federal income tax purposes, (i) a citizen or resident of the United States, (ii) a corporation created or organized in or under the laws of the United States, (iii) an estate, the income of which is subject to U.S. federal income taxation regardless of its source, or (iv) a trust if (a) its administration is subject to the primary supervision of a court within the United States and one or more U.S. persons have authority to control all of its substantial decisions, or (b) it was in existence on August 20, 1996, and has elected to continue to be treated as a U.S. trust. For U.S. federal income tax purposes, income earned through a foreign or domestic partnership or similar entity is generally attributed to its owners. A non-U.S. holder means a holder of a note or common stock that is not a U.S. holder for U.S. federal income tax purposes.

### U.S. HOLDERS

The following is a summary of the material U.S. federal income tax consequences resulting from the ownership and disposition of the notes and common stock by U.S. holders.

#### Payment of interest

##### *Stated interest*

Any interest we pay on a note generally will be includable in the income of a U.S. holder as ordinary income at the time the interest is received or accrued, in accordance with each U.S. holder's method of accounting for U.S. federal income tax purposes.

##### *Make whole payments*

If we call the notes for provisional redemption, holders would be entitled to a "make whole" payment in excess of stated principal and interest, either upon the redemption or upon a conversion of the notes after they are called for redemption but before they are actually redeemed. We intend to treat the possibility that we will pay such make whole payments as subject to a remote and incidental contingency, within the meaning of applicable Treasury Regulations and, therefore, we believe that any make whole payments will not affect the yield to maturity on the notes and thus will be taxable to U.S. holders at the time make whole payments accrue or are received in accordance with each such holder's method of accounting. However, because of the lack of authority on point, the tax consequences of these additional payments are uncertain. In general, a redemption premium payment paid in cash on a note called for provisional redemption would likely be treated as capital gain in accordance with the rules described in the following paragraph. However, since any make whole payment would be calculated by reference to foregone interest, a U.S. holder could be required to recognize interest income on the receipt of such payment. Our determination that there is a remote likelihood of paying

make whole payments upon provisional redemption of the notes is binding on each U.S. holder unless the holder explicitly discloses in the manner required by applicable Treasury Regulations that its determination is different from ours. Our determination is not, however, binding on the IRS.

#### **Sale, exchange or redemption of the notes**

Except as set forth below under "—U.S. Holders—Conversion of the notes" and "—U.S. Holders—Market discount," upon the sale, exchange or redemption of a note (including the repurchase of a note for cash pursuant to the exercise of a repurchase right in the event of a change in control), a U.S. holder generally will recognize capital gain or loss equal to the difference between the amount realized on the sale, exchange or redemption and the U.S. holder's adjusted tax basis in that note. For these purposes, the amount realized on the sale, exchange or redemption of a note does not include any amount attributable to accrued but unpaid interest, which will be taxable as such unless previously taken into account. A U.S. holder's adjusted tax basis in a note generally will be the U.S. dollar value of the purchase price of that note on the date of purchase increased by any market discount previously included in income by the holder and reduced by any amortized premium. Gain or loss so recognized will generally be capital gain or loss and will be long-term capital gain or loss if, at the time of the sale, exchange or redemption, the note was held for more than one year. In general, the maximum federal tax rate for noncorporate taxpayers on long-term capital gain is 20% with respect to capital assets including the notes and common stock (18% if such capital assets are held for more than five years). Capital gain on assets having a holding period of one year or less at the time of their disposition is taxed as short-term capital gain at a current maximum federal rate of 38.6% in the hands of noncorporate taxpayers. For individual taxpayers, the deductibility of capital losses is subject to limitations. For corporate taxpayers, both capital gains and ordinary income are subject to a maximum regular federal tax rate of 35%.

#### **Constructive dividends on the notes**

The conversion price of the notes may adjust under certain circumstances. Section 305 of the Internal Revenue Code treats as a distribution taxable as a dividend (to the extent of our current or accumulated earnings and profits) certain actual or constructive distributions of stock with respect to stock or convertible securities. Under applicable Treasury Regulations, an adjustment of conversion price may, under certain circumstances, be treated as a constructive dividend to the extent it increases the proportional interest of a U.S. holder of a note in our fully diluted common stock, whether or not the holder ever converts the note into our common stock. Generally, a holder's tax basis in a note will be increased by the amount of any constructive dividend. Similarly, a failure to adjust the conversion price of the notes to reflect a stock dividend or similar event could in some circumstances give rise to constructive dividend income to U.S. holders of common stock.

#### **Conversion of the notes**

A U.S. holder generally will not recognize any income, gain or loss upon conversion of a note into our common stock, other than with respect to cash received in lieu of a fractional share of common stock, except to the extent that the common stock issued upon conversion is treated as attributable to accrued interest on the note (which will be treated as interest for federal income tax purposes) and except with respect to market discount, as described below under "—U.S. Holders—Market discount." A U.S. holder's tax basis in the common stock received on conversion or repurchase of a note will be the same as that U.S. holder's adjusted tax basis in the note at the time of conversion or repurchase reduced by any basis allocable to a fractional share. The holding period for the common stock received on conversion or repurchase will generally include the holding period of the note converted or repurchased. However, a holder's tax basis in shares of common stock attributable to accrued interest

generally will equal the amount of accrued interest included in income and the holding period will begin on the day following the date of conversion or repurchase.

You should treat cash received in lieu of a fractional share of common stock upon conversion or repurchase as a payment in exchange for a fractional share of common stock. The receipt of cash in lieu of a fractional share of common stock generally will result in capital gain or loss (measured by the difference between the cash you received for the fractional share and your adjusted tax basis in the fractional share). The fair market value of the shares of common stock received which is attributable to accrued interest will be taxable as ordinary income.

#### **Dividends on common stock**

If we make distributions on our common stock, those distributions will generally be treated as a dividend, subject to tax as ordinary income, to the extent of our current or accumulated earnings and profits as of the year of distribution, then as a tax-free return of capital to the extent of the U.S. holder's adjusted tax basis in the common stock and thereafter as gain from the sale or exchange of that stock.

In general, a dividend distribution to a corporate U.S. holder may qualify for the 70% dividends received deduction if the U.S. holder owns less than 20% of the voting power and value of our stock (other than any non-voting, non-convertible, non-participating preferred stock). A corporate U.S. holder that owns 20% or more of the voting power and value of our stock (other than any non-voting, non-convertible, non-participating preferred stock) generally will qualify for an 80% dividends received deduction.

#### **Sale of common stock**

Upon the sale or exchange of our common stock, a U.S. holder generally will recognize capital gain or loss equal to the difference between (i) the amount of cash and the fair market value of any property received upon the sale or exchange and (ii) the U.S. holder's adjusted tax basis in the common stock. That capital gain or loss will be long-term if the U.S. holder's holding period is more than one year and will be short-term if the holding period is equal to or less than one year. In the case of certain noncorporate taxpayers, including individuals, long-term capital gains are taxed at a maximum federal rate of 20% (18% if such capital assets are held for more than five years), and short-term capital gains are taxed at a current maximum federal rate of 38.6%. A U.S. holder's basis and holding period in our common stock received upon conversion of a note are determined as discussed above under "—U.S. Holders—Conversion of the notes." Corporate taxpayers are subject to a maximum regular federal tax rate of 35% on all capital gains and ordinary income.

### **Market discount**

The resale of notes may be affected by the impact on a purchaser of the market discount provisions of the Internal Revenue Code. For this purpose, the market discount on a note generally will equal the amount, if any, by which the stated redemption price at maturity of the note immediately after its acquisition exceeds the U.S. holder's adjusted tax basis in the note. Subject to a limited exception, these provisions generally require a U.S. holder who acquires a note at a market discount to treat as ordinary income any gain recognized on the disposition of that note to the extent of the accrued market discount on that note at the time of maturity or disposition, unless the U.S. holder elects to include accrued market discount in income over the life of the note.

This election to include market discount in income over the life of the note, once made, applies to all market discount obligations acquired on or after the first taxable year to which the election applies and may not be revoked without the consent of the IRS. In general, market discount will be treated as accruing on a straight-line basis over the remaining term of the note at the time of acquisition, or, at

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the election of the U.S. holder, under a constant yield method. If an election is made, it will apply only to the note with respect to which it is made, and may not be revoked. A U.S. holder who acquires a note at a market discount and who does not elect to include accrued market discount in income over the life of the note may be required to defer the deduction of a portion of the interest on any indebtedness incurred or maintained to purchase or carry the note until maturity or until the note is disposed of in a taxable transaction. If a U.S. holder acquires a note with market discount and receives common stock upon conversion of the note, the amount of accrued market discount not previously included in income with respect to the converted note through the date of conversion will be treated as ordinary income when the holder disposes of the common stock.

### **Amortizable premium**

A U.S. holder who purchases a note at a premium over its stated principal amount, plus accrued interest, generally may elect to amortize that premium (referred to as Section 171 premium) from the purchase date to the note's maturity date under a constant-yield method that reflects semiannual compounding based on the note's payment period. Amortizable premium, however, will not include any premium attributable to a note's conversion feature. The premium attributable to the conversion feature is the excess, if any, of the note's purchase price over what the note's fair market value would be if there were no conversion feature. Amortized Section 171 premium is treated as an offset to interest income on a note and not as a separate deduction. The election to amortize premium on a constant yield method, once made, applies to all debt obligations held or subsequently acquired by the electing U.S. holder on or after the first day of the first taxable year to which the election applies and may not be revoked without the consent of the IRS.

### **Backup withholding and information reporting**

A U.S. holder of notes or common stock may be subject to backup withholding at a rate of 30% with respect to certain reportable payments, including interest payments, dividend payments and, under certain circumstances, principal payments on the notes. These backup withholding rules apply if the U.S. holder, among other things, (i) fails to furnish a social security number or other taxpayer identification number certified under penalties of perjury within a reasonable time after the request therefor, (ii) furnishes an incorrect taxpayer identification number, (iii) fails to report properly interest or dividends or (iv) under certain circumstances, fails to provide a certified statement, signed under penalties of perjury, that the taxpayer identification number furnished is the correct number and that the U.S. holder is not subject to backup withholding. A U.S. holder who does not provide us with its correct taxpayer identification number may also be subject to penalties imposed by the IRS. Any amount withheld from a payment to a holder under the backup withholding rules is creditable against the holder's federal income tax liability. Backup withholding will not apply, however, with respect to payments made to certain U.S. holders, including corporations and tax-exempt organizations, provided their exemption from backup withholding is properly established. We will report to U.S. holders of notes and common stock and to the IRS the amount of any reportable payments for each calendar year and the amount of tax withheld, if any, with respect to those payments.

### **NON-U.S. HOLDERS**

The following discussion is a summary of the principal U.S. federal income and estate tax consequences resulting from the ownership of the notes or our common stock by non-U.S. holders.

#### **Payment of interest**

Generally, interest income of a non-U.S. holder that is not effectively connected with a U.S. trade or business will be subject to a withholding tax at a 30% rate (or lower rate specified by an applicable income tax treaty). However, interest income earned on the notes by a non-U.S. holder may qualify for

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an exemption, referred to as the portfolio interest exemption, and as a result should not be subject to U.S. federal income tax or withholding (subject to the discussion below of backup withholding). Interest we pay on the notes to a non-U.S. holder generally should qualify for the portfolio interest exemption if:

- (1) the interest is not effectively connected with the conduct of a trade or business within the United States by the non-U.S. holder;
- (2) the non-U.S. holder does not actually or constructively own 10% or more of the total voting power of all classes of our stock entitled to vote;

- (3) the non-U.S. holder is not a controlled foreign corporation that is related to us through stock ownership (for this purpose, the holder of notes would be deemed to own constructively the common stock into which it could be converted);
- (4) the non-U.S. holder, under penalty or perjury, certifies to us or our agent that it is not a U.S. person and provides its name and address (or otherwise satisfies the applicable identification requirements); and
- (5) the non-U.S. holder is not a bank receiving interest pursuant to a loan agreement entered into in the ordinary course of its trade or business.

If a non-U.S. holder satisfies certain requirements, the certification described above may be provided by a securities clearing organization, a bank, or other financial institution that holds customers' securities in the ordinary course of its trade or business.

Recently revised Treasury regulations have modified the certification and identification requirements. These regulations now require foreign partnerships and certain foreign trusts to provide additional documentation which (i) certifies that the individual partners, beneficiaries, or owners of the partnership or trust are not U.S. holders, and (ii) provides the individual partners', beneficiaries' or owners' names and addresses.

A non-U.S. holder that is not exempt from tax under these rules will be subject to U.S. federal income tax withholding at a rate of 30% on payments of interest, unless the interest is effectively connected with the conduct of a U.S. trade or business of the holder or a lower treaty rate applies and, in either case, the non-U.S. holder provides us with proper certification as to the holder's exemption from withholding. If the interest is effectively connected to the conduct of a U.S. trade or business, it will be subject to the U.S. federal income tax on net income that applies to U.S. persons generally (and, with respect to corporate holders and under certain circumstances, the branch profits tax, which is generally imposed at a 30% rate). Non-U.S. holders should consult applicable income tax treaties, which may provide different rules. Even though effectively connected interest is subject to income tax, and may be subject to the branch profits tax, it is not subject to withholding tax if the holder delivers a properly executed IRS Form W-8ECI to us or to our agent. It is not clear whether the above discussion would be applicable to make whole payments, if any, received by non-U.S. holders.

### **Conversion of the notes**

A non-U.S. holder generally will not be subject to U.S. federal income tax on the conversion of a note into shares of our common stock. To the extent a non-U.S. holder receives cash in lieu of a fractional share of common stock on conversion, that cash may give rise to gain that would be subject to the rules described below with respect to the sale or exchange of a note or common stock.

### **Constructive dividends on notes**

The conversion price of the notes may adjust in certain circumstances. An adjustment could potentially give rise to a deemed distribution to non-U.S. holders of the notes. See "—U.S. Holders—

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Constructive dividends on the notes" above. In that case, the deemed distribution would be subject to the rules below regarding withholding of U.S. federal tax on dividends in respect of common stock. See "—Non-U.S. Holders—Dividends" below.

### **Dividends**

Subject to the discussion below of backup withholding, dividends, if any, paid on our common stock to a non-U.S. holder generally will be subject to a 30% U.S. federal withholding tax, subject to reduction for non-U.S. holders eligible for the benefits of certain income tax treaties. Dividends for this purpose may include stock distributions treated as deemed dividends as discussed in "—U.S. Holders—Constructive dividends on the notes" above. Under recently revised Treasury regulations holders will be required to satisfy certain certification requirements to claim treaty benefits.

Except to the extent otherwise provided under an applicable tax treaty, a non-U.S. holder generally will be taxed in the same manner as a U.S. holder on dividends paid (or deemed paid) that are effectively connected with the conduct of a trade or business in the United States by the non-U.S. holder (and, if required by a tax treaty, are attributable to a permanent establishment maintained in the United States).

If that non-U.S. holder is a foreign corporation, it may also be subject to a U.S. branch profits tax on that effectively connected income at a 30% rate or a lower rate as may be specified by an applicable income tax treaty.

### **Gain on disposition of the notes and common stock**

A non-U.S. holder generally will not be subject to U.S. federal income tax or withholding tax on gain realized on the sale, exchange or redemption of a note, or the sale or exchange of common stock, unless:

- (i) in the case of an individual non-U.S. holder, that holder is present in the United States for 183 days or more in the year of the sale, exchange or redemption and certain other requirements are met; or
- (ii) the gain is effectively connected with the conduct of a U.S. trade or business of the non-U.S. holder.

However, if we were to become a U.S. real property holding corporation, or USRPHC, a non-U.S. holder could be subject to federal income tax withholding with respect to gain realized on the disposition of notes or shares of common stock. In that case, any withholding tax withheld pursuant to the rules applicable to dispositions of U.S. real property interests would be creditable against that non-U.S. holder's U.S. federal income tax liability and could entitle that non-U.S. holder to a refund upon furnishing required information to the IRS. We do not believe that we are a USRPHC or will become a USRPHC in the future.

If we call the notes for provisional redemption, non-U.S. holders could also be subject to U.S. federal income tax and withholding on any make whole payments received either upon redemption or upon conversion of the notes after they are called for redemption but before they are actually redeemed. If these payments were later determined not to be subject to U.S. federal income tax, a non-U.S. holder would be entitled to a refund of the tax withheld.

### **U.S. federal estate tax**



A note held by an individual who at the time of death is not a citizen or resident of the United States, as specially defined for U.S. federal estate tax purposes, will not be subject to U.S. federal estate tax if the individual did not actually or constructively own 10% or more of the total combined

voting power of all classes of our stock and, at the time of the individual's death, payments with respect to that note would not have been effectively connected with the conduct by that individual of a trade or business in the United States. Common stock held by an individual who at the time of death is not a citizen or resident of the United States, as specially defined for U.S. federal estate tax purposes, will be included in that individual's estate for U.S. federal estate tax purposes, and the applicable rate of tax may be reduced or eliminated if an estate tax treaty otherwise applies. Estates of non-resident aliens are generally allowed a statutory credit which has the effect of offsetting the U. S. federal estate tax imposed on the first \$60,000 of the taxable estate.

### **Backup withholding and information reporting**

We must report annually to the IRS and to each non-U.S. holder the amount of any interest or dividends paid to that non-U.S. holder, and tax withheld, if any, with respect to those payments. Copies of these information returns may also be made available under the provisions of a specific treaty or agreement to the tax authorities of the country in which the non-U.S. holder resides or is incorporated.

U.S. backup withholding and information reporting will not apply to payments of interest or principal on the notes by us or our agent to a non-U.S. holder if the non-U.S. holder satisfies the certification or identification requirements described in "—Non-U.S. Holders—Payment of interest," above, unless the payor knows or has reason to know that the holder is not entitled to an exemption from information reporting or backup withholding tax. The payment of the proceeds on the disposition of notes or shares of common stock to or through the U.S. office of a U.S. or foreign broker will be subject to information reporting and backup withholding unless the owner provides the certification described above or otherwise establishes an exemption. The proceeds of the disposition by a non-U.S. holder of notes or shares of common stock effected outside the United States to or through a foreign office of a broker generally will not be subject to backup withholding or information reporting. However, if the broker is a U.S. person or has certain connections to the United States, information reporting requirements, but not backup withholding, will apply unless the broker has documentary evidence in its files of the holder's non-U.S. status and has no actual knowledge (or reason to know) to the contrary or unless the holder otherwise establishes an exemption.

### **THE COMPANY**

#### **Deductibility of interest**

Generally, under Section 279 of the Internal Revenue Code, an interest deduction in excess of \$5.0 million is not permitted with respect to certain corporate acquisition indebtedness. Corporate acquisition indebtedness includes any indebtedness that is:

- issued to provide consideration for the direct or indirect acquisition of stock or assets of another corporation;
- subordinated;
- convertible directly or indirectly into the stock of the issuing corporation; and
- issued by a corporation that has a debt to equity ratio that exceeds 2 to 1.

Our ability to deduct all of the interest payable on the notes will depend on the application of the foregoing tests to us. The availability of an interest deduction with respect to the notes was not determinative in our issuance of the notes in the initial private placement of the notes.

Under Section 163(l) of the Internal Revenue Code, no deduction is permitted for interest paid or accrued on any indebtedness of a corporation that is payable in equity of the issuer or a related party. Debt is treated as debt payable in equity of the issuer if the debt is part of an arrangement designed to result in payment of the instrument with or by reference to the equity. These arrangements could

include debt instruments that are convertible at the holder's option if it is substantially certain that the option will be exercised. The legislative history indicates that it is not expected the provision will affect debt with a conversion feature where the conversion price is significantly higher than the market price of the stock on the date of the debt issuance. Accordingly, we do not believe that our interest deduction with respect to interest payments on the notes will be adversely affected by these rules.

### **LEGAL MATTERS**

The validity of the issuance of the notes and the common stock issuable upon conversion of the notes offered hereby will be passed upon for us by Grantland E. Bryce, our Vice President, Legal and General Counsel.

### **EXPERTS**

Ernst & Young LLP, independent auditors, have audited our financial statements included in our Annual Report on Form 10-K for the year ended December 31, 2001, as set forth in their report, which is incorporated by reference in this prospectus and elsewhere in the registration statement. Our financial statements are incorporated by reference in reliance on Ernst & Young LLP's report, given upon their authority as experts in accounting and auditing.

## WHERE YOU CAN FIND MORE INFORMATION

This prospectus is part of a registration statement on Form S-3 that we filed with the Securities and Exchange Commission. Certain information in the registration statement has been omitted from this prospectus in accordance with the rules of the SEC. We are a public company and file proxy statements and annual, quarterly and special reports and other information with the SEC. You can inspect and copy the registration statement as well as the reports, proxy statements and other information we have filed with the SEC at the public reference room maintained by the SEC at 450 Fifth Street, N.W., Washington, D.C. 20549, and at the SEC Regional Offices located at 175 West Jackson Blvd., Ste. 900, Chicago, Illinois 60604 and 233 Broadway, New York, New York 10279. You can call the SEC at 1-800-732-0330 for further information about the public reference rooms. We are also required to file electronic versions of these documents with the SEC, which may be accessed from the SEC's World Wide Web site at <http://www.sec.gov>.

## INCORPORATION OF CERTAIN DOCUMENTS BY REFERENCE

The SEC allows us to "incorporate by reference" certain of our publicly-filed documents into this prospectus, which means that information included in those documents is considered part of this prospectus. Information that we file with the SEC after the effective date of the registration statement of which this prospectus is a part will automatically update and supersede this information. We incorporate by reference the documents listed below and any future filings made with the SEC under Sections 13(a), 13(c), 14 or 15(d) of the Exchange Act, until the offering is completed.

The following documents filed with the SEC are incorporated by reference in this prospectus:

- our Annual Report on Form 10-K for the year ended December 31, 2001;
- our Quarterly Report on Form 10-Q for the quarter ended March 31, 2002;
- our Current Report on Form 8-K, filed with the SEC on January 4, 2002;
- our Current Report on Form 8-K, filed with the SEC on January 7, 2002;
- our Current Report on Form 8-K, filed with the SEC on April 23, 2002;
- our Current Report on Form 8-K, filed with the SEC on April 24, 2002;
- our Current Report on Form 8-K, filed with the SEC on April 24, 2002; and
- the description of our common stock in our Registration Statement on Form 8-A filed with the SEC on April 12, 1991, as updated by our Certificate of Amendment of our Restated Certificate of Incorporation filed with our Quarterly Report on Form 10-Q for the period ended June 30, 2001.

We will furnish without charge to you, on written or oral request, a copy of any or all of the documents incorporated by reference, other than exhibits to those documents. You should direct any requests for documents to Vice President of Finance at our principal executive offices at 2292 Faraday Avenue, Carlsbad, California 92008, telephone number (760) 931-9200.

Any statement contained in a document incorporated or deemed to be incorporated by reference in this prospectus shall be deemed modified, superseded or replaced for purposes of this prospectus to the extent that a statement contained in this prospectus or in any subsequently filed document that also is or is deemed to be incorporated by reference in this prospectus modifies, supersedes or replaces such statement. Any statement so modified, superceded or replaced, shall not be deemed, except as so modified, superceded or replaced, to constitute a part of this prospectus.

## Part II

### INFORMATION NOT REQUIRED IN PROSPECTUS

#### Item 14. Other Expenses of Issuance and Distribution

The following table sets forth all expenses payable by the Registrant in connection with the resales of the securities being registered. All the amounts shown are estimates except for the registration fee. None of the expenses listed below will be paid by the selling security holders.

SEC registration fee	\$	11,500
Legal fees and expenses	\$	10,000
Accounting fees and expenses	\$	10,000
Miscellaneous	\$	8,500
Total	\$	40,000

#### Item 15. Indemnification of Officers and Directors

Under Section 145 of the Delaware General Corporation Law, the Registrant has broad powers to indemnify its directors and officers against liabilities they may incur in such capacities, including liabilities under the Securities Act of 1933.

The Registrant's Certificate of Incorporation and Bylaws include provisions to (i) eliminate the personal liability of its directors for monetary damages resulting from breaches of their fiduciary duty to the extent permitted by Section 102(b)(7) of the General Corporation Law of Delaware (the "Delaware Law") and (ii) require the Registrant to indemnify its directors and officers to the fullest extent permitted by Section 145 of the Delaware Law, including circumstances in which indemnification is otherwise discretionary. Pursuant to Section 145 of the Delaware Law, a corporation generally has the power to indemnify its present and former directors, officers, employees and agents against expenses incurred by them in connection with any suit to which they are, or are threatened to be made, a party by reason of their serving in such positions so long as they acted in good faith and in a manner they reasonably believed to be in, or not opposed to, the best interest of the corporation, and with respect to any criminal action, they had no reasonable cause to believe their conduct was unlawful. The Registrant believes that these provisions are necessary to attract and retain qualified persons as directors and officers. These provisions do not eliminate the directors' duty of care, and, in appropriate circumstances, equitable remedies such as injunctive or other forms of non-monetary relief will remain available under Delaware Law. In addition, each director will continue to be subject to liability for breach of the directors' duty of loyalty to the Registrant, for acts or omissions not in good faith or involving intentional misconduct, for knowing violations of law, for acts or omissions that the director believes to be contrary to the best interests of the Registrant or its stockholders, for any transaction from which the director derived an improper personal benefit, for acts or omissions involving a reckless disregard for the directors' duty to the Registrant or its stockholders when the director was aware or should have been aware of a risk of serious injury to the Registrant or its stockholders, for acts or omissions that constitute an unexcused pattern of inattention that amounts to an abdication of the director's duty to the Registrant or its stockholders, for improper transactions between the director and the Registrant and for improper distributions to stockholders and loans to directors and officers. The provision also does not affect a director's responsibilities under any other law, such as the federal securities law or state or federal environmental laws.

The Registrant has entered into indemnity agreements with each of its directors and executive officers that require the Registrant to indemnify such persons against expenses, judgments, fines, settlements and other amounts incurred (including expenses of a derivative action) in connection with any proceeding, whether actual or threatened, to which any such person may be made a party by reason of the fact that such person is or was a director or an executive officer of the Registrant or any

## II-1

of its affiliated enterprises, provided such person acted in good faith and in a manner such persons reasonably believed to be in or not opposed to the best interests of the Registrant and, with respect to any criminal proceeding, has no reasonable cause to believe his conduct was unlawful. The indemnification agreements also set forth certain procedures that will apply in the event of a claim for indemnification thereunder.

At present, there is no pending litigation or proceeding involving a director or officer of the Registrant as to which indemnification is being sought, nor is the Registrant aware of any threatened litigation that may result in claims for indemnification by any officer or director.

The Registrant has an insurance policy covering the officers and directors of the Registrant with respect to certain liabilities, including liabilities arising under the Securities Act or otherwise.

### Item 16. Exhibits

Exhibit Number	Description of Document
1.1	— Purchase Agreement, dated April 26, 2002, among the Registrant, UBS Warburg LLC, Robertson Stephens, Inc., Needham & Company, Inc., and Roth Capital Partners, LLC
4.1	— Amended and Restated Certificate of Incorporation filed June 19, 1991.(1)
4.2	— Certificate of Amendment to Restated Certificate of Incorporation filed April 9, 2001.(9)
4.3	— Bylaws.(9)
4.4	— Certificate of Designation of the Series A Convertible Preferred Stock.(3)
4.5	— Certificate of Designation of the Series B Convertible Preferred Stock.(6)
4.6	— Certificate of Designation of the Series C Junior Participating Preferred Stock.(7)
4.7	— Specimen Common Stock Certificate.(1)
4.8	— Specimen Series A Preferred Stock Certificate.(8)
4.9	— Specimen Series B Preferred Stock Certificate.(8)
4.10	— Form of Right Certificate.(7)
4.11	— Stock Purchase Agreement between the Registrant and Boehringer Ingelheim International GmbH, dated as of July 18, 1995 (with certain confidential information deleted).(2)
4.12	— Subscription, Joint Development and Operating Agreement, dated April 20, 1999 among the Registrant, Elan Corporation, plc, Elan International Services, Ltd. and Orasense Ltd. (with certain confidential information deleted), together with the related Securities Purchase Agreement, Convertible Promissory Note, Warrant to Purchase Shares of Common Stock, Registration Rights Agreement and License Agreements.(4)
4.13	— Agreement dated August 31, 1999 between Boehringer Ingelheim International GmbH and the Registrant, together with the related Amendment to the Stock Purchase Agreement.(5)
4.14	— Subscription, Joint Development and Operating Agreement dated January 14, 2000 among the Registrant, Elan Corporation, plc, Elan

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- 4.15 — Securities Purchase Agreement, dated August 17, 2001, between the Registrant and Eli Lilly and Company.(10)
  - 4.16 — Registration Rights and Standstill Agreement, dated August 17, 2001, between the Registrant and Eli Lilly and Company.(10)
  - 4.17 — Loan Agreement, dated August 17, 2001, between the Registrant and Eli Lilly and Company.(10)
  - 4.18 — Registration Rights Agreement, dated May 1, 2002, among the Registrant, UBS Warburg LLC, Robertson Stephens, Inc., Needham & Company, Inc., and Roth Capital Partners, LLC.
  - 4.19 — Indenture, dated as of May 1, 2002, between the Registrant and Wells Fargo Bank Minnesota, National Association, as Trustee, with respect to the \$125,000,000 5<sup>1</sup>/<sub>2</sub>% Convertible Subordinated Notes due 2009.
  - 4.20 — Form of 5<sup>1</sup>/<sub>2</sub>% Convertible Subordinated Note due 2009.
  - 5.1 — Opinion of Grantland E. Bryce
  - 12.1 — Statement Regarding Computation of Ratio of Earnings to Fixed Charges
  - 23.1 — Consent of Ernst & Young LLP.
  - 23.2 — Consent of Grantland E. Bryce. Reference is made to Exhibit 5.1
  - 24.1 — Power of Attorney. Reference is made to page II-5
  - 25.1 — Statement of Eligibility of Trustee

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- (1) Filed as an exhibit to the Registrant's Registration Statement on Form S-1 (No. 33-39640) or amendments thereto and incorporated herein by reference.
  - (2) Filed as an exhibit to the Registrant's Report on Form 8-K dated July 18, 1995 and incorporated herein by reference.
  - (3) Filed as an exhibit to the Registrant's Registration Statement on Form S-3 (No. 333-71911) or amendments thereto and incorporated herein by reference.
  - (4) Filed as an exhibit to the Registrant's Report on Form 8-K dated April 20, 1999 and incorporated herein by reference.
  - (5) Filed as an exhibit to the Registrant's Report on Form 8-K dated August 31, 1999 and incorporated herein by reference.
  - (6) Filed as an exhibit to the Registrant's Report on Form 8-K dated January 28, 2000, as amended on October 5, 2001, and incorporated herein by reference.
  - (7) Filed as an exhibit to Registrant's Report on Form 8-K dated December 8, 2000 and incorporated herein by reference.
  - (8) Filed as an exhibit to the Registrant's Report on Form 10-Q/A for the quarter ended June 30, 2000 and incorporated herein by reference.
  - (9) Filed as an exhibit to the Registrant's report on Form 10-Q/A for the quarter ended June 30, 2001 and incorporated herein by reference.
  - (10) Filed as an exhibit to the Registrant's Report on Form 8-K dated August 29, 2001 and incorporated herein by reference.

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**Item 17. Undertakings**

- (a) The undersigned registrant hereby undertakes:
  - (1) To file, during any period in which offers or sales are being made, a post-effective amendment to this registration statement
    - (i) to include any prospectus required by Section 10(a)(3) of the Securities Act of 1933;
    - (ii) to reflect in the prospectus any facts or events arising after the effective date of the registration statement (or the most recent post-effective amendment thereof) which, individually or in the aggregate, represent a fundamental change in the information set forth in the registration statement. Notwithstanding the foregoing, any increase or decrease in volume of securities offered (if the total dollar value of securities offered would not exceed that which was registered) and any deviation from the low or high end of the estimated maximum offering range may be reflected in the form of prospectus filed with the Commission pursuant to Rule 424(b) if, in the aggregate, the changes in volume



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/s/ STANLEY T. CROOKE

Chairman of the Board and Chief Executive Officer  
(Principal executive officer)

May 22, 2002

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Stanley T. Crooke, M.D., Ph.D.

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/s/ B. LYNNE PARSHALL

Executive Vice President, Chief Financial Officer and  
Director (Principal financial and accounting officer)

May 22, 2002

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B. Lynne Parshall

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/s/ CHRISTOPHER F.O. GABRIELI

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Christopher F.O. Gabrieli

Director

May 22, 2002

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/s/ WILLIAM R. MILLER

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William R. Miller

Director

May 22, 2002

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/s/ FREDERICK T. MUTO

---

Frederick T. Muto

Director

May 22, 2002

---

/s/ JOSEPH H. WENDER

---

Joseph H. Wender

Director

May 22, 2002

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/s/ MARK B. SKALETSKY

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Mark B. Skaletsky

Director

May 22, 2002

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/s/ JOHN C. REED

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John C. Reed

Director

May 22, 2002

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\$125,000,000

Isis Pharmaceuticals, Inc.

5 ½% Convertible Subordinated Notes

due 2009

PURCHASE AGREEMENT

April 26, 2002

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PURCHASE AGREEMENT

April 26, 2002

UBS Warburg LLC  
Robertson Stephens, Inc.  
Needham & Company, Inc.  
Roth Capital Partners, LLC  
as Initial Purchasers

c/o UBS Warburg LLC  
299 Park Avenue  
New York, New York 10171

Ladies and Gentlemen:

Isis Pharmaceuticals, Inc., a Delaware corporation, (the "Company"), proposes to issue and sell to the initial purchasers named in Schedule A hereto (the "Initial Purchasers") \$125,000,000 aggregate principal amount of its 5½% Convertible Subordinated Notes due 2009 (the "Firm Notes"). In addition, solely for the purpose of covering over-allotments, the Company proposes to grant to the Initial Purchasers the option to purchase from the Company up to an additional \$18,750,000 aggregate principal amount of the Company's 5 ½% Convertible Subordinated Notes due 2009 (the "Additional Notes"). The Firm Notes and the Additional Notes are hereinafter collectively sometimes referred to as the "Notes."

The Notes are to be issued pursuant to an indenture (the "Indenture") to be dated as of May 1, 2002, between the Company and Wells Fargo Bank Minnesota, N. A., as trustee (the "Trustee"). Copies of the Indenture, in substantially final form, have been delivered to the Initial Purchasers. The Notes will be convertible in accordance with their terms and the terms of the Indenture into shares of the common stock (the "Common Stock") of the Company, par value \$0.001 per share (the "Shares").

The Notes and the Shares will be offered without being registered under the Securities Act of 1933, as amended, and the rules and regulations thereunder (collectively, the "Act"), to "qualified institutional buyers" in compliance with the exemption from registration provided by Rule 144A under the Act ("Rule 144A") and in offshore transactions in reliance on Regulation S under the Act ("Regulation S").

The Initial Purchasers and their direct and indirect transferees will be entitled to the benefits of a Registration Rights Agreement to be entered into at or prior to the time of purchase (as defined herein) between the Company and the Initial Purchasers (the "Registration Rights Agreement").

In connection with the sale of the Notes, the Company has prepared a preliminary offering memorandum (the "Preliminary Memorandum") and will prepare a final offering memorandum (the "Final Memorandum" and, with the Preliminary Memorandum, each an "Offering Memorandum"), including or incorporating by reference a description of the terms of the Notes and the Shares, the terms of the offering and a description of the Company. As used herein, the terms "Preliminary Memorandum," "Final Memorandum" and "Offering Memorandum" shall include in each case the documents incorporated by reference therein, if any. The terms "supplement," "amendment" and "amend" as used herein with respect to an Offering Memorandum shall include all documents deemed to be incorporated by reference in the Preliminary Memorandum or Final Memorandum, if any, that are filed subsequent to the

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date of such Offering Memorandum, but prior to the completion of the offering of the Notes, with the Securities and Exchange Commission (the "Commission") pursuant to the Securities Exchange Act of 1934, as amended, and the rules and regulations thereunder (collectively, the "Exchange Act").

The Company and the Initial Purchasers agree as follows:

1. Sale and Purchase. Upon the basis of the representations and warranties and subject to the terms and conditions herein set forth, the Company agrees to sell to the Initial Purchasers, and each of the Initial Purchasers, severally and not jointly, agrees to purchase from the Company, the aggregate principal amount of Firm Notes set forth opposite the name of such Initial Purchaser in Schedule A hereto at a purchase price of 97% of the principal amount thereof.

In addition, the Company hereby grants to the several Initial Purchasers the option to purchase, and upon the basis of the representations and warranties and subject to the terms and conditions herein set forth, the Initial Purchasers shall have the right to purchase, severally and not jointly, from the Company all or a portion of the Additional Notes as may be necessary to cover over-allotments made in connection with the offering of the Firm Notes, at a purchase price of 97% of the principal amount thereof, plus accrued interest, if any, from the time of purchase (as hereinafter defined) to the additional time of purchase (as hereinafter defined). This option may be exercised by the Initial Purchasers, at any time and from time to time on or before the 30<sup>th</sup> day following the date hereof by written notice to the Company. Such notice shall set forth the aggregate initial principal amount of Additional Notes as to which the option is being exercised and the date and time when the Additional Notes are to be delivered (such date and time being herein referred to as the "additional time of purchase"); provided, however, that the additional time of purchase shall not be earlier than (i) the time of purchase or (ii) the second business day after the date on which the option shall have been exercised nor later than the tenth business day(1) after the date on which the option shall have been exercised. The principal amount of Additional Notes to be sold to each Initial Purchaser shall be the amount which bears the same proportion to the aggregate amount of Additional Notes being purchased as the principal amount of Firm Notes set forth opposite the name of such Initial Purchaser on Schedule A hereto bears to the total amount of Firm Notes.

2. Payment and Delivery. Payment of the purchase price for the Firm Notes shall be made to the Company by Federal (same day) funds, at the offices of Dewey Ballantine LLP in New York, New York, or at such other place as may be agreed upon by the parties hereto, for the respective accounts of the Initial Purchasers. Such payment and delivery shall be made at 10:00 A.M., New York City time, on May 1, 2002 (unless another time shall be agreed to by you and the Company or unless postponed in accordance with the provisions of Section 9 hereof). The time at which such payment and delivery are actually made is hereinafter sometimes called the "time of purchase."

Payment of the purchase price for the Additional Notes shall be made at the additional time of purchase in the same manner and at the same office as the payment for the Firm Notes.

Certificates for the Notes shall be in definitive form or global form, as specified by you, and registered in such names and in such denominations as you shall specify in writing not later than one full business day prior to the time of purchase or the additional time of purchase, as the case may be. For the purpose of expediting the checking of the certificates for the Notes by you, the Company agrees to

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(1) As used herein "business day" shall mean a day on which the New York Stock Exchange is open for trading.

make such certificates available to you for such purpose at least one full business day preceding the time of purchase or the additional time of purchase, as the case may be.

3. Representations and Warranties of the Company. The Company represents and warrants to each of the Initial Purchasers that:

(a) the Preliminary Memorandum does not contain and the Final Memorandum, as amended or supplemented, as applicable, will not contain an untrue statement of a material fact or omit to state a material fact required to be stated therein or necessary to make the statements therein, in light of the circumstances under which they were made, not misleading; provided, however, that the Company makes no representation or warranty with respect to any statement contained in the Offering Memorandum in reliance upon and in conformity with information concerning the Initial Purchasers furnished in writing by or on behalf of any Initial Purchaser through you to the Company for use in the Offering Memorandum; and neither the Company nor any of its affiliates has distributed any offering material in connection with the offer or sale of the Notes other than the Offering Memorandum or any other materials, if any, permitted by the Act;

(b) the Company's capitalization (i) on December 31, 2001 was in all material respects as set forth under the heading entitled "Actual" in the section of the Offering Memorandum entitled "Capitalization"; and (ii) as of the time of purchase shall be in all material respects as set forth on an as adjusted basis to give effect to the sale of the Firm Notes, as set forth under the heading entitled "As Adjusted" in the section of the Offering Memorandum entitled "Capitalization" (subject to the issuance of shares of Common Stock upon the exercise of stock options disclosed as outstanding and issued under the plans described in the Offering Memorandum and subject to the issuance of shares of Common Stock pursuant to agreements described in the Offering Memorandum); all of the issued and outstanding shares of capital stock of the Company have been duly and validly authorized and issued and are fully paid and non-assessable, have been issued in compliance with all federal and state securities laws and were not issued in violation of any preemptive right, resale right, right of first refusal or similar right;

(c) the Company has been duly incorporated and is validly existing as a corporation in good standing under the laws of the State of Delaware, with the requisite corporate power and authority to own, lease and operate its properties and conduct its business as described in the Offering Memorandum;

(d) the Company is duly qualified to do business as a foreign corporation and is in good standing in each jurisdiction where the ownership or leasing of its properties or the conduct of its business requires such qualification, except where the failure to so qualify would not reasonably be expected to have a material adverse effect on the business, operations, prospects, properties, condition (financial or otherwise) or results of operation of the Company and the Subsidiaries (as hereinafter defined) taken as a whole (a "Material Adverse Effect"). The Company has no subsidiaries (as defined in the Act) other than as listed in Schedule B annexed hereto (the "Subsidiaries") and except for such other inactive

subsidiaries that do not possess, individually or in the aggregate, any assets, liabilities or rights that are material to the Company and the Subsidiaries taken as a whole; the Company owns such interest in the Subsidiaries as is set forth in the Offering Memorandum; except for the Subsidiaries or as described in the Offering Memorandum, the Company does not own, directly or indirectly, any long-term debt or any material equity interest in any firm, corporation, partnership, joint venture, association or other entity; complete and correct copies of the certificates of incorporation and of the bylaws of the

Company and all amendments thereto have been made available to you; each of the Subsidiaries has been duly incorporated and is validly existing as a corporation in good standing under the laws of the jurisdiction of its incorporation, with the requisite corporate power and authority to own, lease and operate its properties and to conduct its business as described in the Offering Memorandum; each of the Subsidiaries is duly qualified to do business as a foreign corporation and is in good standing in each jurisdiction where the ownership or leasing of the properties or the conduct of its business requires such qualification, except where the failure to so qualify would not reasonably be expected to have a Material Adverse Effect; all of the outstanding shares of capital stock of each of the Subsidiaries have been duly authorized and validly issued, are fully paid and non-assessable, have been issued in compliance with all applicable securities laws and were not issued in violation of any preemptive right, resale right, right of first refusal or similar right;

(e) neither the Company nor any of the Subsidiaries is in breach or violation of, or in default under (nor has any event occurred which with notice, lapse of time, or both would result in the Company's or any Subsidiary's breach or violation of, or constitute the Company's or any Subsidiary's default under) (each such breach, violation, default or event of the Company or any of the Subsidiaries, a "Default Event"), (i) its charter, bylaws or other organizational documents, (ii) any obligation, agreement, covenant or condition contained in any license, permit, indenture, mortgage, deed of trust, bank loan or credit agreement or other evidence of indebtedness, or any lease, contract or other agreement or instrument to which the Company or any of the Subsidiaries is a party or by which any of them or any of their properties may be bound or affected, (iii) any federal, state, local or foreign law, regulation or rule or (iv) any decree, judgment or order applicable to the Company, any of the Subsidiaries or any of their respective properties, other than, in the case of clauses (ii) and (iii), such Default Events as would not, individually or in the aggregate, reasonably be expected to have a Material Adverse Effect; and the execution, delivery and performance of this Agreement, the Registration Rights Agreement, the Indenture and the Notes and consummation of the other transactions contemplated hereby and thereby, including the issuance and sale of the Notes and the issuance of the Shares upon conversion of the Notes, does not constitute and will not result in a Default Event under (w) any provisions of the charter, bylaws or other organizational documents of the Company or any of the Subsidiaries, (x) under any provision of any license, permit, indenture, mortgage, deed of trust, bank loan or credit agreement or other evidence of indebtedness, or any lease, contract or other agreement or instrument to which the Company or any of the Subsidiaries or by which any of them or their respective properties may be bound or affected, (y) under any federal, state, local or foreign law, regulation or rule or (z) under any decree, judgment or order applicable to the Company, any of the Subsidiaries or any of their respective properties, except, in the case of clauses (x) and (y), for such Default Events as would not, individually or in the aggregate, reasonably be expected to have a Material Adverse Effect;

(f) this Agreement has been duly authorized, executed and delivered by the Company and is a legal, valid and binding agreement of the Company;

(g) the Registration Rights Agreement has been duly authorized by the Company and when executed and delivered by the Company and the other parties thereto will be a legal, valid and binding agreement of the Company, enforceable against the Company in accordance with its terms except as the enforceability thereof may be limited by bankruptcy, insolvency, fraudulent conveyance, reorganization, moratorium or similar laws affecting creditors' rights generally and general principles of equity and except to the extent the rights to indemnity may be limited by applicable law;

(h) the Notes have been duly authorized by the Company and when executed and delivered by the Company and duly authenticated in accordance with the terms of the Indenture and delivered to and paid for by the Initial Purchasers in accordance with the terms hereof will constitute legal, valid and binding obligations of the Company, enforceable against the Company in accordance with their terms except as the enforceability thereof may be limited by bankruptcy, insolvency, fraudulent conveyance, reorganization, moratorium or similar laws affecting creditors' rights generally and general principles of equity, and will be entitled to the benefits of the Indenture and the Registration Rights Agreement; the Shares initially issuable upon conversion of the Notes have been duly authorized and validly reserved for issuance upon conversion of the Notes, and upon conversion of the Notes in accordance with their terms and the terms of the Indenture will be issued free of statutory and contractual preemptive rights and are sufficient in number to meet the current conversion requirements, and such Shares, when so issued upon such conversion in accordance with the terms of the Indenture, will be duly and validly issued and fully paid and non-assessable;

(i) the Indenture has been duly authorized by the Company and when executed and delivered by the Company and the other parties thereto will be a legal, valid and binding agreement of the Company, enforceable against the Company in accordance with its terms except as the enforceability thereof may be limited by bankruptcy, insolvency, fraudulent conveyance, reorganization, moratorium or similar laws affecting creditors' rights generally and general principles of equity and except to the extent the rights to indemnity may be limited by applicable law;

(j) the terms of the Notes, the Registration Rights Agreement, the Indenture and the capital stock of the Company, including the Shares, conform in all material respects to the description thereof contained in the Offering Memorandum;

(k) no approval, authorization, consent or order of or filing with any national, state, local or other governmental or regulatory commission, board, body, authority or agency is required to be obtained or made by the Company or any of the Subsidiaries in connection with the issuance and sale of the Notes and the Shares as contemplated hereby or the consummation by the Company of the other transactions contemplated hereby other than (i) as may be required (A) under the securities or blue sky laws of the various jurisdictions in which the Notes and the Shares are being offered by the Initial Purchasers, (B) by federal and state securities laws with respect to the Company's obligations under the Registration Rights Agreement, (C) with respect to the Notes, under the applicable listing criteria of the National Association of Securities Dealers, Inc. (the "NASD") for its PORTAL trading market ("PORTAL") and (D) with respect to the Shares, under the applicable listing criteria of the Nasdaq National Market and (ii) as have been made or obtained on or prior to the time of purchase or the additional time of purchase, as the case may be (or, if not required to be made or obtained on or prior to the time of purchase or the additional time of purchase, as the case may be, that will be made or obtained when required);

(l) except as set forth in the Offering Memorandum (i) no person has the right, contractual or otherwise, to cause the Company to issue or sell to it the Notes or the Shares or any shares of Common Stock or shares of any other capital stock or other equity interests of the Company, (ii) no person has any preemptive rights, co-sale rights, rights of first refusal or other rights to purchase the Notes or the Shares or any shares of Common Stock or shares of any other capital stock or other equity interests of the Company and (iii) no person has the right to act as an underwriter, or as a financial advisor to the Company, in connection with the offer and sale

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of the Notes and the Shares, in the case of each of the foregoing clauses (i), (ii) and (iii), whether as a result of the sale of the Notes and the Shares as contemplated hereby or otherwise; no person has the right, contractual or otherwise, to cause the Company to register under the Act any shares of Common Stock or shares of any other capital stock or other equity interests of the Company whether as a result of the sale of the Notes and the Shares as contemplated hereby, the transactions contemplated by the Registration Rights Agreement or otherwise, except as disclosed in the Offering Memorandum and except for such rights as have been complied with or waived, or, with respect to the transactions contemplated by the Registration Rights Agreement, except as such rights will be complied with or waived;

(m) Ernst & Young LLP, whose report on the consolidated financial statements of the Company and the Subsidiaries is included in the Offering Memorandum, are independent public accountants as required by the Act;

(n) the Company and each of the Subsidiaries has all necessary licenses, permits, authorizations, consents and approvals and has made all necessary filings required under any federal, state, local or foreign law, regulation or rule (collectively, "Permits"), and has obtained all authorizations, consents and approvals from other persons (collectively, "Approvals") that are necessary in order to conduct its business as described in the Offering Memorandum, other than such Permits and Approvals the failure of which to obtain would not, individually or in the aggregate, reasonably be expected to have a Material Adverse Effect; to its knowledge, neither the Company nor any of the Subsidiaries is in violation of, or any default under, any such Permit or Approval or any federal, state, local or foreign law, regulation or rule or any decree, order or judgment applicable to the Company or any of the Subsidiaries the effect of which would, individually or in the aggregate, reasonably be expected to have a Material Adverse Effect;

(o) all legal or governmental proceedings, related party transactions, contracts, leases or documents of a character required to be filed pursuant to the Exchange Act have been so filed, and all descriptions of such documents contained in the Offering Memorandum are correct in all material respects;

(p) except as disclosed in the Offering Memorandum, there are no actions, suits, claims, investigations or proceedings pending or threatened to which the Company, its directors or officers, any of the Subsidiaries or, to the Company's knowledge, any of the Subsidiaries' directors or officers is a party or of which any of their respective properties is subject at law or in equity, or before or by any federal, state, local or foreign governmental or regulatory commission, board, body, authority or agency which, if adversely decided, would reasonably be expected to result in a judgment, decree or order having a Material Adverse Effect or prevent consummation of the transactions contemplated hereby;

(q) the financial statements, together with the related schedules and notes, included in the Offering Memorandum present fairly in all material respects the consolidated financial position of the Company and the Subsidiaries as of the dates indicated and the consolidated results of operations and cash flows of the Company and the Subsidiaries for the periods specified and have been prepared in compliance in all material respects with the requirements of the Act and in conformity with generally accepted accounting principles applied on a consistent basis during the periods involved; the other financial and statistical data set forth under "Summary Consolidated Financial Data," "Capitalization," and "Selected Consolidated Financial Data" in the Offering Memorandum are accurately presented in all material respects and

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prepared on a basis consistent with such financial statements and books and records of the Company;

(r) subsequent to the respective dates as of which information is given in the Final Memorandum, there has not been (i) any material adverse change, or any development which could reasonably be expected to result in a material adverse change in the business, operations, properties, condition (financial or otherwise), or results of operations of the Company and the Subsidiaries taken as a whole, (ii) any transaction of the Company or the Subsidiaries which is material to the Company and the Subsidiaries taken as a whole, (iii) any obligation, direct or contingent, which is material to the Company and the Subsidiaries taken as a whole, incurred by the Company or any of the Subsidiaries, or (iv) any dividend or distribution of any kind declared, paid or made on the capital stock of the Company other than accrued, paid in kind dividends for the Company's

Series A Convertible Exchangeable 5% Preferred Stock and Series B Convertible Exchangeable 5% Preferred Stock; neither the Company nor any of the Subsidiaries has any material contingent obligation which is not disclosed in the Offering Memorandum;

(s) the Company has obtained for the benefit of the Initial Purchasers the agreement (a "Lock-Up Agreement"), in the form set forth as Exhibit A hereto, of each of its executive officers and directors; the Company will not release or purport to release any of its executive officers or directors from any Lock-Up Agreement without the prior written consent of UBS Warburg LLC;

(t) the Company is not and, after giving effect to the offering and sale of the Notes, will not be an "investment company" or an entity "controlled" by an "investment company," as such terms are defined in the Investment Company Act of 1940, as amended (the "Investment Company Act");

(u) any statistical and market related data included in the Offering Memorandum are based on or derived from sources that the Company believes to be reliable and accurate, and the Company has obtained the written consent to the use of such data from such sources to the extent required;

(v) neither the Company nor any of the Subsidiaries nor, to the Company's knowledge, any of their respective affiliates has taken, directly or indirectly, any action designed to or which has constituted or which might reasonably be expected to cause or result, under the Exchange Act or otherwise, in the stabilization or manipulation of the price of any security of the Company to facilitate the sale or resale of the Notes;

(w) the Company and each of the Subsidiaries maintain insurance of the types and in amounts reasonably adequate for their respective businesses, including, but not limited to, insurance covering real and personal property owned or leased by the Company against theft, damage, destruction, acts of vandalism and other risks customarily insured against, all of which insurance is in full force and effect;

(x) neither the Company nor any of the Subsidiaries has sustained since the date of the latest financial statements included in the Offering Memorandum any losses or interferences with its business from fire, explosion, flood or other calamity, whether or not covered by insurance, or from any labor dispute or court or governmental action, order or decree, otherwise than as set forth or contemplated in the Offering Memorandum or other than any losses

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or interferences which would not, individually or in the aggregate, reasonably be expected to have a Material Adverse Effect;

(y) the Company and each of the Subsidiaries have good title to all personal property owned by them as described in the Offering Memorandum, which to the Company's knowledge is free and clear of all liens, encumbrances and defects except such as (i) are described in the Offering Memorandum, (ii) were incurred in the ordinary course of business and are not material or (iii) would not, individually or in the aggregate, reasonably be expected to have a Material Adverse Effect; except as described in the Offering Memorandum, any real property and buildings held under lease by the Company are held by it under valid, subsisting and enforceable leases with such exceptions as are not material and do not interfere with the use made and presently proposed to be made of such property and buildings by the Company or any of the Subsidiaries, as the case may be;

(z) neither the Company nor, to the Company's knowledge, any of the Subsidiaries has violated any foreign, federal, state or local law or regulation relating to the protection of human health and safety, the environment or hazardous or toxic substances or wastes, pollutants or contaminants, nor any federal or state law relating to discrimination in the hiring, promotion or pay of employees nor any applicable federal or state wages and hours laws, nor any provisions of the Employee Retirement Income Security Act or the rules and regulations promulgated thereunder, which would, individually or in the aggregate, reasonably be expected to result in a Material Adverse Effect;

(aa) the Company and each of the Subsidiaries maintain a system of internal accounting controls sufficient to provide reasonable assurance that (i) transactions are executed in accordance with management's general or specific authorizations; (ii) transactions are recorded as necessary to permit preparation of financial statements in conformity with generally accepted accounting principles and to maintain asset accountability; (iii) access to assets is permitted only in accordance with management's general or specific authorization; and (iv) the recorded accountability for assets is compared with the existing assets at reasonable intervals and appropriate action is taken with respect to any differences;

(bb) except as would not individually or in the aggregate reasonably be expected to have a Material Adverse Effect, all tax returns required to be filed by the Company and each of the Subsidiaries have been filed, other than those filings being contested in good faith, and all taxes, including withholding taxes, penalties and interest, assessments, fees and other charges due pursuant to such returns or pursuant to any assessment received by the Company or any of the Subsidiaries have been paid, other than those being contested in good faith and for which adequate reserves have been provided;

(cc) all documents incorporated by reference by the Offering Memorandum complied in all material respects, as of the date of the Offering Memorandum, with the requirements of the Exchange Act;

(dd) other than as set forth in the Offering Memorandum, or as would not individually or in the aggregate, reasonably be expected to have a Material Adverse Effect, the Company and the Subsidiaries own, possess, license or have other rights to use, all patents, trademarks, servicemarks, trade names, copyrights, trade secrets, information, proprietary rights and processes ("Intellectual Property") necessary for their business as described in the Offering Memorandum, without any known conflict with or infringement of the interests of others. Except

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as described in the Offering Memorandum, the Company is not aware of any options, licenses or agreements of any kind relating to the Intellectual Property of the Company or the Subsidiaries that are outstanding and required to be described in a document incorporated by reference into the Offering Memorandum, and, except as described in the Offering Memorandum, neither the Company nor either of the Subsidiaries is a party to or bound by any options, licenses or agreements with respect to the Intellectual Property of any other person or entity that are required to be described in a document incorporated by reference into the Offering Memorandum; none of the technology employed by the Company and the Subsidiaries has been obtained or is used or proposed to be used by the Company or the Subsidiaries in violation of any contractual obligation binding on the Company or the Subsidiaries or any of their respective directors or executive officers or, to the Company's knowledge, any employees of the Company or the Subsidiaries, other than any violation which would not reasonably be expected to individually or in the aggregate have a Material Adverse Effect; except as described in the Offering Memorandum, to the Company's knowledge neither the Company nor either of the Subsidiaries has violated, infringed or conflicted with, or, by conducting its business as described in the Offering Memorandum and commercializing the products under development described therein, would violate, infringe or conflict with any of the Intellectual Property of any other person or entity other than any such violation, infringement or conflict which would not reasonably be expected to individually or in the aggregate have a Material Adverse Effect;

(ee) the clinical, pre-clinical and other studies and tests conducted by or on behalf of or sponsored by the Company or any Subsidiary or in which the Company, any Subsidiary or their respective products or product candidates have participated that are described in the Offering Memorandum or the results of which are referred to in the Offering Memorandum were and, if still pending, are being conducted in accordance with standard medical and scientific research procedures; except to the extent disclosed in the Offering Memorandum, the Company and each Subsidiary has operated and currently is in compliance in all material respects with all applicable rules, regulations and policies of the U.S. Food and Drug Administration and comparable drug regulatory agencies outside of the United States (collectively, the "Regulatory Authorities"); and except to the extent disclosed in the Offering Memorandum, the Company has not received any notices or other correspondence from the Regulatory Authorities or any other governmental agency requiring the termination or suspension of any clinical or pre-clinical studies or tests that are described in the Offering Memorandum or the results of which are referred to in the Offering Memorandum;

(ff) when the Notes are issued pursuant to this Agreement, the Notes will not be of the same class (within the meaning of Rule 144A) as securities of the Company that are listed on a national securities exchange registered pursuant to Section 6 of the Exchange Act or quoted in a U.S. automated inter-dealer quotation system;

(gg) none of the Company, the Subsidiaries or any affiliate (as defined in Rule 501(b) of Regulation D under the Act, an "Affiliate") of the Company has directly, or through any agent, (i) sold, offered for sale, solicited offers to buy or otherwise negotiated in respect of, any security (as defined in the Act) which is or will be integrated with the sale of the Notes in a manner that would require the registration under the Act of the Notes or (ii) offered, solicited offers to buy or sold the Notes by any form of general solicitation or general advertising (as those terms are used in Regulation D under the Act) or in any manner involving a public offering within the meaning of Section 4(2) of the Act;

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(hh) none of the Company, its Affiliates or any person acting on its or their behalf (other than the Initial Purchasers, for which parties the Company makes no representations), or, to the knowledge of the Company, the Subsidiaries, has engaged or will engage in any directed selling efforts (within the meaning of Regulation S) with respect to any offer or sale of the Notes made in reliance on Regulation S, and the Company and its Affiliates and any person acting on its or their behalf (other than the Initial Purchasers, for which parties the Company makes no representations), and to the knowledge of the Company, the Subsidiaries, have complied and will comply with the offering restrictions requirement of Regulation S with respect to any offer or sale of the Notes made in reliance on Regulation S; and

(ii) it is not necessary in connection with the offer, sale and delivery of the Notes to the Initial Purchasers pursuant to this Agreement to register the Notes under the Act or to qualify the Indenture under the Trust Indenture Act of 1939, as amended.

4. Representations and Warranties of the Initial Purchasers. The Initial Purchasers propose to offer the Notes for sale upon the terms and conditions set forth in this Agreement and the Offering Memorandum, and each Initial Purchaser hereby represents and warrants to and agrees with the Company that:

(a) It will offer and sell the Notes only: (i) to persons whom it reasonably believes are "qualified institutional buyers" ("QIBs") within the meaning of Rule 144A in transactions meeting the requirements of Rule 144A and (ii) outside the United States to persons other than U.S. persons (as defined in Regulation S) in compliance with Regulation S, who, in each case, in purchasing such Notes, are deemed to have represented and agreed as provided in the Offering Memorandum under the caption "Notice to investors";

(b) It is a QIB within the meaning of Rule 144A;

(c) It has not and will not directly or indirectly, solicit offers in the United States for, or offer or sell, the Notes by any form of general solicitation, general advertising (as such terms are used in Regulation D) or in any manner involving a public offering within the meaning of Section 4(2) of the Act; and

(d) With respect to offers and sales outside the United States:

(i) It understands that no action has been or will be taken in any jurisdiction by the Company that would permit a public offering of the Notes, or possession or distribution of the Offering Memorandum or any other offering or publicity material relating to the Notes, in any country or jurisdiction where action for that purpose is required;

(ii) The Notes have not been registered under the Act and may not be offered or sold within the United States or to, or for the account or benefit of, U.S. persons except in accordance with Rule 144A or Regulation S or pursuant to another exemption from the

registration requirements of the Act; and

(iii) It has offered the Notes and will offer and sell the Notes (A) as part of their distribution at any time and (B) otherwise until one year after the later of the commencement of the offering and the time of purchase (or the additional time of purchase, if later) (the "Distribution Compliance Period"), only in accordance with Rule 903 of Regulation S or as otherwise permitted in this Section 4; accordingly, neither it, its

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Affiliates nor any persons acting on its or their behalf have engaged or will engage in any directed selling efforts (within the meaning of Regulation S) with respect to the Notes, and it, its Affiliates and such persons have complied and will comply with the offering restrictions requirement of Regulation S, including, during the Distribution Compliance Period:

- a) no such offer or sale will be made to a U.S. person or for the account or benefit of a U.S. person (other than an Initial Purchaser);
- b) it will not engage in hedging transactions involving the Notes or the Shares unless in compliance with the Act and will include in any information provided to publishers of publicly available databases a statement that the Notes are subject to restrictions under Regulation S and Rule 144A; and
- c) it, its Affiliates and any person acting on its behalf, if selling Notes to another Initial Purchaser, a dealer or a person receiving a selling concession, fee or other remuneration in respect of the Notes, will send a confirmation or other notice to the purchaser stating that the purchaser is subject to the same restrictions on offers and sales as set forth in this Section 4.

5. Certain Covenants of the Company. The Company hereby agrees:

- (a) to prepare the Offering Memorandum in a form approved by the Initial Purchasers and not to make any amendment or supplement to the Final Memorandum which shall reasonably be disapproved by counsel to the Initial Purchasers promptly after reasonable notice thereof;
- (b) to furnish such information as may be required and otherwise to cooperate in qualifying the Notes and the Shares for offering and sale under the securities or blue sky laws of such states as you may designate and to maintain such qualifications in effect so long as required for the distribution of the Notes; provided that the Company shall not be required to qualify as a foreign corporation or to consent to the service of process under the laws of any such state (except service of process with respect to the offering and sale of the Notes); and to promptly advise you of the receipt by the Company of any notification with respect to the suspension of the qualification of the Notes and the Shares for sale in any jurisdiction or the initiation or threat of any proceeding for such purpose;
- (c) to furnish, upon request, to the Initial Purchasers for as long as the Notes are outstanding (i) copies of any reports or other communications which the Company shall send to its stockholders or shall from time to time publish or publicly disseminate, (ii) copies of all annual, quarterly and current reports filed with the Commission on Forms 10-K, 10-Q and 8-K, or such other similar forms, as may be designated by the Commission, (iii) copies of documents or reports filed with any national securities exchange on which any class of securities of the Company is listed and (iv) such other public information as you may reasonably request regarding the Company or any of the Subsidiaries, in each case as soon as reasonably practicable after such reports, communications, documents or information become available;

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(d) to furnish the Initial Purchasers with as many copies of the Offering Memorandum, any documents incorporated by reference therein and any amendment or supplement thereto as the Initial Purchasers may from time to time reasonably request, and if, at any time prior to the completion of the resale of the Notes by the Initial Purchasers, any event shall have occurred as a result of which the Offering Memorandum as then amended or supplemented would include an untrue statement of material fact or omit to state a material fact necessary to make the statements therein, in the light of the circumstances under which they were made when such Offering Memorandum is delivered, not misleading, or, if for any other reason it shall be necessary or desirable during such time to amend or supplement the Offering Memorandum, to notify the Initial Purchasers and upon the request of the Initial Purchasers to prepare and furnish, at the Company's expense, to the Initial Purchasers and to any dealer in securities as many copies as the Initial Purchasers may from time to time reasonably request of an amended Offering Memorandum or a supplement to the Offering Memorandum which will correct such statement or omission or effect such compliance;

(e) to furnish to you as early as reasonably practicable prior to the time of purchase and the additional time of purchase, as the case may be but not later than two business days prior thereto, a copy of the latest available unaudited interim consolidated financial statements, if any, of the Company and the Subsidiaries which have been read by the Company's independent certified public accountants, as stated in their letter to be furnished pursuant to Section 7(d) hereof;

(f) at any time when the Company is not subject to Section 13 or 15(d) of the Exchange Act and so long as any of the Notes (or Shares issued upon conversion thereof) are "restricted securities" within the meaning of Rule 144(a)(3) under the Act, for the benefit of holders from time to time of the Notes, to furnish at its expense, upon request, to holders of Notes and prospective purchasers of Notes information satisfying the requirements of subsection (d)(4)(i) of Rule 144A;

- (g) to use its best efforts to cause the Notes to be eligible for trading in PORTAL;
- (h) to apply the net proceeds from the sale of the Notes in the manner set forth under the caption "Use of proceeds" in the Offering Memorandum;
- (i) to reserve and keep available at all times free of preemptive rights, Shares for the purpose of enabling the Company to satisfy any obligations to issue Shares upon conversion of the Notes;
- (j) to use its best efforts to list, as promptly as practicable but in no event later than the time that the registration statement is declared effective in accordance with the Registration Rights Agreement, and subject to notice of issuance, the Shares on the Nasdaq National Market;
- (k) to pay all costs, expenses, fees and taxes in connection with (i) the preparation of each Preliminary Memorandum, Final Memorandum and any amendments or supplements thereto, and the printing and furnishing of copies of each thereof to the Initial Purchasers and to dealers (including costs of mailing and shipment), (ii) the preparation, issue, execution, authentication, transfer and delivery of the Notes and the Shares, (iii) the printing of this Agreement, the Registration Rights Agreement, the Indenture and any closing documents

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(including compilations thereof) and the reproduction and/or printing and furnishing of copies of each thereof to the Initial Purchasers and (except closing documents) to dealers (including costs of mailing and shipment), (iv) the qualification of the Notes and the Shares for offering and sale under state laws and the determination of their eligibility for investment under state law as aforesaid (including associated filing fees and the reasonable legal fees and disbursements of counsel for the Initial Purchasers) and the printing and furnishing of copies of any blue sky surveys or legal investment surveys to the Initial Purchasers and to dealers, (v) any fees payable to investment rating agencies with respect to the rating of the Notes, (vi) the cost and charges of the Trustee and any transfer agent, registrar or depository, (vii) the costs and expenses of the Company relating to presentations or meetings undertaken in connection with the marketing of the offer and sale of the Notes to prospective investors and the Initial Purchasers' sales forces, including, without limitation, expenses associated with the production of road show slides and graphics, fees and expenses of any consultants engaged in connection with the road show presentations, travel, lodging and other expenses incurred by the officers of the Company and any such consultants, and the cost of any aircraft chartered in connection with the road show and (viii) the performance of the other obligations of the Company hereunder;

(l) not to sell, offer or agree to sell, contract to sell, hypothecate, pledge, grant any option to sell or otherwise dispose of, directly or indirectly, any Notes or shares of Common Stock or securities convertible into or exchangeable or exercisable for Common Stock or other rights to purchase Common Stock or any other securities of the Company that are substantially similar to the Notes or the Common Stock, or file or cause to be declared effective a registration statement under the Act relating to the offer and sale of any Notes or shares of Common Stock or securities convertible into or exercisable or exchangeable for Common Stock or other rights to purchase Common Stock or any other securities of the Company that are substantially similar to the Notes or the Common Stock, for a period of ninety (90) days after the date hereof (the "Lock-up Period"), without the prior written consent of UBS Warburg LLC except for (i) the issuance and sale of the Notes pursuant to this Agreement and the issuance of Shares upon conversion of the Notes, (ii) the registration of the offer and sale of the Notes and the Shares pursuant to the Registration Rights Agreement, (iii) issuances of Common Stock upon the exercise of options or warrants or upon the conversion of convertible securities disclosed as outstanding in the Offering Memorandum, (iv) the issuance of stock options not exercisable during the Lock-up Period pursuant to stock option plans described in the Offering Memorandum and (v) the issuance and registration of securities which may be required pursuant to the Company's or the Subsidiaries' currently outstanding agreements which are described in the Offering Memorandum, including without limitation the issuance of Common Stock to Hybridon, Inc. and the registration thereof under the Act. During the first 45 days of the Lock-up Period UBS Warburg LLC may withhold its consent to the actions described in this Section 5(l) for any or no reason. If after the expiration of the first 45 days of the Lock-up Period the average last reported sales price of the Common Stock on the Nasdaq National Market for any five consecutive trading days equals or exceeds \$19.95 per share (adjusted for any stock split, combination or similar transaction), then UBS Warburg LLC may not thereafter withhold its consent to such actions unreasonably.

(m) not to sell, offer for sale or solicit offers to buy or otherwise negotiate in respect of any security (as defined in the Act), either directly or by an Affiliate, which could be integrated with the sale of the Notes in a manner which would require the registration under the Act of the offer and sale of the Notes;

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(n) not to solicit any offer to buy or offer or sell the Notes or the Shares by means of any form of general solicitation or general advertising (as those terms are used in Regulation D) or in any manner involving a public offering within the meaning of Section 4(2) of the Act;

(o) with respect to those Notes sold in reliance on Regulation S, (i) not to, either directly or by any of its affiliates or any person acting on its or their behalf (other than the Initial Purchasers), engage in any directed selling efforts (within the meaning of Regulation S) and (ii) directly and its affiliates and any person acting on its or their behalf (other than the Initial Purchasers) to comply with the requirements of Regulation S and, during the Distribution Compliance Period, to include in any information provided to publishers of publicly available databases a statement that the Notes are subject to restrictions under Regulation S and Rule 144A;



(p) during the period of two years after the time of purchase or the additional time of purchase, if later, not to directly, nor permit any of its affiliates (as defined in Rule 144 under the Act ("Rule 144")) to, resell any of the Notes or the Shares which constitute "restricted securities" under Rule 144 that have been reacquired by any of them except pursuant to an effective registration statement under the Act;

(q) not to take any action prohibited by Regulation M under the Exchange Act in connection with the distribution of the Notes contemplated hereby; and

(r) to file in a timely manner a Form D with the Securities and Exchange Commission pursuant to Regulation D under the Act relating to the offer and sale of the Notes.

6. Reimbursement of Initial Purchasers' Expenses. If the Notes are not delivered for any reason other than the termination of this Agreement pursuant to the last paragraph of Section 9 hereof or the default by one or more of the Initial Purchasers in its or their respective obligations hereunder, the Company agrees, in addition to paying the amounts described in Section 5(k) hereof, to reimburse the Initial Purchasers for all of their out-of-pocket expenses, including the reasonable fees and disbursements of their counsel.

7. Conditions of Initial Purchasers' Obligations. The several obligations of the Initial Purchasers hereunder are subject to the accuracy of the representations and warranties on the part of the Company on the date hereof and at the time of purchase (and the several obligations of the Initial Purchasers at the additional time of purchase are subject to the accuracy of the representations and warranties on the part of the Company on the date hereof and at the time of purchase (unless previously waived) and at the additional time of purchase, as the case may be), the performance by the Company of its obligations hereunder and to the following additional conditions precedent:

(a) You shall have received, at the time of purchase and at the additional time of purchase, as the case may be, an opinion of Cooley Godward LLP, counsel for the Company, addressed to the Initial Purchasers, and dated the time of purchase or the additional time of purchase, as the case may be, with reproduced copies for each of the other Initial Purchasers and in form reasonably satisfactory to Dewey Ballantine LLP, counsel for the Initial Purchasers, stating that:

(i) the Company has been duly incorporated and is validly existing as a corporation and in good standing under the laws of the State of Delaware, with full corporate power and authority to own, lease and operate its properties and conduct its

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business as described in the Offering Memorandum, to execute and deliver this Agreement, the Registration Rights Agreement and the Indenture and to issue, sell and deliver the Notes and, if issued on the date hereof, the Shares in accordance with the terms of the Indenture, as herein contemplated;

(ii) the Company is duly qualified to do business as a foreign corporation and is in good standing in each jurisdiction in which such qualification is necessary, except where the failure to so qualify would not reasonably be expected to have a Material Adverse Effect;

(iii) this Agreement has been duly authorized, executed and delivered by the Company;

(iv) the Registration Rights Agreement has been duly authorized, executed and delivered by the Company and is a legal, valid and binding agreement of the Company, enforceable against the Company in accordance with its terms;

(v) the Indenture has been duly authorized, executed and delivered by the Company and is a legal, valid and binding agreement of the Company, enforceable against the Company in accordance with its terms;

(vi) the Company has authorized and outstanding (as of the dates indicated) shares of capital stock as set forth in the Offering Memorandum under the caption "Capitalization"; the outstanding shares of capital stock of the Company (A) have been duly authorized and validly issued and are fully paid and non-assessable and (B) were issued in compliance with all preemptive rights, co-sale rights and rights of first refusal under (1) the Delaware General Corporation Law (the "DGCL"), (2) the Certificate of Incorporation, as amended, and Bylaws of the Company and (3) any contract, commitment or instrument filed as an exhibit to a document filed by the Company pursuant to the Exchange Act and incorporated by reference in the Offering Memorandum (collectively, the "Material Agreements"); with respect to the Company's issuance of the Shares upon conversion of the Notes, there are no applicable preemptive rights under the DGCL, the Certificate of Incorporation, as amended, or Bylaws of the Company or any of the Material Agreements;

(vii) the common stock of the Company conforms in all material respects to the description thereof contained in the Offering Memorandum (as incorporated by reference therein from the Company's Registration Statement on Form 8-A filed with the Commission on April 12, 1991 and from the Company's Certificate of Amendment of Restated Certificate of Incorporation filed with the Company's Quarterly Report on Form 10-Q for the period ended June 30, 2001, as amended);

(viii) no approval, authorization, consent or order of or filing with any national, state or local governmental or regulatory commission, board, body, authority or agency is required to be obtained or made by the Company in connection with the execution and delivery of this Agreement, the Registration Rights Agreement and the Indenture and the issuance and sale of the Notes and, if issued on the date hereof, the Shares, except for such as (A) may be required under state securities laws and except for the filing of a Form D with the Securities and Exchange Commission pursuant to Regulation D under the Act, (B) are required in connection with the filing of the shelf registration

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statement(s) as contemplated by the Registration Rights Agreement and (C) have been obtained or made prior to the date hereof;

(ix) the execution and delivery of this Agreement, the Registration Rights Agreement, the Indenture and the Notes by the Company, the issuance of the Notes and, if issued on the date hereof, the issuance of the Shares upon the conversion of the Notes do not constitute, and will not result in, a Default Event pursuant to (A) any provision of the Certificate of Incorporation, as amended, or Bylaws of the Company, (B) any Material Agreement, (C) any law, regulation or rule applicable to the Company (other than state or foreign securities laws, as to which such counsel expresses no opinion) or (D) any decree, judgment or order known by such counsel to be applicable to the Company or any of the Subsidiaries other than, in the case of clause (B) such Default Events as would not, individually or in the aggregate, reasonably be expected to have a Material Adverse Effect;

(x) to the best of such counsel's knowledge, there are no related party transactions, contracts, licenses, agreements, leases or documents of a character which are required to be filed as exhibits to the documents incorporated by reference in the Offering Memorandum or to be summarized or described in such documents which have not been so filed, summarized or described;

(xi) to the best of such counsel's knowledge, except as disclosed in the Offering Memorandum, there are no actions, suits, claims, investigations or proceedings pending or overtly threatened to which the Company or any of the Subsidiaries is subject or of which any of their respective properties is subject, whether at law, in equity or before or by any federal, state, local or foreign governmental or regulatory commission, board, body, authority or agency which, if determined adversely to the Company, would, individually or in the aggregate, reasonably be expected to have a Material Adverse Effect;

(xii) the Company is not and, after giving effect to the offer and sale of the Notes, will not be an "investment company" or an entity "controlled" by an "investment company," as such terms are defined in the Investment Company Act;

(xiii) the Notes have been duly authorized and executed by the Company and when duly authenticated in accordance with the terms of the Indenture and delivered to and paid for by the Initial Purchasers in accordance with the terms of this Agreement will constitute legal, valid and binding obligations of the Company;

(xiv) the Shares initially issuable upon conversion of the Notes have been duly authorized and reserved for issuance upon conversion of the Notes and are initially sufficient in number to meet the conversion requirements of the Notes, and such Shares, when so issued in accordance with the terms of the Indenture, will be duly and validly issued and fully paid and non-assessable;

(xv) assuming (A) the veracity of the representations and warranties of the Company set forth in Section 3 of this Agreement and of the Initial Purchasers set forth in Section 4 of this Agreement and (B) compliance by the Company with the covenants and agreements set forth in Section 5 of this Agreement and by the Initial Purchasers with the covenants and agreements set forth in Section 4 of this Agreement, it is not

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necessary in connection with (x) the offer, sale and delivery of the Notes to the Initial Purchasers pursuant to this Agreement or (y) the initial resales of the Notes by the Initial Purchasers in the manner contemplated in the Offering Memorandum to register the Notes under the Act or to qualify the Indenture in respect thereof under the Trust Indenture Act of 1939, as amended, it being understood that no opinion is expressed as to any subsequent resale of any Note or Share;

(xvi) the statements set forth in the Offering Memorandum under the caption "Description of convertible notes," insofar as such description purports to describe the provisions of documents referred to therein, fairly present in all material respects such documents;

(xvii) those statements in the Offering Memorandum under the captions "Risk factors—Provisions in our certificate of incorporation, other agreements and Delaware law may prevent stockholders from receiving a premium for their shares" and "Risk factors—If registration rights that we have previously granted are exercised, then the price of our securities may be negatively affected" that are descriptions of contracts, agreements or other legal documents or of legal proceedings, or refer to statements of law or legal conclusions, are accurate in all material respects and present fairly the information or applicable law referred to therein;

(xviii) those statements in the Offering Memorandum under the caption "Material United States federal income tax considerations," insofar as such statements constitute a discussion of the United States federal tax laws referred to therein, are accurate in all material respects and fairly present in all material respects the United States federal tax laws referred to therein; and

(xix) except as described in the Offering Memorandum (including those documents incorporated by reference therein), no person has the right, pursuant to the terms of any Material Agreement, to have any securities issued by the Company and owned by such person registered pursuant to the Act, as a result of the transactions contemplated by this Agreement or otherwise, except for such rights as have been complied with or waived.

In addition, such counsel shall state that, during the course of the preparation of the Offering Memorandum (it being understood that such counsel did not participate in the preparation of the documents incorporated by reference), such counsel has participated in conferences with officers and other representatives of the Company, representatives of the independent public accountants of the Company and representatives of the Initial Purchasers at which the contents of the Offering Memorandum were discussed. Although such counsel has not independently verified and is not passing upon and does not assume responsibility for the accuracy, completeness or fairness of the statements contained in the Offering Memorandum (except as and to the extent stated in

subparagraphs (vii), (xvi), (xvii) and (xviii) above), on the basis of the foregoing nothing has come to the attention of such counsel that causes such counsel to believe that the Offering Memorandum or any amendment or supplement thereto at the date of such Offering Memorandum or such amendment or supplement, and at all times up to and including the time of purchase or additional time of purchase, as the case may be, contained or contains an untrue statement of a material fact or omitted or omits to state a material fact required to be stated therein or necessary to make the statements therein, in light of the circumstances under which they were made, not misleading (it being understood that such counsel need express no opinion with respect to the financial statements and schedules and other financial or statistical data included in the Offering Memorandum).

(b) You shall have received at the time of purchase and at the additional time of purchase, as the case may be, the opinion of Woodcock Washburn LLP, patent counsel to the Company, dated the time of purchase or the additional time of purchase, as the case may be, with reproduced copies for each of the other Initial Purchasers and in form reasonably satisfactory to Dewey Ballantine LLP, counsel for the Initial Purchasers, stating that:

(i) based on information brought to such counsel's attention by the Company with respect to the Company's investigation of the published literature and patent references relating to the inventions claimed in its patent applications in such counsel's care (the "relevant applications"), such counsel has disclosed all pertinent art references to the United States Patent and Trademark Office in such applications. To the best of such counsel's knowledge, all information submitted to the United States Patent and Trademark Office in the relevant applications and in connection with the prosecution of the relevant applications was accurate. Neither such counsel nor, to the best of its knowledge, the Company has made any misrepresentation or concealed any material fact from the Patent and Trademark Office in any of the relevant applications, or in connection with the prosecution of such applications;

(ii) the statements in the Offering Memorandum under the heading "Risk factors—Intellectual property litigation could be expensive and prevent us from pursuing our programs" and in the Company's Annual Report on Form 10-K for the year ended December 31, 2001 under the caption "Patents and Proprietary Rights" constitute an accurate summary of the matters referred to therein and fairly present the information called for with respect to such matters; and

(iii) other than as disclosed in the Offering Memorandum, to the best of such counsel's knowledge, the Company's products and products under development do not, and would not upon commercialization, infringe or conflict with asserted rights of any third party with respect to any material patents, trademarks, licenses, copyrights and proprietary or other confidential information employed by the Company in connection with its business.

With respect to subparagraph (i) of paragraph (b) above, Woodcock Washburn LLP may state that they have not independently conducted any investigation of the published literature and patent references relating to the inventions claimed in the Company's patent applications.

(c) You shall have received at the time of purchase and at the additional time of purchase, as the case may be, the opinion of Dewey Ballantine LLP, counsel for the Initial Purchasers, dated the time of purchase or the additional time of purchase, as the case may be, with respect to the issuance and sale of the Notes by the Company, the Offering Memorandum (together with any supplement thereto) and other related matters as the Initial Purchasers may require.

(d) You shall have received from Ernst & Young LLP letters dated, respectively, the date of this Agreement and the time of purchase and additional time of purchase, as the case may be, and addressed to the Initial Purchasers (with reproduced copies for each of the Initial Purchasers) in the forms heretofore approved by UBS Warburg LLC.

(e) No amendment or supplement to the Offering Memorandum, or document which upon filing with the Commission would be incorporated by reference therein, shall at any time have been made or filed to which you have objected or shall object in writing.

(f) At the time of purchase or the additional time of purchase, as the case may be, the Offering Memorandum and all amendments or supplements thereto, or modifications thereof, if any, shall not contain an untrue statement of a material fact or omit to state a material fact required to be stated therein or necessary to make the statements therein, in the light of the circumstances under which they are made, not misleading.

(g) Between the time of execution of this Agreement and the time of purchase or the additional time of purchase, as the case may be, (i) no material and adverse change or any development involving a prospective material and adverse change (other than as specifically described in the Offering Memorandum), in the business, properties, condition (financial or otherwise) or results of operations of the Company and the Subsidiaries, taken as a whole, shall occur or become known and (ii) no transaction which is material and adverse to the Company shall have been entered into by the Company or any of the Subsidiaries.

(h) The Company will, at the time of purchase or additional time of purchase, as the case may be, deliver to you a certificate signed by one of the Company's executive officers to the effect that the representations and warranties of the Company as set forth in this Agreement are true and correct as of each such date, that the Company has performed such of its obligations under this Agreement as are to be performed at or before the time of purchase and at or before the additional time of purchase, as the case may be, and the conditions set forth in paragraphs (f) and (g) of this Section 7 have been met.

(i) You shall have received the letters referred to in Section 3(s).

(j) The Company shall have furnished to you such other documents and certificates as to the accuracy and completeness of any statement in the Offering Memorandum as of the time of purchase and the additional time of purchase, as the case may be, as you may reasonably request.

(k) The Notes shall have been designated for trading on PORTAL, subject only to notice of issuance at or prior to the time of purchase.

(l) Between the time of execution of this Agreement and the time of purchase or additional time of purchase, as the case may be, there shall not have occurred any downgrading, nor shall any notice or announcement have been given or made of (i) any intended or potential downgrading or (ii) any review or possible change that does not indicate an improvement, in the rating accorded any securities of or guaranteed by the Company or any Subsidiary by any "nationally recognized statistical rating organization", as that term is defined in rule 436(g)(2) under the Act.

8. Effective Date of Agreement; Termination. This Agreement shall become effective when the parties hereto have executed and delivered this Agreement.

The obligations of the several Initial Purchasers hereunder shall be subject to termination in the absolute discretion of UBS Warburg LLC or any group of Initial Purchasers (which may include UBS Warburg LLC) which has agreed to purchase in the aggregate at least 50% of the Firm Notes, (i) if, since the time of execution of this Agreement or the respective dates as of which information is given in

the Offering Memorandum, there has been any material adverse change, financial or otherwise (other than as specifically described in the Preliminary Offering Memorandum at the time of execution of this Agreement), in the operations, business, condition or prospects of the Company and the Subsidiaries taken as a whole, which would, in the judgment of UBS Warburg LLC or in the judgment of such group of Initial Purchasers, make it impracticable to market the Notes in the manner and on the terms set forth in the Final Offering Memorandum, (ii) there shall have occurred any downgrading, or any notice shall have been given of (x) any intended or potential downgrading or (y) any review or possible change that does not indicate an improvement, in the rating accorded any securities of or guaranteed by the Company or any Subsidiary by any "nationally recognized statistical rating organization", as that term is defined in Rule 436(g)(2) under the Act or (iii) if, at any time prior to the time of purchase or, with respect to the purchase of any Additional Notes, the additional time of purchase, as the case may be, trading in securities on the New York Stock Exchange, the American Stock Exchange or the Nasdaq National Market shall have been suspended or limitations or minimum prices shall have been established on the New York Stock Exchange, the American Stock Exchange or the Nasdaq National Market, or if a banking moratorium shall have been declared either by the United States or New York State authorities, or if the United States shall have declared war in accordance with its constitutional processes or there shall have occurred any material outbreak or escalation of hostilities or other national or international calamity or crisis of such magnitude in its effect on the financial markets of the United States as, in the judgment of UBS Warburg LLC or in the judgment of such group of Initial Purchasers, to make it impracticable to market the Notes in the manner and on the terms set forth in the Final Offering Memorandum.

If you or any group of Initial Purchasers elects to terminate this Agreement as provided in this Section 8, the Company and each other Initial Purchaser shall be notified promptly by letter or telegram from such terminating Initial Purchaser.

If the sale to the Initial Purchasers of the Notes, as contemplated by this Agreement, is not carried out by the Initial Purchasers for any reason permitted under this Agreement or if such sale is not carried out because the Company shall be unable to comply with any of the terms of this Agreement, the Company shall not be under any obligation or liability under this Agreement (except to the extent provided in Sections 5(k), 6 and 10 hereof), and the Initial Purchasers shall be under no obligation or liability to the Company under this Agreement (except to the extent provided in Section 10 hereof) or to one another hereunder.

9. Increase in Initial Purchasers' Commitments. Subject to Sections 7 and 8, if any Initial Purchaser shall default in its obligation to purchase and pay for the Firm Notes to be purchased by it hereunder (otherwise than for a reason sufficient to justify the termination of this Agreement under the provisions of Section 8 hereof) and if the aggregate principal amount of Firm Notes which all Initial Purchasers so defaulting shall have agreed but failed to purchase and pay for does not exceed 10% of the total aggregate principal amount of Firm Notes to be purchased at such time, the non-defaulting Initial Purchasers shall purchase and pay for (in addition to the aggregate number of Firm Notes they are obligated to purchase pursuant to Section 1 hereof) the aggregate principal amount of Firm Notes agreed to be purchased by all such defaulting Initial Purchasers, as hereinafter provided. Such Notes shall be purchased and paid for by such non-defaulting Initial Purchaser or Initial Purchasers in such amount or amounts as you may designate with the consent of each Initial Purchaser so designated or, in the event no such designation is made, such Notes shall be purchased and paid for by all non-defaulting Initial Purchasers pro rata in proportion to the aggregate principal amount of Firm Notes set opposite the names of such non-defaulting Initial Purchasers in Schedule A.

Without relieving any defaulting Initial Purchaser from its obligations hereunder, the Company agrees with the non-defaulting Initial Purchasers that it will not sell any Firm Notes hereunder

If a new Initial Purchaser or Initial Purchasers are substituted by the Initial Purchasers or by the Company for a defaulting Initial Purchaser or Initial Purchasers in accordance with the foregoing provision, the Company or you shall have the right to postpone the time of purchase for a period not exceeding five business days in order that any necessary changes in the Offering Memorandum and other documents may be effected.

The term Initial Purchaser as used in this Agreement shall refer to and include any Initial Purchaser substituted under this Section 9 with like effect as if such substituted Initial Purchaser had originally been named in Schedule A.

If the aggregate principal amount of Notes which the defaulting Initial Purchaser or Initial Purchasers agreed to purchase exceeds 10% of the total aggregate principal amount of Notes which all Initial Purchasers agreed to purchase hereunder, and if neither the non-defaulting Initial Purchasers nor the Company shall make arrangements within the five business day period stated above for the purchase of all the Notes which the defaulting Initial Purchaser or Initial Purchasers agreed to purchase hereunder, this Agreement shall terminate without further act or deed and without any liability on the part of the Company to any non-defaulting Initial Purchaser and without any liability on the part of any non-defaulting Initial Purchaser to the Company. Nothing in this paragraph, and no action taken hereunder, shall relieve any defaulting Initial Purchaser from liability in respect of any default of such Initial Purchaser under this Agreement.

10. Indemnity and Contribution.

(a) The Company agrees to indemnify, defend and hold harmless each Initial Purchaser, its partners, directors and officers, and any person who controls any Initial Purchaser within the meaning of Section 15 of the Act or Section 20 of the Exchange Act, and the successors and assigns of all of the foregoing persons from and against any loss, damage, expense, liability or claim (including the reasonable cost of investigation) which, jointly or severally, any such Initial Purchaser or any such person may incur under the Act, the Exchange Act, the common law or otherwise, insofar as such loss, damage, expense, liability or claim arises out of or is based upon (i) any untrue statement or alleged untrue statement of a material fact contained in the Offering Memorandum (the term Offering Memorandum for the purpose of this Section 10 being deemed to include any Preliminary Memorandum, the Final Memorandum and the Offering Memorandum as amended or supplemented by the Company), or arises out of or is based upon any omission or alleged omission to state a material fact required to be stated in the Offering Memorandum or necessary to make the statements made therein not misleading, except insofar as any such loss, damage, expense, liability or claim arises out of or is based upon any untrue statement or alleged untrue statement of a material fact contained in and in conformity with information furnished in writing by or on behalf of any Initial Purchaser through you to the Company expressly for use with reference to such Initial Purchaser in such Offering Memorandum or arises out of or is based upon any omission or alleged omission to state a material fact in connection with such information required to be stated in such Offering Memorandum or necessary to make such information not misleading, or (ii) any untrue statement or alleged untrue statement made by the Company in Section 3 of this Agreement or the failure by the Company to perform when and as required any agreement or covenant contained herein or (iii) any untrue statement or alleged untrue statement of any material fact contained in any audio or visual materials provided by the Company or based upon written information furnished by or

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on behalf of the Company including, without limitation, slides, videos, films, tape recordings, used in connection with the marketing of the Notes or (iv) the matters to be covered in the Final Memorandum under the caption "Risk factors—If this offering violated securities laws, purchasers in this offering would have the right to seek refunds or damages" (such description to be substantially as set forth on Exhibit B hereto), provided, however, that the indemnity agreement contained in clause (i) of this subsection (a) with respect to any Preliminary Memorandum or amended Preliminary Memorandum shall not inure to the benefit of any Initial Purchaser from whom the person asserting any such loss, damage, expense, liability or claim purchased the Notes which is the subject thereof if the Final Memorandum corrected any such alleged untrue statement or omission and if such Initial Purchaser failed to send or give a copy of the Final Memorandum to such person at or prior to the written confirmation of the sale of such Notes to such person, unless the failure is the result of noncompliance by the Company with Section 5(d) hereof.

If any action, suit or proceeding (together, a "Proceeding") is brought against an Initial Purchaser or any such person in respect of which indemnity may be sought against the Company pursuant to the foregoing paragraph, such Initial Purchaser or such person shall promptly notify the Company in writing of the institution of such Proceeding and the Company shall assume the defense of such Proceeding, including the employment of counsel reasonably satisfactory to such indemnified party and payment of all fees and expenses; provided, however, that the omission to so notify the Company shall not relieve the Company from any liability which the Company may have to any Initial Purchaser or any such person or otherwise, except to the extent the Company is materially prejudiced thereby. Such Initial Purchaser or such person shall have the right to employ its or their own counsel in any such case, but the fees and expenses of such counsel shall be at the expense of such Initial Purchaser or of such person unless the employment of such counsel shall have been authorized in writing by the Company in connection with the defense of such Proceeding or the Company shall not have, within a reasonable period of time in light of the circumstances, employed counsel to have charge of the defense of such Proceeding or such indemnified party or parties shall have reasonably concluded that there may be defenses available to it or them which are different from, additional to or in conflict with those available to the Company (in which case the Company shall not have the right to direct the defense of such Proceeding on behalf of the indemnified party or parties), in any of which events such fees and expenses shall be borne by the Company and paid as incurred (it being understood, however, that the Company shall not be liable for the expenses of more than one separate counsel (in addition to any local counsel) in any one Proceeding or series of related Proceedings in the same jurisdiction representing the indemnified parties who are parties to such Proceeding). The Company shall not be liable for any settlement of any Proceeding effected without the written consent of the Company, but if settled with the written consent of the Company, the Company agrees to indemnify and hold harmless any Initial Purchaser and any such person from and against any loss or liability by reason of such settlement. Notwithstanding the foregoing sentence, if at any time an indemnified party shall have requested an indemnifying party to reimburse the indemnified party for fees and expenses of counsel as contemplated by the second sentence of this paragraph, then the indemnifying party agrees that it shall be liable for any settlement of any Proceeding effected without the Company's written consent if (i) such settlement is entered into more than 60 business days after receipt by the indemnifying party of the aforesaid request, (ii) such indemnifying party shall not have reimbursed the indemnified party in accordance with such request prior to the date of such settlement and (iii) such indemnified party shall have given the indemnifying party at least 30 days' prior notice of its intention to settle. No indemnifying party shall, without the prior written consent of the indemnified party, effect any settlement of any pending or threatened Proceeding in respect of which any indemnified party is or could have been a party and indemnity could have been sought hereunder by such indemnified party, unless such settlement includes an unconditional release of such indemnified party from all liability on claims that are

the subject matter of such Proceeding and does not include an admission of fault, culpability or a failure to act, by or on behalf of such indemnified party.

(b) Each Initial Purchaser severally agrees to indemnify, defend and hold harmless the Company, its directors and officers, and any person who controls the Company within the meaning of Section 15 of the Act or Section 20 of the Exchange Act and the successors and assigns of all of the foregoing persons from and against any loss, damage, expense, liability or claim (including the reasonable cost of investigation) which the Company or any such person may incur under the Act, the Exchange Act, the common law or otherwise, insofar as such loss, damage, expense, liability or claim arises out of or is based upon any untrue statement or alleged untrue statement of a material fact contained in and in conformity with information furnished in writing by or on behalf of such Initial Purchaser through you to the Company expressly for use with reference to such Initial Purchaser in the Offering Memorandum (or in the Offering Memorandum as amended by the Company), or arises out of or is based upon any omission or alleged omission to state a material fact in connection with such information required to be stated in such Offering Memorandum or necessary to make such information not misleading.

(c) If any Proceeding is brought against the Company or any such person in respect of which indemnity may be sought against any Initial Purchaser pursuant to the foregoing paragraph, the Company or such person shall promptly notify such Initial Purchaser in writing of the institution of such Proceeding and such Initial Purchaser shall assume the defense of such Proceeding, including the employment of counsel reasonably satisfactory to such indemnified party and payment of all fees and expenses; provided, however, that the omission to so notify such Initial Purchaser shall not relieve such Initial Purchaser from any liability which such Initial Purchaser may have to the Company or any such person or otherwise, except to the extent such Initial Purchaser is materially prejudiced thereby. The Company or such person shall have the right to employ their or its own counsel in any such case, but the fees and expenses of such counsel shall be at the expense of the Company or such person unless the employment of such counsel shall have been authorized in writing by such Initial Purchaser in connection with the defense of such Proceeding or such Initial Purchaser shall not have, within a reasonable period of time in light of the circumstances, employed counsel to defend such Proceeding or such indemnified party or parties shall have reasonably concluded that there may be defenses available to it or them which are different from or additional to or in conflict with those available to such Initial Purchaser (in which case such Initial Purchaser shall not have the right to direct the defense of such Proceeding on behalf of the indemnified party or parties, but such Initial Purchaser may employ counsel and participate in the defense thereof but the fees and expenses of such counsel shall be at the expense of such Initial Purchaser), in any of which events such fees and expenses shall be borne by such Initial Purchaser and paid as incurred (it being understood, however, that such Initial Purchaser shall not be liable for the expenses of more than one separate counsel (in addition to any local counsel) in any one Proceeding or series of related Proceedings in the same jurisdiction representing the indemnified parties who are parties to such Proceeding). No Initial Purchaser shall be liable for any settlement of any such Proceeding effected without the written consent of such Initial Purchaser but if settled with the written consent of such Initial Purchaser, such Initial Purchaser agrees to indemnify and hold harmless the Company and any such person from and against any loss or liability by reason of such settlement. Notwithstanding the foregoing sentence, if at any time an indemnified party shall have requested an indemnifying party to reimburse the indemnified party for fees and expenses of counsel as contemplated by the second sentence of this paragraph, then the indemnifying party agrees that it shall be liable for any settlement of any Proceeding effected without its written consent if (i) such settlement is entered into more than 60 business days after receipt by such indemnifying party of the aforesaid request, (ii) such indemnifying party shall not have reimbursed the indemnified party in accordance with such request prior to the date of such settlement and (iii) such indemnified party shall have given the indemnifying party at least 30 days' prior notice of its intention to settle. No indemnifying party shall,

without the prior written consent of the indemnified party, effect any settlement of any pending or threatened Proceeding in respect of which any indemnified party is or could have been a party and indemnity could have been sought hereunder by such indemnified party, unless such settlement includes an unconditional release of such indemnified party from all liability on claims that are the subject matter of such Proceeding and does not include an admission of fault, culpability or a failure to act, by or on behalf of such indemnified party.

(d) If the indemnification provided for in this Section 10 is unavailable to an indemnified party under subsections (a) and (b) of this Section 10 in respect of any losses, damages, expenses, liabilities or claims referred to therein, then each applicable indemnifying party, in lieu of indemnifying such indemnified party, shall contribute to the amount paid or payable by such indemnified party as a result of such losses, damages, expenses, liabilities or claims (i) in such proportion as is appropriate to reflect the relative benefits received by the Company on the one hand and the Initial Purchasers on the other hand from the offering of the Notes or (ii) if the allocation provided by clause (i) above is not permitted by applicable law, in such proportion as is appropriate to reflect not only the relative benefits referred to in clause (i) above but also the relative fault of the Company on the one hand and of the Initial Purchasers on the other in connection with the statements or omissions which resulted in such losses, damages, expenses, liabilities or claims, as well as any other relevant equitable considerations. The relative benefits received by the Company on the one hand and the Initial Purchasers on the other shall be deemed to be in the same respective proportions as the total proceeds from the offering (net of discounts and commissions but before deducting expenses) received by the Company and the total discounts and commissions received by the Initial Purchasers. The relative fault of the Company on the one hand and of the Initial Purchasers on the other shall be determined by reference to, among other things, whether the untrue statement or alleged untrue statement of a material fact or omission or alleged omission relates to information supplied by the Company or by the Initial Purchasers and the parties' relative intent, knowledge, access to information and opportunity to correct or prevent such statement or omission. The amount paid or payable by a party as a result of the losses, damages, expenses, liabilities and claims referred to in this subsection shall be deemed to include any legal or other fees or expenses reasonably incurred by such party in connection with investigating, preparing to defend or defending any Proceeding.

(e) The Company and the Initial Purchasers agree that it would not be just and equitable if contribution pursuant to this Section 10 were determined by pro rata allocation (even if the Initial Purchasers were treated as one entity for such purpose) or by any other method of allocation that does not take account of the equitable considerations referred to in subsection (c) above. Notwithstanding the provisions of this Section 10, in no case shall any Initial Purchaser be required to contribute any amount in excess of the amount by which the total price at which the

Notes resold by it in the initial placement of such Notes with investors exceeds the amount of any damage which such Initial Purchaser has otherwise been required to pay by reason of such untrue statement or alleged untrue statement or omission or alleged omission. No person guilty of fraudulent misrepresentation (within the meaning of Section 11(f) of the Act) shall be entitled to contribution from any person who was not guilty of such fraudulent misrepresentation. The Initial Purchasers' obligations to contribute pursuant to this Section 10 are several in proportion to the respective principal amount of Notes they have purchased hereunder, and not joint.

(f) The indemnity and contribution agreements contained in this Section 10 and the covenants, warranties and representations of the Company and the Initial Purchasers contained in this Agreement shall remain in full force and effect regardless of any investigation

made by or on behalf of any Initial Purchaser, its partners, directors or officers or any person (including each partner, officer or director of such person) who controls any Initial Purchaser within the meaning of Section 15 of the Act or Section 20 of the Exchange Act, or by or on behalf of the Company, its directors or officers or any person who controls any of the foregoing within the meaning of Section 15 of the Act or Section 20 of the Exchange Act, and shall survive any termination of this Agreement or the issuance and delivery of the Notes. The Company and each Initial Purchaser agree promptly to notify each other of the commencement of any Proceeding against it and against any of the officers or directors of the Company in connection with the issuance and sale of the Notes, or in connection with the Offering Memorandum.

11. Notices. Except as otherwise herein provided, all statements, requests, notices and agreements shall be in writing and, if to the Initial Purchasers, shall be sufficient in all respects if delivered or sent to UBS Warburg LLC, 299 Park Avenue, New York, NY 10171-0026, Attention: Syndicate Department; and if to the Company, shall be sufficient in all respects if delivered or sent to the Company at the offices of the Company at 2292 Faraday Avenue, Carlsbad, CA 92008, Attention: B. Lynne Parshall, Esq., Executive Vice President and Chief Financial Officer.

12. Information Furnished by the Initial Purchasers. The statements set forth in the last paragraph on the cover page of the Offering Memorandum and the statements set forth in the ninth paragraph (regarding over-allotment, stabilizing and syndicate covering transactions) under the caption "Plan of distribution" in the Offering Memorandum constitute the only information furnished by or on behalf of the Initial Purchasers as such information is referred to in Sections 3 and 10 hereof.

13. Governing Law; Construction. This Agreement and any claim, counterclaim or dispute of any kind or nature whatsoever arising out of or in any way relating to this Agreement ("Claim"), directly or indirectly, shall be governed by, and construed in accordance with, the laws of the State of New York. The section headings in this Agreement have been inserted as a matter of convenience of reference and are not a part of this Agreement.

14. Submission to Jurisdiction. Except as set forth below, no Claim may be commenced, prosecuted or continued in any court other than the courts of the State of New York located in the City and County of New York or in the United States District Court for the Southern District of New York, which courts shall have jurisdiction over the adjudication of such matters, and you and the Company consent to the jurisdiction of such courts and personal service with respect thereto. The Company hereby consents to personal jurisdiction, service and venue in any court in which any Claim arising out of or in any way relating to this Agreement is brought by any third party against an Initial Purchaser or any indemnified party. Each Initial Purchaser and the Company (on its behalf and, to the extent permitted by applicable law, on behalf of its stockholders and affiliates) waives all right to trial by jury in any action, proceeding or counterclaim (whether based upon contract, tort or otherwise) in any way arising out of or relating to this Agreement. The Company agrees that a final judgment not subject to appeal in any such action, proceeding or counterclaim brought in any such court shall be conclusive and binding thereupon, and may be enforced in any other courts in the jurisdiction to which the Company is or may be subject, by suit upon such judgment.

15. Parties at Interest. The Agreement herein set forth has been and is made solely for the benefit of the Initial Purchasers, the Company and, to the extent provided in Section 10 hereof, the controlling persons, directors and officers referred to in such section, and their respective successors, assigns, heirs, personal representatives and executors and administrators. No other person, partnership, association or corporation (including a purchaser, as such purchaser, from any of the Initial Purchasers) shall acquire or have any right under or by virtue of this Agreement.

16. Counterparts. This Agreement may be signed by the parties in one or more counterparts which together shall constitute one and the same agreement among the parties.

17. Successors and Assigns. This Agreement shall be binding upon the Initial Purchasers and the Company and their successors and assigns and any successor or assign of any substantial portion of the Company's and any of the Initial Purchasers' respective businesses and/or assets.

18. Miscellaneous. UBS Warburg LLC, an indirect, wholly owned subsidiary of UBS AG, is not a bank and is separate from any affiliated bank, including any U.S. branch or agency of UBS Warburg LLC. Because UBS Warburg LLC is a separately incorporated entity, it is solely responsible for its own contractual obligations and commitments, including obligations with respect to sales and purchases of securities. Securities sold, offered or recommended by UBS Warburg LLC are not deposits, are not insured by the Federal Deposit Insurance Corporation, are not guaranteed by a branch or agency, and are not otherwise an obligation or responsibility of a branch or agency.

A lending affiliate of UBS Warburg LLC may have lending relationships with issuers of securities underwritten or privately placed by UBS Warburg LLC. To the extent required under the securities laws, prospectuses and other disclosure documents for securities underwritten or privately placed by UBS Warburg LLC will disclose the existence of any such lending relationships and whether the proceeds of the issue will be used to repay debts owed to affiliates of UBS Warburg LLC.

If the foregoing correctly sets forth the understanding between the Company and the Initial Purchasers, please so indicate in the space provided below for the purpose, whereupon this letter and your acceptance shall constitute a binding agreement between the Company and the Initial Purchasers.

Very truly yours,

ISIS PHARMACEUTICALS, INC.

By: /s/ B. Lynne Parshall  
 Name:  
 Title:

Accepted and agreed to as of the date first above written:

UBS WARBURG LLC  
 ROBERTSON STEPHENS, INC.  
 NEEDHAM & COMPANY, INC.  
 ROTH CAPITAL PARTNERS, LLC

on behalf of itself and the other Initial Purchasers named in Schedule A hereto:

By: UBS WARBURG LLC

By: /s/ Steve Meehan  
 Name: Steve Meehan  
 Title: Managing Director

By: /s/ S. Kelly  
 Name: S. Kelly  
 Title: Director

SCHEDULE A

<u>Initial Purchasers</u>	<u>Principal Amount of Firm Notes</u>
UBS WARBURG LLC	\$ 122,375,000
ROBERTSON STEPHENS, INC.	1,500,000
NEEDHAM & COMPANY, INC.	750,000
ROTH CAPITAL PARTNERS, LLC	375,000
Total	<u>\$ 125,000,000</u>

Sch-B

SCHEDULE B

<u>Name</u>	<u>Jurisdiction of Incorporation</u>
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## EXHIBIT A

Isis Pharmaceuticals, Inc.

Common Stock

(\$0.001 Par Value)

, 2002

UBS Warburg LLC  
Robertson Stephens, Inc.

c/o UBS Warburg LLC  
299 Park Avenue  
New York, New York 10171

Ladies and Gentlemen:

This Lock-Up Letter Agreement is being delivered to you in connection with the proposed Purchase Agreement (the "Purchase Agreement") to be entered into by and among Isis Pharmaceuticals, Inc. (the "Company"), you and the other Initial Purchasers named therein, with respect to an offering without registration under the Securities Act of 1933, as amended (the "Act"), in reliance on Rule 144A, Regulation S and Regulation D under the Act, Convertible Subordinated Notes due 2009 (the "Notes") of the Company (the "Offering").

In order to induce you to enter into the Purchase Agreement, the undersigned agrees that for a period of 90 days after the date of the Final Memorandum relating to the Offering the undersigned will not, without the prior written consent of UBS Warburg LLC, (i) sell, offer to sell, contract to sell, hypothecate, pledge, grant any option to purchase or otherwise dispose of, or establish or increase a put equivalent position or liquidate or decrease a call equivalent position within the meaning of Section 16 of the Securities Exchange Act of 1934, as amended, and the rules and regulations of the Commission promulgated thereunder with respect to, any Notes or Common Stock or any securities convertible into or exercisable or exchangeable for Common Stock or any securities substantially similar to the Notes or the Common Stock, (ii) enter into any swap or other arrangement that transfers to another, in whole or in part, any of the economic consequences of ownership of Common Stock or any securities convertible into or exercisable or exchangeable for any Notes or Common Stock or any securities substantially similar to the Notes or the Common Stock, whether any such transaction is to be settled by delivery of Common Stock or such other securities, in cash or otherwise, or (iii) publicly announce an intention to effect any transaction specified in clause (i) or (ii). The foregoing sentence shall not apply to (a) the sale of any Common Stock to the Initial Purchasers pursuant to the Purchase Agreement, (b) bona fide gifts, provided the recipient or recipients thereof agree in writing to be bound by the terms of this Lock-Up Letter Agreement, (c) dispositions to any trust for the direct or indirect benefit of the undersigned and/or the immediate family of the undersigned, provided that such trust agrees in writing to be bound by the terms of this Lock-Up Letter Agreement, or (d) the sale of up to **[The Number Equal to the greater of (A) the number of shares subject to stock options that will expire by the end of 2002, or (B) 20,000 shares for**

Exhibit B-1

**Executive Officers and 8,000 shares for Directors]** shares of Common Stock made after the tenth (10<sup>th</sup>) business day following the time of purchase (as defined in the Purchase Agreement). For sales of Common Stock made under the exception set forth in clause (d) above, the Company will recommend that the undersigned use designated personnel of UBS Warburg LLC previously approved by the Company to effectuate such sales.

In addition, the undersigned hereby waives any rights the undersigned may have to require registration of Common Stock in connection with the filing of a registration statement relating to the Offering. The undersigned further agrees that, for a period of 90 days after the date of the Final Memorandum relating to the Offering, the undersigned will not, without the prior written consent of UBS Warburg LLC, make any demand for, or exercise any right with respect to, the registration of Common Stock of the Company or any securities convertible into or exercisable or exchangeable for Common Stock.

If for any reason the Purchase Agreement shall be terminated prior to the time of purchase (as defined in the Purchase Agreement), this Lock-Up Letter Agreement shall be terminated and the undersigned shall be released from its obligations hereunder.

Yours very truly,

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Name:

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Exhibit A-2

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EXHIBIT B

**If this offering violated securities laws, purchasers in this offering would have the right to seek refunds or damages.**

On April 24, 2002, an article appeared in a San Diego newspaper regarding this offering in which one of our officers was interviewed. The newspaper article could form the basis for a claim that we have engaged in an unregistered public offering of the convertible notes in violation of securities laws. We would dispute any such claim. However, if such a claim were made and it prevailed, the initial purchasers and persons who purchase the convertible notes from the initial purchasers in this offering would have the right, for a period of one year, to obtain recovery of the consideration paid in connection with their purchase of the convertible notes or, if they have already sold the convertible notes, to recover any losses resulting from their purchase of the convertible notes.

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## REGISTRATION RIGHTS AGREEMENT

THIS REGISTRATION RIGHTS AGREEMENT (the "Agreement") is made and entered into as of May 1, 2002, by and between Isis Pharmaceuticals, Inc., a Delaware corporation (the "Company") and UBS Warburg LLC and the other Initial Purchasers named in the Purchase Agreement referred to below (collectively, the "Initial Purchasers"), for whom UBS Warburg LLC is acting as representative, pursuant to that certain Purchase Agreement, dated as of April 26, 2002 (the "Purchase Agreement") between the Company and the Initial Purchasers.

In order to induce the Initial Purchasers to enter into the Purchase Agreement, the Company has agreed to provide the registration rights set forth in this Agreement. The execution of this Agreement is a condition to the closing under the Purchase Agreement.

The Company agrees with the Initial Purchasers (i) for their benefit as Initial Purchasers and (ii) for the benefit of the beneficial owners (including the Initial Purchasers) from time to time of the Notes (as defined herein) and the beneficial owners from time to time of the Underlying Common Stock (as defined herein) issued upon conversion of the Notes (each of the foregoing a "Holder" and together the "Holders"), as follows:

Section 1. *Definitions.* Capitalized terms used herein without definition shall have their respective meanings set forth in the Purchase Agreement. As used in this Agreement, the following terms shall have the following meanings:

"Affiliate" means with respect to any specified person, an "affiliate," as defined in Rule 144, of such person.

"Amendment Effectiveness Deadline Date" has the meaning set forth in Section 2(d) hereof.

"Applicable Conversion Price" means, as of any date of determination, \$1,000 divided by the Conversion Rate then in effect as of the date of determination or, if no Notes are then outstanding, the Conversion Rate that would be in effect were Notes then outstanding.

"Notes" means the 5 ½% Convertible Subordinated Notes due 2009 of the Company to be purchased pursuant to the Purchase Agreement.

"Business Day" means each day on which the New York Stock Exchange is open for trading.

"Common Stock" means the shares of common stock, par value \$0.001 per share, of the Company and any other shares of capital stock as may constitute "Common Stock" for purposes of the Indenture, including the Underlying Common Stock.

"Conversion Rate" has the meaning assigned to such term in the Indenture.

"Damages Accrual Period" has the meaning set forth in Section 2(e) hereof.

"Damages Payment Date" means each interest payment date under the Indenture in the case of Notes, and each May 1 and November 1 in the case of the Underlying Common Stock.

"Effectiveness Deadline Date" has the meaning set forth in Section 2(a) hereof.

"Effectiveness Period" means a period (subject to extension pursuant to Section 3(i) hereof ) of two years after the later of (1) the original issuance of the Notes and (2) the last date that the Company or any of its Affiliates was the owner of such Notes (or any predecessor thereto), or such shorter period of time (x) after which the Registrable Securities held by each Notice Holder are eligible for resale as permitted by Rule 144(k) under the Securities Act or any successor provisions thereunder or (y) that will terminate when each of the Registrable Securities covered by the Shelf Registration Statement ceases to be a Registrable Security.

"Event" has the meaning set forth in Section 2(e) hereof.

"Event Date" has the meaning set forth in Section 2(e) hereof.

"Exchange Act" means the Securities Exchange Act of 1934, as amended, and the rules and regulations of the SEC promulgated thereunder.

"Filing Deadline Date" has the meaning set forth in Section 2(a) hereof.

"Holder" has the meaning set forth in the third paragraph of this Agreement.

"Indenture" means the Indenture, dated as of May 1, 2002, between the Company and Wells Fargo Bank Minnesota, N.A., as trustee, pursuant to which the Notes are being issued.

"Initial Purchasers" has the meaning set forth in the preamble hereto.

"Initial Shelf Registration Statement" has the meaning set forth in Section 2(a) hereof.

"Issue Date" means the first date of original issuance of the Notes.

"Liquidated Damages Amount" has the meaning set forth in Section 2(e) hereof.

“Material Event” has the meaning set forth in Section 3(i) hereof.

“Notice and Questionnaire” means a written notice and questionnaire delivered to the Company containing substantially the information called for by the Selling Securityholder Notice and Questionnaire attached as Annex A to the Offering Memorandum dated April 26, 2002 relating to the Notes.

“Notice Holder” means, on any date, any Holder that has delivered a Notice and Questionnaire to the Company on or prior to such date, so long as such Holder has not sold all Registrable Securities that have been registered for resale pursuant to a Notice and Questionnaire.

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“Purchase Agreement” has the meaning set forth in the preamble hereof.

“Prospectus” means the prospectus included in any Shelf Registration Statement (including, without limitation, a prospectus that discloses information previously omitted from a prospectus filed as part of an effective registration statement in reliance upon Rule 415 promulgated under the Securities Act), as amended or supplemented by any amendment or prospectus supplement, including post-effective amendments, and all materials incorporated by reference or explicitly deemed to be incorporated by reference in such Prospectus.

“Record Holder” means (i) with respect to any Damages Payment Date relating to any Notes as to which any such Liquidated Damages Amount has accrued, the holder of record of such Note on the record date with respect to the interest payment date under the Indenture on which such Damages Payment Date shall occur and (ii) with respect to any Damages Payment Date relating to the Underlying Common Stock as to which any such Liquidated Damages Amount has accrued, the registered holder of such Underlying Common Stock fifteen (15) days prior to such Damages Payment Date.

“Registrable Securities” means the Notes until such Notes have been converted into the Underlying Common Stock and, at all times the Underlying Common Stock and any securities into or for which such Underlying Common Stock has been converted, and any security issued with respect thereto upon any stock dividend, split or similar event until, in the case of any such security, the earliest of (x) the date on which such security has been effectively registered under the Securities Act and disposed of, whether or not in accordance with the Shelf Registration Statement and (y) the date that is two years after the later of (1) the original issuance of the Notes and (2) the last date that the Company or any of its Affiliates was the owner of such Notes (or any predecessor thereto), or such shorter period of time after which the Registrable Securities held by each Notice Holder are eligible for resale as permitted by Rule 144(k) under the Securities Act or any successor provisions thereunder.

“Registration Expenses” has the meaning set forth in Section 5 hereof.

“Registration Statement” means any registration statement of the Company that covers any of the Registrable Securities pursuant to the provisions of this Agreement including the Prospectus, amendments and supplements to such registration statement, including post-effective amendments, all exhibits, and all materials incorporated by reference or explicitly deemed to be incorporated by reference in such registration statement.

“Rule 144” means Rule 144 under the Securities Act, as such Rule may be amended from time to time, or any similar rule or regulation hereafter adopted by the SEC.

“Rule 144A” means Rule 144A under the Securities Act, as such Rule may be amended from time to time, or any similar rule or regulation hereafter adopted by the SEC.

“SEC” means the Securities and Exchange Commission.

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“Securities Act” means the Securities Act of 1933, as amended, and the rules and regulations promulgated by the SEC thereunder.

“Shelf Registration Statement” has the meaning set forth in Section 2(a) hereof.

“Subsequent Shelf Registration Statement” has the meaning set forth in Section 2(b) hereof.

“Suspension Notice” has the meaning set forth in Section 3(i) hereof.

“Suspension Period” has the meaning set forth in Section 3(i) hereof.

“TIA” means the Trust Indenture Act of 1939, as amended.

“Trustee” means Wells Fargo Bank Minnesota, N. A., the Trustee under the Indenture.

“Underlying Common Stock” means the Common Stock into which the Notes are convertible or issued upon any such conversion.

Section 2. *Shelf Registration.* (a) The Company shall prepare and file or cause to be prepared and filed with the SEC, as soon as practicable but in any event by the date (the “Filing Deadline Date”) that is ninety (90) days after the Issue Date, a Registration Statement for an offering to be made on a delayed or continuous basis pursuant to Rule 415 of the Securities Act (a “Shelf Registration Statement”) registering the resale from time to time by Holders thereof of

all of the Registrable Securities (the “Initial Shelf Registration Statement”). The Initial Shelf Registration Statement shall be on Form S-1 or S-3 or another appropriate form permitting registration of such Registrable Securities for resale by such Holders in accordance with the reasonable methods of distribution elected by the Holders, approved by the Company, and set forth in the Initial Shelf Registration Statement. The Company shall use its commercially reasonable best efforts to cause the Initial Shelf Registration Statement to be declared effective under the Securities Act as promptly as is practicable but in any event by the date (the “Effectiveness Deadline Date”) that is one hundred eighty (180) days after the Issue Date, and to keep the Initial Shelf Registration Statement (or any Subsequent Shelf Registration Statement) continuously effective under the Securities Act (subject to the provisions of Section 3(i)) until the expiration of the Effectiveness Period. At the time the Initial Shelf Registration Statement is declared effective, each Holder that became a Notice Holder on or prior to the date that is ten (10) Business Days prior to such time of effectiveness shall be named as a selling securityholder in the Initial Shelf Registration Statement and the related Prospectus in such a manner as to permit such Holder to deliver such Prospectus to purchasers of Registrable Securities in accordance with applicable law.

(b) If the Initial Shelf Registration Statement or any Subsequent Shelf Registration Statement ceases to be effective for any reason at any time during the Effectiveness Period, the Company shall (subject to the provisions of Section 3(i)) use its commercially reasonable best efforts to obtain the prompt withdrawal of any order suspending the effectiveness thereof, and in any event shall (subject to the provisions of Section 3(i)) within thirty (30) days of such cessation

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of effectiveness amend the Shelf Registration Statement in a manner reasonably expected to obtain the withdrawal of the order suspending the effectiveness thereof, or file an additional Shelf Registration Statement covering all of the securities that as of the date of such filing are Registrable Securities (a “Subsequent Shelf Registration Statement”). If a Subsequent Shelf Registration Statement is filed, the Company shall (subject to the provisions of Section 3(i)) use its commercially reasonable best efforts to cause the Subsequent Shelf Registration Statement to become effective as promptly as is practicable after such filing and to keep such Shelf Registration Statement (or subsequent Shelf Registration Statement) continuously effective until the end of the Effectiveness Period.

(c) The Company shall supplement and amend the Shelf Registration Statement if required by the rules, regulations or instructions applicable to the registration form used by the Company for such Shelf Registration Statement, if required by the Securities Act or as reasonably requested by the Initial Purchasers or by the Trustee on behalf of the Holders of the Registrable Securities covered by such Shelf Registration Statement in order to exercise the rights of such Initial Purchasers or Holders, as the case may be, hereunder.

(d) Each Holder of Registrable Securities agrees that if such Holder wishes to sell Registrable Securities pursuant to a Shelf Registration Statement and related Prospectus, it will do so only in accordance with this Section 2(d) and Section 3(i). Each Holder of Registrable Securities wishing to sell Registrable Securities pursuant to a Shelf Registration Statement and related Prospectus agrees to deliver a completed and executed Notice and Questionnaire to the Company prior to any attempted or actual distribution of Registrable Securities under the Shelf Registration Statement; provided that Holders of Registrable Securities shall have at least twenty (20) Business Days from the date on which a Notice and Questionnaire is first sent to such Holders by the Company to complete and return such Notice and Questionnaire to the Company in order to be included in the initial filing of the Initial Shelf Registration Statement. From and after the date the Initial Shelf Registration Statement is declared effective, the Company shall, as promptly as practicable after the date a Notice and Questionnaire is delivered, and in any event within the later of (x) fifteen (15) Business Days after such date or (y) fifteen (15) Business Days after the expiration of any Suspension Period (1) in effect when the Notice and Questionnaire is delivered or (2) put into effect within ten (10) Business Days of such delivery date, (i) if required by applicable law, file with the SEC a post-effective amendment to the Shelf Registration Statement or, if required by applicable law, prepare and file a supplement to the related Prospectus or a supplement or amendment to any document incorporated therein by reference or file any other required document so that the Holder delivering such Notice and Questionnaire is named as a selling securityholder in the Shelf Registration Statement and the related Prospectus in such a manner as to permit such Holder to deliver such Prospectus to purchasers of the Registrable Securities in accordance with applicable law and, if the Company shall file a post-effective amendment to the Shelf Registration Statement, use its commercially reasonable best efforts to cause such post-effective amendment to be declared effective under the Securities Act as promptly as is practicable, but in any event by the date (the “Amendment Effectiveness Deadline Date”) that is thirty (30) days after the date such post-effective amendment is required by this clause to be filed; (ii) provide such Holder a reasonable number of copies of any documents filed pursuant to Section 2(d)(i); and (iii) notify such Holder as promptly as

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practicable after the effectiveness under the Securities Act of any post-effective amendment filed pursuant to Section 2(d)(i); provided that if such Notice and Questionnaire is delivered during a Suspension Period, or a Suspension Period is put into effect within ten (10) Business Days after such delivery date, the Company shall so inform the Holder delivering such Notice and Questionnaire and shall take the actions set forth in clauses (i), (ii) and (iii) above within fifteen (15) Business Days after expiration of the Suspension Period in accordance with Section 3(i); provided further that if under applicable law, the Company has more than one option as to the type or manner of making any such filing, the Company shall make the required filing or filings in the manner or of a type that is reasonably expected to result in the earliest availability of the Prospectus for effecting resales of Registrable Securities. Notwithstanding anything contained herein to the contrary, the Company shall be under no obligation to name any Holder that is not a Notice Holder as a selling securityholder in any Shelf Registration Statement or related Prospectus; provided, however, that any Holder that becomes a Notice Holder pursuant to the provisions of this Section 2(d) (whether or not such Holder was a Notice Holder at the time the Shelf Registration Statement was declared effective) shall be named as a selling securityholder in the Shelf Registration Statement or related Prospectus in accordance with the requirements of this Section 2(d).

(e) The parties hereto agree that the Holders of Registrable Securities will suffer damages, and that it would not be feasible to ascertain the extent of such damages with precision, if (i) the Initial Shelf Registration Statement has not been filed on or prior to the Filing Deadline Date, (ii) the Initial Shelf Registration Statement has not been declared effective under the Securities Act on or prior to the Effectiveness Deadline Date or (iii) the Initial Shelf Registration Statement is filed and declared effective but shall thereafter cease to be effective (without being succeeded immediately by an additional

registration statement filed and declared effective) or usable for the offer and sale of Registrable Securities for a period of time (including any Suspension Period) which shall exceed thirty (30) days in the aggregate in any three (3) month period or sixty (60) days in the aggregate in any twelve (12) month period (each of the events of a type described in any of the foregoing clauses (i) through (iii) are individually referred to herein as an “Event,” and the Filing Deadline Date in the case of clause (i), the Effectiveness Deadline Date in the case of clause (ii), the date on which the duration of the ineffectiveness or unusability of the Initial Shelf Registration Statement in any period exceeds the number of days permitted by clause (iii) hereof in the case of clause (iii), being referred to herein as an “Event Date”). Events shall be deemed to continue until the following dates with respect to the respective types of Events: the date the Initial Shelf Registration Statement is filed in the case of an Event of the type described in clause (i), the date the Initial Shelf Registration Statement is declared effective under the Securities Act in the case of an Event of the type described in clause (ii), and the date the Initial Shelf Registration Statement becomes effective or usable again in the case of an Event of the type described in clause (iii).

Accordingly, commencing on (and including) any Event Date and ending on (but excluding) the next date on which there are no Events that have occurred and are continuing (a “Damages Accrual Period”), the Company agrees to pay, as liquidated damages and not as a penalty, an amount (the “Liquidated Damages Amount”) at the rate described below, payable periodically on each Damages Payment Date to Record Holders of Notes that are Registrable

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Securities and of shares of Underlying Common Stock issued upon conversion of Notes that are Registrable Securities, as the case may be, to the extent of, for each such Damages Payment Date, accrued and unpaid Liquidated Damages Amount to (but excluding) such Damages Payment Date (or, if the Damages Accrual Period shall have ended prior to such Damages Payment Date, the date of the end of the Damages Accrual Period); provided that any Liquidated Damages Amount accrued with respect to any Note or portion thereof called for redemption on a redemption date or converted into Underlying Common Stock on a conversion date prior to the Damages Payment Date, shall, in any such event, be paid instead to the Holder who submitted such Note or portion thereof for redemption or conversion on the applicable redemption date or conversion date, as the case may be, on such date (or promptly following the conversion date, in the case of conversion). The Liquidated Damages Amount shall accrue at a rate per annum equal to one-quarter of one percent (0.25%) for the first 90-day period from the Event Date, at a rate per annum equal to one-half of one percent (0.5%) for the next 90-day period and thereafter at a rate per annum equal to three-quarters of one percent (0.75%) of (i) the principal amount of such Notes or, without duplication, (ii) in the case of Notes that have been converted into Underlying Common Stock, the Applicable Conversion Price of such shares of Underlying Common Stock, as the case may be, in each case determined as of the Business Day immediately preceding the next Damages Payment Date. Notwithstanding the foregoing, no Liquidated Damages Amounts shall accrue as to any Registrable Security from and after the earlier of (x) the date such security is no longer a Registrable Security and (y) expiration of the Effectiveness Period. The rate of accrual of the Liquidated Damages Amount with respect to any period shall not exceed the rate provided for in this paragraph notwithstanding the occurrence of multiple concurrent Events. Following the cure of all Events requiring the payment by the Company of Liquidated Damages Amounts to the Holders of Registrable Securities pursuant to this Section, the accrual of Liquidated Damages Amounts shall cease (without in any way limiting the effect of any subsequent Event requiring the payment of Liquidated Damages Amount by the Company).

The Trustee shall be entitled, on behalf of Holders of Notes, to seek any available remedy for the enforcement of this Agreement, including for the payment of any Liquidated Damages Amount. Notwithstanding the foregoing, the parties agree that the sole damages payable for a violation of the terms of this Agreement with respect to which liquidated damages are expressly provided shall be such liquidated damages.

All of the Company’s obligations set forth in this Section 2(e) that are outstanding with respect to any Registrable Security at the time such security ceases to be a Registrable Security shall survive until such time as all such obligations with respect to such security have been satisfied in full (notwithstanding termination of this Agreement pursuant to Section 8(k)).

The parties hereto agree that the liquidated damages provided for in this Section 2(e) constitute a reasonable estimate of the damages that may be incurred by Holders of Registrable Securities by reason of the failure of the Shelf Registration Statement to be filed or declared effective or available for effecting resales of Registrable Securities in accordance with the provisions hereof.

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Section 3. *Registration Procedures.* In connection with the registration obligations of the Company under Section 2 hereof, the Company shall:

(a) Prepare and file with the SEC a Shelf Registration Statement or Shelf Registration Statements on Form S-1 or S-3 or any other appropriate form under the Securities Act available for the sale of the Registrable Securities by the Holders thereof in accordance with the intended method or methods of distribution thereof, and use its commercially reasonable best efforts to cause each such Shelf Registration Statement to become effective and remain effective as provided herein (subject to the provisions of Section 3(i)); provided that before filing any Shelf Registration Statement or Prospectus or any amendments or supplements thereto with the SEC, the Company shall furnish to the Initial Purchasers and counsel for the Holders and for the Initial Purchasers copies of all such documents proposed to be filed and use its commercially reasonable best efforts to reflect in each such document when so filed with the SEC such comments as such counsel reasonably shall propose within three (3) Business Days of the delivery of such copies to the Initial Purchasers and such counsel.

(b) Prepare and file with the SEC such amendments and post-effective amendments to each Shelf Registration Statement as may be necessary to keep such Shelf Registration Statement continuously effective until the expiration of the Effectiveness Period (subject to the provisions of Section 3(i)); cause the related Prospectus to be supplemented by any required Prospectus supplement, and as so supplemented to be filed pursuant to Rule 424 (or any similar provisions then in force) under the Securities Act; and use its commercially reasonable best efforts to comply with the provisions of the Securities Act applicable to it with respect to the disposition of all securities covered by such Shelf Registration Statement during the Effectiveness Period in accordance with the intended methods of disposition by the sellers thereof set forth in such Shelf Registration Statement as so amended or such Prospectus as so supplemented.

(c) As promptly as practicable give notice to the Notice Holders, the Initial Purchasers and counsel for the Holders and for the Initial Purchasers (i) when any Prospectus, Prospectus supplement, Shelf Registration Statement or post-effective amendment to a Shelf Registration Statement has been filed with the SEC and, with respect to a Shelf Registration Statement or any post-effective amendment, when the same has been declared effective, (ii) of any request, following the effectiveness of the Initial Shelf Registration Statement under the Securities Act, by the SEC or any other federal or state governmental authority for amendments or supplements to any Shelf Registration Statement or related Prospectus or for additional information, (iii) of the issuance by the SEC or any other federal or state governmental authority of any stop order suspending the effectiveness of any Shelf Registration Statement or the initiation or threatening of any proceedings for that purpose, (iv) of the receipt by the Company of any notification with respect to the suspension of the qualification or exemption from qualification of any of the Registrable Securities for sale in any jurisdiction or the initiation or threatening of any proceeding for such purpose and (v) of the determination by the Company that a post-effective amendment to a Shelf Registration Statement will be filed with the SEC, which notice may, at the discretion of the Company (or as required pursuant to Section 3(i)), state that it constitutes a Suspension Notice, in which event the provisions of Section 3(i) shall apply.

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(d) Use its commercially reasonable best efforts to prevent the issuance of, and, if issued, to obtain the withdrawal of any order suspending the effectiveness of a Shelf Registration Statement or the lifting of any suspension of the qualification (or exemption from qualification) of any of the Registrable Securities for sale in any jurisdiction in which they have been qualified for sale, in either case at the earliest possible moment, and provide prompt notice to each Notice Holder and the Initial Purchasers of the withdrawal of any such order.

(e) If requested by the Initial Purchasers or any Notice Holder, as promptly as practicable incorporate in a Prospectus supplement or post-effective amendment to a Shelf Registration Statement such information as the Initial Purchasers, such Notice Holder or counsel for the Holders and for the Initial Purchasers shall determine to be required to be included therein by applicable law or so that a Shelf Registration Statement or a Prospectus Supplement does not contain an untrue statement of a material fact or omit to state a material fact required to be stated therein or necessary to make the statements therein, in light of the circumstances under which they were made, not misleading, and make any required filings of such Prospectus supplement or such post-effective amendment; provided that the Company shall not be required to take any actions under this Section 3(e) that, in the opinion of counsel for the Company, are not required under applicable law or so that a Shelf Registration Statement or a Prospectus Supplement does not contain an untrue statement of a material fact or omit to state a material fact required to be stated therein or necessary to make the statements therein, in light of the circumstances under which they were made, not misleading.

(f) As promptly as practicable furnish, upon request, to each Notice Holder and counsel for the Holders, without charge, at least one (1) conformed copy of the Shelf Registration Statement and any amendment thereto, including financial statements but excluding schedules, all documents incorporated or deemed to be incorporated therein by reference and all exhibits (unless requested in writing to the Company by such Notice Holder or such counsel).

(g) During the Effectiveness Period, deliver to each Notice Holder in connection with any sale of Registrable Securities pursuant to a Shelf Registration Statement, without charge, as many copies of the Prospectus or Prospectuses relating to such Registrable Securities (including each preliminary prospectus) and any amendment or supplement thereto as such Notice Holder may reasonably request; and the Company hereby consents (except during such periods that a Suspension Notice is outstanding and has not been revoked) to the use of such Prospectus or each amendment or supplement thereto by each Notice Holder, in connection with any offering and sale of the Registrable Securities covered by such Prospectus or any amendment or supplement thereto in the manner set forth therein.

(h) Prior to any public offering of the Registrable Securities pursuant to the Shelf Registration Statement, use its commercially reasonable best efforts to register or qualify or cooperate with the Notice Holders in connection with the registration or qualification (or exemption from such registration or qualification) of such Registrable Securities for offer and sale under the securities or Blue Sky laws of such jurisdictions within the United States as any Notice Holder reasonably requests in writing (which request may be included in the Notice and Questionnaire); prior to any public offering of the Registrable Securities pursuant to the Shelf

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Registration Statement, use its commercially reasonable best efforts to keep each such registration or qualification (or exemption therefrom) effective during the Effectiveness Period in connection with such Notice Holder's offer and sale of Registrable Securities pursuant to such registration or qualification (or exemption therefrom) and do any and all other acts or things reasonably necessary or advisable to enable the disposition in such jurisdictions of such Registrable Securities in the manner set forth in the relevant Shelf Registration Statement and the related Prospectus; provided that the Company will not be required to (i) qualify as a foreign corporation or as a dealer in securities in any jurisdiction where it would not otherwise be required to qualify but for this Agreement or (ii) take any action that would subject it to general service of process in suits or to taxation in any such jurisdiction where it is not then so subject.

(i) Upon (A) the issuance by the SEC of a stop order suspending the effectiveness of the Shelf Registration Statement or the initiation of proceedings with respect to the Shelf Registration Statement under Section 8(d) or 8(e) of the Securities Act, (B) the occurrence of any event or the existence of any fact as a result of which any Shelf Registration Statement shall contain any untrue statement of a material fact or omit to state any material fact required to be stated therein or necessary to make the statements therein not misleading, or any Prospectus shall contain any untrue statement of a material fact or omit to state any material fact necessary in order to make the statements therein, in the light of the circumstances under which they were made, not misleading, or (C) the occurrence or existence of any pending corporate development (a "Material Event") that, in the reasonable discretion of the Company, makes it appropriate to suspend the availability of the Shelf Registration Statement and the related Prospectus, (i) in the case of clause (B) or (C) above, subject to the next sentence, as promptly as practicable, prepare and file, if necessary pursuant to applicable law, a post-effective amendment to such Shelf Registration Statement or a supplement to the related Prospectus or any document incorporated therein by reference or file any other required document that would be incorporated by

reference into such Shelf Registration Statement and Prospectus so that such Shelf Registration Statement does not contain any untrue statement of a material fact or omit to state any material fact required to be stated therein or necessary to make the statements therein not misleading, and such Prospectus does not contain any untrue statement of a material fact or omit to state any material fact necessary in order to make the statements therein, in the light of the circumstances under which they were made, not misleading (it being understood that the Company may rely on information provided by each Notice Holder with respect to such Notice Holder), as thereafter delivered to the purchasers of the Registrable Securities being sold thereunder, and, in the case of a post-effective amendment to a Shelf Registration Statement, subject to the next sentence, use its commercially reasonable best efforts to cause it to be declared effective as promptly as is practicable, and (ii) give notice to the Notice Holders and counsel for the Holders and for the Initial Purchasers that the availability of the Shelf Registration Statement is suspended (a “Suspension Notice”) and, upon receipt of any Suspension Notice, each Notice Holder agrees not to sell any Registrable Securities pursuant to such Shelf Registration Statement until such Notice Holder’s receipt of copies of the supplemented or amended Prospectus provided for in clause (i) above, or until it is advised in writing by the Company that the Prospectus may be used, and has received copies of any additional or supplemental filings that are incorporated or deemed incorporated by reference in such Prospectus. The Company will use its commercially reasonable best efforts to ensure that the use of the Prospectus may be resumed (x) in the case of

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clause (A) above, as promptly as is practicable, (y) in the case of clause (B) above, as soon as, in the reasonable judgment of the Company, the Shelf Registration Statement does not contain any untrue statement of a material fact or omits to state any material fact required to be stated therein or necessary to make the statements therein not misleading and the Prospectus does not contain any untrue statement of a material fact or omits to state any material fact necessary in order to make the statements therein, in the light of the circumstances under which they were made, not misleading, and (z) in the case of clause (C) above, as soon as, in the reasonable discretion of the Company, such suspension is no longer appropriate. The period during which the availability of the Shelf Registration Statement and any Prospectus may be suspended (the “Suspension Period”) without the Company incurring any obligation to pay liquidated damages pursuant to Section 2(e) shall not exceed thirty (30) days in any three (3) month period and sixty (60) days in any twelve (12) month period.

(j) Make available for inspection during normal business hours by representatives for the Notice Holders of such Registrable Securities, and any broker-dealers, attorneys and accountants retained by such Notice Holders, all relevant financial and other records and pertinent corporate documents and properties of the Company and its subsidiaries, and cause the appropriate officers, directors and employees of the Company and its subsidiaries to make available for inspection during normal business hours all relevant information reasonably requested by such representatives for the Notice Holders, or any such broker-dealers, attorneys or accountants in connection with such disposition, in each case as is customary for similar “due diligence” examinations; provided, however, that such persons shall, at the Company’s request, first agree in writing with the Company that any information that is provided to such persons in the course of such due diligence examination shall be kept confidential by such persons and shall be used solely for the purposes of exercising rights under this Agreement, unless (i) disclosure of such information is required by court or administrative order or is necessary to respond to inquiries of regulatory authorities, (ii) disclosure of such information is required by law (including any disclosure requirements pursuant to federal securities laws in connection with the filing of any Shelf Registration Statement or the use of any Prospectus referred to in this Agreement), (iii) such information is or becomes generally available to the public other than as a result of a disclosure or failure to safeguard by any such person or (iv) such information becomes available to any such person from a source other than the Company and such source is not bound by a confidentiality agreement or is not otherwise under a duty of trust to the Company, and provided that the foregoing inspection and information gathering shall be coordinated on behalf of all the Notice Holders and the other parties entitled thereto by the counsel referred to in Section 5.

(k) Comply with all applicable rules and regulations of the SEC as they relate to the registration or qualification of the Registrable Securities.

(l) Make generally available to its securityholders, and to furnish to the Initial Purchasers upon request, an earnings statement of the Company (which will satisfy the provisions of Section 11(a) of the Securities Act) covering a period of twelve months beginning after the effective date of the Shelf Registration Statement (as defined in Rule 158(c) of the Securities Act) and ending not later than 15 months thereafter.

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(m) Cooperate with each Notice Holder to facilitate the timely preparation and delivery of certificates representing Registrable Securities sold pursuant to a Shelf Registration Statement, which certificates shall not bear any restrictive legends, and cause such Registrable Securities to be in such denominations as are permitted by the Indenture and registered in such names as such Notice Holder may request in writing at least (2) Business Days prior to any sale of such Registrable Securities.

(n) Provide a CUSIP number for all Registrable Securities covered by each Shelf Registration Statement not later than the effective date of such Shelf Registration Statement and provide the Trustee and the transfer agent for the Common Stock with certificates for the Registrable Securities that are in a form eligible for deposit with The Depository Trust Company.

(o) Cooperate and assist in any filings required to be made with the National Association of Securities Dealers, Inc.

(p) Upon (i) the filing of the Initial Registration Statement and (ii) the effectiveness of the Initial Registration Statement, announce the same, in each case by its customary press release practices.

(q) Enter into such customary agreements and take all such other necessary actions in connection therewith (including those requested by the holders of a majority of the Registrable Securities being sold) in order to expedite or facilitate disposition of such Registrable Securities.

(r) Cause the Indenture to be qualified under the TIA not later than the effective date of any Shelf Registration Statement; and in connection therewith, cooperate with the Trustee to effect such changes to the Indenture as may be required for the Indenture to be so qualified in accordance with the



terms of the TIA and execute, and use its commercially reasonable best efforts to cause the Trustee to execute, all documents as may be required to effect such changes, and all other forms and documents required to be filed with the SEC to enable the Indenture to be so qualified in a timely manner.

Section 4. *Holder's Obligations.* Each Holder agrees, by acquisition of the Registrable Securities, that no Holder of Registrable Securities shall be entitled to sell any of such Registrable Securities pursuant to a Shelf Registration Statement or to receive a Prospectus relating thereto, unless such Holder has furnished the Company with a Notice and Questionnaire as required pursuant to Section 2(d) hereof (including the information required to be included in such Notice and Questionnaire) and the information set forth in the next sentence. Each Notice Holder agrees promptly to furnish to the Company all information required to be disclosed in order to make the information previously furnished to the Company by such Notice Holder not misleading and any other information regarding such Notice Holder and the distribution of such Registrable Securities as the Company may from time to time reasonably request. Any sale of any Registrable Securities by any Holder shall constitute a representation and warranty by such Holder that the information relating to such Holder and its plan of distribution is as set forth in the Prospectus delivered by such Holder in connection with such disposition, that such Prospectus does not as of the time of such sale contain any untrue statement of a material fact relating to or provided by such Holder or its plan of distribution and that such Prospectus does not as of the time of such sale omit to state any material fact

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relating to or provided by such Holder or its plan of distribution necessary in order to make the statements in such Prospectus, in the light of the circumstances under which they were made, not misleading.

Section 5. *Registration Expenses.* The Company shall bear all fees and expenses incurred in connection with the performance by the Company of its obligations under Section 2 and 3 of this Agreement whether or not any of the Shelf Registration Statements are declared effective. Such fees and expenses ("Registration Expenses") shall include, without limitation, (i) all registration and filing fees (including, without limitation, fees and expenses (x) with respect to filings required to be made with the National Association of Securities Dealers, Inc. and (y) of compliance with federal and state securities or Blue Sky laws (including, without limitation, reasonable fees and disbursements of counsel for the Holders in connection with Blue Sky qualifications of the Registrable Securities under the laws of such jurisdictions as the Notice Holders of a majority of the Registrable Securities being sold pursuant to a Shelf Registration Statement may designate), (ii) printing expenses (including, without limitation, expenses of printing certificates for Registrable Securities in a form eligible for deposit with The Depository Trust Company), (iii) duplication and mailing expenses relating to copies of any Shelf Registration Statement or Prospectus delivered to any Holders hereunder, (iv) fees and disbursements of counsel for the Company and the reasonable fees and disbursements of counsel for the Holders in connection with the Shelf Registration Statement, (v) fees and disbursements of the Trustee and its counsel and of the registrar and transfer agent for the Common Stock and (vi) Securities Act liability insurance obtained by the Company in its sole discretion. In addition, the Company shall pay the internal expenses of the Company (including, without limitation, all salaries and expenses of officers and employees performing legal or accounting duties), the expense of any annual audit, the fees and expenses incurred in connection with the listing by the Company of the Registrable Securities on any securities exchange on which similar securities of the Company are then listed and the fees and expenses of any person, including special experts, retained by the Company.

Section 6. *Indemnification; Contribution.*

(a) The Company agrees to indemnify, defend and hold harmless each Holder and each person who controls any Holder within the meaning of Section 15 of the Securities Act or Section 20 of the Exchange Act (each, a "Holder Indemnified Party"), from and against any loss, damage, expense, liability or claim (including the reasonable cost of investigation) which such Holder Indemnified Party may incur under the Securities Act, the Exchange Act or otherwise, insofar as such loss, damage, expense, liability or claim arises out of or is based upon any untrue statement or alleged untrue statement of a material fact contained in any Shelf Registration Statement or Prospectus or in any amendment or supplement thereto or in any preliminary prospectus, or arises out of or is based upon any omission or alleged omission to state a material fact required to be stated in any Shelf Registration Statement or in any amendment or supplement thereto or necessary to make the statements therein not misleading, or arises out of or is based upon any omission or alleged omission to state a material fact necessary in order to make the statements made in any Prospectus or in any amendment or supplement thereto or in

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any preliminary prospectus, in the light of the circumstances under which they were made, not misleading, except insofar as any such loss, damage, expense, liability or claim arises out of or is based upon any untrue statement or omission or alleged untrue statement or omission of a material fact contained in, or omitted from, and in conformity with information furnished in writing by or on behalf of any Holder to the Company expressly for use therein, including, without limitation, all information regarding such Holder and its affiliates included in the Notice and Questionnaire.

(b) Each Holder, severally and not jointly, agrees to indemnify, defend and hold harmless the Company, its directors and officers and any person who controls the Company within the meaning of Section 15 of the Securities Act or Section 20 of the Exchange Act (each, a "Company Indemnified Party") from and against any loss, damage, expense, liability or claim (including the reasonable cost of investigation) which such Company Indemnified Party may incur under the Securities Act, the Exchange Act or otherwise, insofar as such loss, damage, expense, liability or claim arises out of or is based upon any untrue statement or alleged untrue statement of a material fact contained in information furnished in writing by or on behalf of such Holder to the Company expressly for use in any Shelf Registration Statement or Prospectus or in any amendment or supplement thereto or in any preliminary prospectus, including, without limitation, all information regarding such Holders and its affiliates included in the Notice and Questionnaire, or arises out of or is based upon any omission or alleged omission to state a material fact required to be stated in any Shelf Registration Statement or in any amendment or supplement thereto or necessary to make the statements therein not misleading, or arises out of or is based upon any omission or alleged omission to state a material fact necessary in order to make the statements in any Prospectus or in any amendment or supplement thereto or in any preliminary prospectus, in the light of the circumstances under which they were made, not misleading, in connection with such information. In no event shall the liability of any selling Holder of Registrable Securities

hereunder be greater in amount than the dollar amount of the proceeds received by such Holder upon the sale of the Registrable Securities pursuant to the Shelf Registration Statement giving rise to such indemnification obligation.

(c) If any action, suit or proceeding (each, a “Proceeding”) is brought against any person in respect of which indemnity may be sought pursuant to either subsection (a) or (b) of this Section 6, such person (the “Indemnified Party”) shall promptly notify the person against whom such indemnity may be sought (the “Indemnifying Party”) in writing of the institution of such Proceeding and the Indemnifying Party shall assume the defense of such Proceeding; provided, however, that the omission to notify such Indemnifying Party shall not relieve such Indemnifying Party from any liability which it may have to such Indemnified Party or otherwise. Such Indemnified Party shall have the right to employ its own counsel in any such case, but the fees and expenses of such counsel shall be at the expense of such Indemnified Party unless the employment of such counsel shall have been authorized in writing by such Indemnifying Party in connection with the defense of such Proceeding or such Indemnifying Party shall not have employed counsel to have charge of the defense of such Proceeding within 30 days of the receipt of notice thereof or such Indemnified Party shall have reasonably concluded upon the written advice of counsel that there may be one or more defenses available to it that are different from, additional to or in conflict with those available to such Indemnifying Party (in which case such

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Indemnifying Party shall not have the right to direct that portion of the defense of such Proceeding on behalf of the Indemnified Party, but such Indemnifying Party may employ counsel and participate in the defense thereof but the fees and expenses of such counsel shall be at the expense of such Indemnifying Party), in any of which events such reasonable fees and expenses shall be borne by such Indemnifying Party and paid as incurred (it being understood, however, that such Indemnifying Party shall not be liable for the expenses of more than one separate counsel in any one Proceeding or series of related Proceedings together with reasonably necessary local counsel representing the Indemnified Parties who are parties to such action). An Indemnifying Party shall not be liable for any settlement of such Proceeding effected without the written consent of such Indemnifying Party, but if settled with the written consent of such Indemnifying Party, such Indemnifying Party agrees to indemnify and hold harmless an Indemnified Party from and against any loss or liability by reason of such settlement. Notwithstanding the foregoing sentence, if at any time an Indemnified Party shall have requested an Indemnifying Party to reimburse such Indemnified Party for fees and expenses of counsel as contemplated by the second sentence of this paragraph, then such Indemnifying Party agrees that it shall be liable for any settlement of any Proceeding effected without its written consent if (i) such settlement is entered into more than 60 Business Days after receipt by such Indemnifying Party of the aforesaid request, (ii) such Indemnifying Party shall not have reimbursed such Indemnified Party in accordance with such request prior to the date of such settlement and (iii) such Indemnified Party shall have given such Indemnifying Party at least 30 days’ prior notice of its intention to settle. No Indemnifying Party shall, without the prior written consent of any Indemnified Party, effect any settlement of any pending or threatened Proceeding in respect of which such Indemnified Party is or could have been a party and indemnity could have been sought hereunder by such Indemnified Party, unless such settlement includes an unconditional release of such Indemnified Party from all liability on claims that are the subject matter of such Proceeding and does not include an admission of fault, culpability or a failure to act, by or on behalf of such Indemnified Party.

(d) If the indemnification provided for in this Section 6 is unavailable to an Indemnified Party under subsections (a) and (b) of this Section 6 in respect of any losses, damages, expenses, liabilities or claims referred to therein, then each applicable Indemnifying Party, in lieu of indemnifying such Indemnified Party, shall contribute to the amount paid or payable by such Indemnified Party as a result of such losses, damages, expenses, liabilities or claims (i) in such proportion as is appropriate to reflect the relative benefits received by the Company on the one hand and the Holders on the other hand from the offering of the Registrable Securities or (ii) if the allocation provided by clause (i) above is not permitted by applicable law, in such proportion as is appropriate to reflect not only the relative benefits referred to in clause (i) above but also the relative fault of the Company on the one hand and of the Holders on the other in connection with the statements or omissions which resulted in such losses, damages, expenses, liabilities or claims, as well as any other relevant equitable considerations. The relative fault of the Company on the one hand and of the Holders on the other shall be determined by reference to, among other things, whether the untrue statement or alleged untrue statement of a material fact or omission or alleged omission relates to information supplied by the Company or by the Holders and the parties’ relative intent, knowledge, access to information and opportunity to correct or prevent such statement or omission. The amount paid or payable

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by a party as a result of the losses, damages, expenses, liabilities and claims referred to above shall be deemed to include any reasonable legal or other fees or expenses reasonably incurred by such party in connection with investigating or defending any Proceeding.

(e) The Company and the Holders agree that it would not be just and equitable if contribution pursuant to this Section 6 were determined by pro rata allocation or by any other method of allocation which does not take account of the equitable considerations referred to in subsection (d) above. Notwithstanding the provisions of this Section 6, no Holder shall be required to contribute any amount in excess of the amount by which the total price at which the Registrable Securities sold by it were offered to the public exceeds the amount of any damages which it has otherwise been required to pay by reason of such untrue or alleged untrue statement or omission or alleged omission. No person guilty of fraudulent misrepresentation (within the meaning of Section 11(f) of the Securities Act) shall be entitled to contribution from any person who was not guilty of such fraudulent misrepresentation. The Holders’ respective obligations to contribute pursuant to this Section 6 are several in proportion to the respective amount of Registrable Securities they have sold pursuant to a Shelf Registration Statement, and not joint. The remedies provided for in this Section 6 are not exclusive and shall not limit any rights or remedies which may otherwise be available to any indemnified party at law or in equity.

(f) The indemnity and contribution provisions contained in this Section 6 shall remain operative and in full force and effect regardless of (i) any termination of this Agreement, (ii) any investigation made by or on behalf of any Holder or any person controlling any Holder, or the Company, or the Company’s officers or directors or any person controlling the Company and (iii) the sale of any Registrable Security by any Holder.

Section 7. *Information Requirements.* (a) The Company covenants that, if at any time before the end of the Effectiveness Period it is not subject to the reporting requirements of the Exchange Act, it will cooperate with any Holder of Registrable Securities and take such further action as any Holder of Registrable Securities may reasonably request in writing (including, without limitation, making such representations as any such Holder may reasonably request in order to facilitate sales by such Holder pursuant to Rule 144), all to the extent required from time to time to enable such Holder to sell Registrable Securities without registration under the Securities Act within the limitation of the exemptions provided by Rule 144, Rule 144A, Regulation S and Regulation D under the Securities Act and customarily taken in connection with sales pursuant to such exemptions. Upon the written request of any Holder of Registrable Securities, the Company shall deliver to such Holder a written statement as to whether it has complied with such filing requirements, unless such a statement has been included in the Company's most recent report filed with the SEC pursuant to Section 13 or Section 15(d) of Exchange Act. Notwithstanding the foregoing, nothing in this Section 7 shall be deemed to require the Company to register any of its securities (other than the Common Stock) under any section of the Exchange Act.

(b) The Company shall file the reports required to be filed by it under the Exchange Act in order to allow the Company to be eligible to file registration statements on Form S-1

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or Form S-3 and shall comply with all other requirements set forth in the instructions to Form S-1 or Form S-3, as the case may be, in order to allow the Company to be eligible to file registration statements on Form S-1 or Form S-3.

Section 8. *Miscellaneous.*

(a) *No Conflicting Agreements.* The Company is not, as of the date hereof, a party to, nor shall it, on or after the date of this Agreement, enter into, any agreement with respect to its securities that conflicts with the rights granted to the Holders of Registrable Securities in this Agreement. The Company represents and warrants that the rights granted to the Holders of Registrable Securities hereunder do not in any way conflict with the rights granted to the holders of the Company's securities under any other agreements.

(b) *Amendments and Waivers.* The provisions of this Agreement, including the provisions of this sentence, may not be amended, modified or supplemented, and waivers or consents to departures from the provisions hereof may not be given, unless the Company has obtained the written consent of Holders of a majority of the then outstanding Underlying Common Stock constituting Registrable Securities (with Holders of Notes deemed to be the Holders, for purposes of this Section, of the number of outstanding shares of Underlying Common Stock into which such Notes are or would be convertible as of the date on which such consent is requested). Notwithstanding the foregoing, a waiver or consent to depart from the provisions hereof with respect to a matter that relates exclusively to the rights of Holders of Registrable Securities whose securities are being sold pursuant to a Shelf Registration Statement and that does not directly or indirectly affect the rights of other Holders of Registrable Securities may be given by Holders of at least a majority of the Registrable Securities being sold by such Holders pursuant to such Shelf Registration Statement; provided that the provisions of this sentence may not be amended, modified, or supplemented except in accordance with the provisions of the immediately preceding sentence. Each Holder of Registrable Securities outstanding at the time of any such amendment, modification, supplement, waiver or consent or thereafter shall be bound by any such amendment, modification, supplement, waiver or consent effected pursuant to this Section 8(b), whether or not any notice, writing or marking indicating such amendment, modification, supplement, waiver or consent appears on the Registrable Securities or is delivered to such Holder.

(c) *Notices.* All notices and other communications provided for or permitted hereunder shall be made in writing by hand delivery, by telecopier, by courier guaranteeing overnight delivery or by first-class mail, return receipt requested, and shall be deemed given (i) when made, if made by hand delivery, (ii) upon confirmation, if made by telecopier, (iii) one (1) Business Day after being deposited with such courier, if made by overnight courier or (iv) on the date indicated on the notice of receipt, if made by first-class mail, return receipt requested, to the parties as follows:

- (x) if to a Holder of Registrable Securities, at the most current address given by such Holder to the Company in a Notice and Questionnaire or any amendment thereto;
- (y) if to the Company, to:

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Isis Pharmaceuticals, Inc.  
2292 Faraday Avenue  
Carlsbad, California 92008  
Attention: B. Lynne Parshall  
Telecopy No.: (760) 603-3861

with a copy to (for informational purposes only):

Cooley Godward LLP  
4401 Eastgate Mall  
San Diego, California 92121  
Attention: Julie M. Robinson  
Telecopy No.: (858) 550-6420

(z) if to the Initial Purchasers, to:

c/o UBS Warburg LLC  
299 Park Avenue  
New York, New York 10171  
Attention: Syndicate Department  
Telecopy No.: (212) 713-1205

with a copy to (for informational purposes only):

c/o UBS Warburg LLC  
299 Park Avenue  
New York, New York 10171  
Attention: Legal Department  
Telecopy No.: (212) 821-4042

UBS Warburg LLC  
677 Washington Boulevard  
Stamford, Connecticut 06901  
Attention: Legal Department  
Telecopy No.: (203) 719-0680

or to such other address as such person may have furnished to the other persons identified in this Section 8(c) in writing in accordance herewith.

(d) *Approval of Holders.* Whenever the consent or approval of Holders of a specified percentage of Registrable Securities is required hereunder, Registrable Securities held by the Company or its affiliates (as such term is defined in Rule 405 under the Securities Act) (other than the Initial Purchasers or subsequent Holders of Registrable Securities if such subsequent Holders are deemed to be such affiliates solely by reason of their holdings of such Registrable

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Securities) shall not be counted in determining whether such consent or approval was given by the Holders of such required percentage.

(e) *Successors and Assigns.* Any person who purchases any Registrable Securities from the Initial Purchasers or any Holder shall be deemed, for purposes of this Agreement, to be an assignee of the Initial Purchasers or such Holder, as the case may be. This Agreement shall inure to the benefit of and be binding upon the successors and assigns of each of the parties and shall inure to the benefit of and be binding upon each Holder of any Registrable Securities.

(f) *Counterparts.* This Agreement may be executed in any number of counterparts and by the parties hereto in separate counterparts, each of which when so executed shall be deemed to be original and all of which taken together shall constitute one and the same agreement.

(g) *Headings.* The headings in this Agreement are for convenience of reference only and shall not limit or otherwise affect the meaning hereof.

(h) *Governing Law.* THIS AGREEMENT SHALL BE GOVERNED BY, AND CONSTRUED IN ACCORDANCE WITH, THE LAWS OF THE STATE OF NEW YORK, WITHOUT REGARD TO CONFLICTS OF LAWS PRINCIPLES THEREOF.

(i) *Severability.* If any term, provision, covenant or restriction of this Agreement is held to be invalid, illegal, void or unenforceable, the remainder of the terms, provisions, covenants and restrictions set forth herein shall remain in full force and effect and shall in no way be affected, impaired or invalidated thereby, and the parties hereto shall use their commercially reasonable best efforts to find and employ an alternative means to achieve the same or substantially the same result as that contemplated by such term, provision, covenant or restriction, it being intended that all of the rights and privileges of the parties shall be enforceable to the fullest extent permitted by law.

(j) *Entire Agreement.* This Agreement is intended by the parties as a final expression of their agreement and is intended to be a complete and exclusive statement of the agreement and understanding of the parties hereto in respect of the subject matter contained herein and the registration rights granted by the Company with respect to the Registrable Securities. Except as provided in the Purchase Agreement, there are no restrictions, promises, warranties or undertakings, other than those set forth or referred to herein, with respect to the registration rights granted by the Company with respect to the Registrable Securities. This Agreement supersedes all prior agreements and undertakings among the parties with respect to such registration rights. No party hereto shall have any rights, duties or obligations other than those specifically set forth in this Agreement.

(k) *Termination.* This Agreement and the obligations of the parties hereunder shall terminate upon the end of the Effectiveness Period, except for any liabilities or obligations under Section 4, 5 or 6 hereof and the obligations to make payments of and provide for liquidated damages under Section 2(e) hereof to the extent such damages accrue prior to the end of the Effectiveness Period, each of which shall remain in effect in accordance with its terms.

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(l) *Submission to Jurisdiction.* Except as set forth below, no Proceeding may be commenced, prosecuted or continued in any court other than the courts of the State of New York located in the City and County of New York or in the United States District Court for the Southern District of New York, which

courts shall have jurisdiction over the adjudication of such matters, and the Company hereby consents to the jurisdiction of such courts and personal service with respect thereto. The Company hereby consents to personal jurisdiction, service and venue in any court in which any Proceeding arising out of or in any way relating to this Agreement is brought by any third party against the Initial Purchasers. Each of the Company, the Initial Purchasers and the Holders hereby waives all right to trial by jury in any Proceeding (whether based upon contract, tort or otherwise) in any way arising out of or relating to this Agreement. The Company agrees that a final judgment in any such Proceeding brought in any such court shall be conclusive and binding upon the Company and may be enforced in any other courts in the jurisdiction of which the Company is or may be subject, by suit upon such judgment.

(m) *Counsel for the Holders.* Counsel for the Holders shall be chosen by holders of a majority in interest of the outstanding Registrable Securities, determined by reference to the aggregate principal amount of outstanding Notes and considering for these purposes Underlying Common Stock to be equivalent to the aggregate principal amount of Notes converted in order to result in the issuance of such Underlying Common Stock. Once so chosen, such counsel shall act as counsel for the Holders until such counsel is unable or unwilling to continue to so act. The Company shall have no obligation with respect to providing notice or documents to counsel for the Holders pursuant to Section 3 hereof until such time as the Company has been furnished with the contact information for such counsel.

IN WITNESS WHEREOF, the parties have executed this Agreement as of the date first written above.

ISIS PHARMACEUTICALS, INC.

By: /s/ B. Lynne Parshall  
Name:  
Title:

Confirmed and accepted as of the date  
first above written on behalf of itself  
and the other several Initial Purchasers:

UBS WARBURG LLC  
ROBERTSON STEPHENS, INC.  
NEEDHAM & COMPANY, INC.  
ROTH CAPITAL PARTNERS, LLC

By: UBS WARBURG LLC

By: /s/ Steve Meehan  
Name: Steve Meehan  
Title: Managing Director

By: /s/ S. Kelly  
Name: S. Kelly  
Title: Director

## ISIS PHARMACEUTICALS, INC.

and

## WELLS FARGO BANK MINNESOTA, NATIONAL ASSOCIATION

as Trustee

## INDENTURE

Dated as of May 1, 2002

\$125,000,000 Principal Amount

(Plus Over-allotment Option)

5 ½% CONVERTIBLE SUBORDINATED NOTES DUE 2009

## CROSS-REFERENCE TABLE

TIA Section	Indenture Section
310(a)(1)	7.10
(a)(2)	7.10
(a)(3)	N.A.
(a)(4)	N.A.
(b)	7.08; 7.10; 12.02
(c)	N.A.
311(a)	7.11
(b)	7.11
(c)	N.A.
312(a)	2.05
(b)	12.03
(c)	12.03
313(a)	7.06
(b)(1)	N.A.
(b)(2)	7.06
(c)	7.06; 12.02
(d)	7.06
314(a)	4.03
(b)	N.A.
(c)(1)	12.04
(c)(2)	12.04
(c)(3)	N.A.
(d)	N.A.
(e)	12.05
(f)	N.A.
315(a)	7.01(B)
(b)	7.05; 12.02
(c)	7.01(A)
(d)	7.01(C)
(e)	6.11

316 (a)(last sentence)	2.09
(a)(1)(A)	6.05
(a)(1)(B)	6.04
(a)(2)	N.A.
(b)	6.07
317 (a)(1)	6.08
(a)(2)	6.09
(b)	2.04
318 (a)	12.01

N.A. means Not Applicable

Note: This Cross-Reference Table shall not, for any purpose, be deemed to be a part of the Indenture

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**INDENTURE**, dated as of May 1, 2002 between **ISIS PHARMACEUTICALS, INC.**, a Delaware corporation (the “**Company**”), and **WELLS FARGO BANK MINNESOTA, NATIONAL ASSOCIATION**, as trustee (the “**Trustee**”).

Each party agrees as follows for the benefit of the other parties and for the equal and ratable benefit of the Holders of the Company’s 5 ½% Convertible Subordinated Notes due 2009 (the “**Securities**”).

### **I. DEFINITIONS AND INCORPORATION BY REFERENCE**

#### **1.01 DEFINITIONS.**

“**Affiliate**” means any person directly or indirectly controlling or controlled by or under direct or indirect common control with the Company. For this purpose, “control” shall mean the power to direct the management and policies of a person through the ownership of securities, by contract or otherwise.

“**Agent**” means any Registrar, Paying Agent, Conversion Agent or co-registrar.

“**Board of Directors**” means the board of directors of the Company or any committee thereof authorized to act for it hereunder.

“**Board Resolution**” means a copy of a resolution certified by the Secretary or an Assistant Secretary of the Company to have been duly adopted by its Board of Directors and to be in full force and effect on the date of such certification, and delivered to the Trustee.

“**Capital Stock**” means any and all shares, interests, participations or other equivalents (however designated) of capital stock of the Company and all warrants or options to acquire such capital stock.

“**Common Stock**” means the common stock, par value \$0.001 per share, of the Company.

“**Company**” means the party named as such above until a successor replaces it pursuant to the applicable provision hereof and thereafter means the successor.

“**Company Request**” or “**Company Order**” means a written request or order signed on behalf of the Company by its chairman of the board, its president, any vice president, its treasurer or an assistant treasurer, its chief financial officer, its chief legal officer, its chief executive officer, its comptroller, its secretary or an assistant secretary, and delivered to the Trustee.

“**conversion price**” means, at a given point in time, a fraction which numerator is one thousand (1,000) and which denominator is the conversion rate, in effect at such time, as provided herein.

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“**Corporate Trust Office of the Trustee**” shall be at the address of the Trustee specified in **Section 12.02** or such other address as the Trustee may give notice of to the Company.

“**Daily Market Price**” means the price of a share of Common Stock on the relevant date, determined (a) on the basis of the last reported sale price regular way of the Common Stock as reported on the Nasdaq National Market (the “**NNM**”), or if the Common Stock is not then listed on the NNM, as reported on such national securities exchange upon which the Common Stock is listed, or (b) if there is no such reported sale on the day in question, on the basis of the average of the closing bid and asked quotations regular way as so reported, or (c) if the Common Stock is not listed on the NNM or on any national securities exchange or automated quotation system, on the basis of the average of the high bid and low asked quotations regular way on the day in question in the over-the-counter market as reported by the National Association of Securities Dealers Automated Quotation System, or if not so quoted, as reported by National Quotation Bureau, Incorporated, or a similar organization.

“**Default**” means any event which is, or after notice or passage of time or both would be, an Event of Default.

“**Depository**” means The Depository Trust Company, its nominees and successors.

“**Exchange Act**” means the Securities Exchange Act of 1934, as amended.

“**Holder**” or “**Securityholder**” means a person in whose name a Security is registered on the Registrar’s books.

“**Indenture**” means this Indenture as amended, amended and restated, modified or supplemented from time to time.

“**Initial Purchasers**” means UBS Warburg LLC, Robertson Stephens, Inc., Needham & Company, Inc. and Roth Capital Partners, LLC.

“**interest**” includes liquidated damages, unless the context otherwise requires.

“**liquidated damages**” has the meaning provided in the Registration Rights Agreement.

“**Maturity Date**” means May 1, 2009.

“**Non-U.S. Person**” means a person who is not a U.S. person (as defined in Regulation S pursuant to the Securities Act).

“**Officer**” means the chairman of the board, the president, any vice president, the treasurer, the chief financial officer, the chief legal officer, the chief executive officer or the secretary of the Company.

“**Officers’ Certificate**” means a certificate signed by two Officers or by an Officer and an Assistant Treasurer or an Assistant Secretary of the Company and delivered to the Trustee.

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“**Opinion of Counsel**” means a written opinion from legal counsel who may be an employee of or counsel for the Company, or other counsel reasonably acceptable to the Trustee.

“**person**” means any individual, corporation, partnership, limited liability company, joint venture, association, joint-stock company, trust, unincorporated organization or government or other agency or political subdivision thereof.

“**Physical Securities**” means permanent certificated Securities in registered form in substantially the form set forth in **Exhibit A** which, if applicable, bears any legends required by **Section 2.17**.

“**Purchase Agreement**” means the Purchase Agreement dated as of April 26, 2002 between the Company and the Initial Purchasers.

“**QIB**” means a “qualified institutional buyer” within the meaning of Rule 144A under the Securities Act.

“**Redemption Price**” means, with respect to a Security to be redeemed by the Company in accordance with **Section 3.01**, the percentage of the outstanding principal amount of such Security payable by the Company upon such redemption.

“**Registration Rights Agreement**” means the Registration Rights Agreement dated as of May 1, 2002 between the Company and the Initial Purchasers.

“**Regulation S**” means Regulation S under the Securities Act.

“**Repurchase Price**” means, with respect to a Security duly tendered for purchase by the Company in accordance with **Section 3.08**, 100% of the outstanding principal amount of such Security so tendered.

“**Restricted Security**” means a Security required to bear the restrictive legend in the form set forth in **Exhibit B-1** and **Exhibit B-2** of this Indenture that constitutes a “restricted security” within the meaning of Rule 144(a)(3) under the Securities Act; *provided, however*, that the Trustee shall be entitled to request and conclusively rely on an Opinion of Counsel with respect to whether any Security constitutes a Restricted Security.

“**Rule 144A**” means Rule 144A under the Securities Act.

“**Rule 144A Global Security**” means a permanent Global Security in the form of the Security attached hereto as Exhibit A and that is deposited with the Depository and registered in the name of the Depository representing the aggregate principal amount of Securities sold in reliance on Rule 144A.

“**SEC**” means the Securities and Exchange Commission.

“**Securities**” means the 5 ½% Convertible Subordinated Notes due 2009 or any of them (each, a “Security”) issued by the Company pursuant to this Indenture, as amended or supplemented from time to time.

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“**Securities Act**” means the Securities Act of 1933, as amended.

“**Securityholder**” has the meaning given to such term in the Registration Rights Agreement.

“**subsidiary**” means (i) a corporation a majority of whose capital stock with voting power, under ordinary circumstances, to elect directors is at the time owned by the Company, one or more of its subsidiaries or the Company and one or more of its subsidiaries, directly or indirectly, or (ii) any other person (other than a corporation) in which the Company, one or more of its subsidiaries or the Company and one or more its subsidiaries, directly or indirectly, at the date of determination thereof, have at least majority ownership interest.

“**tender offer**” means both tender offers and exchange offers, all references to “purchases” of shares in tender offers (and all similar references) mean both the purchase of shares in tender offers and the acquisition of shares pursuant to exchange offers and all references to “tendered shares” (and all similar references) mean shares tendered in both tender offers and exchange offers.

“**TIA**” means the Trust Indenture Act of 1939 (15 U.S. Code §§ 77aaa-77bbb) as in effect on the date of this Indenture, except as provided in **Section 9.03**.

“**Trustee**” means the party named as such in this Indenture until a successor replaces it in accordance with the provisions hereof and thereafter means the successor.

“**Trust Officer**” means any officer of the Trustee assigned by the Trustee to administer its corporate trust matters.

## 1.02 OTHER DEFINITIONS.

Term	Defined in Section
“ <b>Additional Securities</b> ”	2.01
“ <b>Bankruptcy Law</b> ”	6.01
“ <b>business day</b> ”	12.07
“ <b>Change in Control</b> ”	3.08
“ <b>Change in Control Notice</b> ”	3.08
“ <b>Combined Amount</b> ”	10.06
“ <b>Commencement Date</b> ”	10.06
“ <b>Conversion Agent</b> ”	2.03
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“ <b>Custodian</b> ”	6.01
“ <b>Determination Date</b> ”	10.06
“ <b>Distribution Declaration Date</b> ”	10.06
“ <b>Event of Default</b> ”	6.01
“ <b>Expiration Date</b> ”	10.06
“ <b>Expiration Time</b> ”	10.06
“ <b>Global Security</b> ”	2.01
“ <b>Incumbent Board</b> ”	3.08

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“Indebtedness”	11.02
“Legal Holiday”	12.07
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“NNM”	1.01
“Notice Date”	3.01
“Participants”	2.15
“Paying Agent”	2.03
“Payment Blockage”	11.04
“Payment Blockage Notice”	11.04
“Private Placement Legend”	2.17
“Provisional Redemption”	3.01
“Provisional Redemption Date”	3.01
“Provisional Redemption Price”	3.01
“Purchased Shares”	10.06
“Registrar”	2.03
“Representative”	11.02
“Repurchase Date”	3.08
“Repurchase Right”	3.08
“Senior Indebtedness”	11.02
“Triggering Distribution”	10.06
“U.S. Government Obligations”	8.01

### 1.03 INCORPORATION BY REFERENCE OF TRUST INDENTURE ACT.

Whenever this Indenture refers to a provision of the TIA, the provision is incorporated by reference in and made a part of this Indenture.

The following TIA terms used in this Indenture have the following meanings:

- “Commission” means the SEC;
- “indenture securities” means the Securities;
- “indenture security holder” means a Securityholder or a Holder;
- “indenture to be qualified” means this Indenture;
- “indenture trustee” or “institutional trustee” means the Trustee; and
- “obligor” on the indenture securities means the Company or any successor.

All other terms used in this Indenture that are defined by the TIA, defined by TIA reference to another statute or defined by SEC rule under the TIA and not otherwise defined herein have the meanings so assigned to them.

### 1.04 RULES OF CONSTRUCTION.

Unless the context otherwise requires:

- (i) a term has the meaning assigned to it;

- (ii) an accounting term not otherwise defined has the meaning assigned to it in accordance with generally accepted accounting principles in effect on the date hereof;

- (iii) “or” is not exclusive;

- (iv) words in the singular include the plural and in the plural include the singular;

- (v) provisions apply to successive events and transactions; and

- (vi) “herein,” “hereof” and other words of similar import refer to this Indenture as a whole and not to any particular Article, Section or other subdivision.

## II. THE SECURITIES

### 2.01 FORM AND DATING.

The Securities and the Trustee’s certificate of authentication shall be substantially in the form set forth in **Exhibit A**, which is incorporated in and forms a part of this Indenture. The Securities may have notations, legends or endorsements required by law, stock exchange rule or usage. Each Security shall be dated the date of its authentication.

The Securities are being offered and sold in reliance on Regulation S under the Securities Act or to QIBs in reliance on Rule 144A under the Securities Act and shall be issued initially in the form of one or more Global Securities, substantially in the form set forth in **Exhibit A** (the “**Global Security**”), deposited with the Trustee, as custodian for the Depositary, duly executed by the Company and authenticated by the Trustee as hereinafter provided and bearing the legends set forth in **Exhibits B-1** and **B-2**. The aggregate principal amount of the Global Security may from time to time be increased or decreased by adjustments made on the records of the Trustee, as custodian for the Depositary, as hereinafter provided; *provided*, that in no event shall the aggregate principal

amount of the Global Security or Securities exceed \$125,000,000, or \$143,750,000 if the Initial Purchasers elect to purchase Additional Securities pursuant to the over-allotment option provided for in **Section 1** of the Purchase Agreement (“**Additional Securities**”).

All Notes offered and sold in reliance on Regulation S shall remain in the form of a Global Security for at least one year after the issue date of the Securities.

## 2.02 EXECUTION AND AUTHENTICATION.

One Officer shall sign the Securities for the Company by manual or facsimile signature.

If an Officer whose signature is on a Security no longer holds that office at the time the Security is authenticated, the Security shall nevertheless be valid.

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A Security shall not be valid until authenticated by the manual signature of the Trustee. The signature shall be conclusive evidence that the Security has been authenticated under this Indenture.

Upon a written order of the Company signed by one Officer of the Company, the Trustee shall authenticate Securities for original issue in the principal amount of \$125,000,000 and such additional principal amount, if any, as shall be determined pursuant to the next sentence of this **Section 2.02**. Upon receipt by the Trustee of an Officers’ Certificate stating that the Initial Purchasers have elected to purchase from the Company a specified principal amount of Additional Securities, not to exceed \$18,750,000, pursuant to **Section I** of the Purchase Agreement, the Trustee shall authenticate and deliver such specified principal amount of Additional Securities to or upon the written order of the Company signed as provided in the immediately preceding sentence. Such Officers’ Certificate must be received by the Trustee not later than the proposed date for delivery of such Additional Securities. The aggregate principal amount of Securities outstanding at any time may not exceed \$143,750,000 except as provided in **Section 2.07**.

Upon a written order of the Company signed by two Officers or by an Officer and an Assistant Treasurer of the Company, the Trustee shall authenticate Securities not bearing the Private Placement Legend to be issued to the transferee when sold pursuant to an effective registration statement under the Securities Act as set forth in **Section 2.16(D)**

The Trustee may appoint an authenticating agent acceptable to the Company to authenticate Securities. An authenticating agent may authenticate Securities whenever the Trustee may do so. Each reference in this Indenture to authentication by the Trustee includes authentication by such Agent. An authenticating agent has the same rights as an Agent to deal with the Company and its Affiliates.

The Securities shall be issuable only in registered form without coupons and only in denominations of \$1,000 principal amount and any positive integral multiple thereof.

## 2.03 REGISTRAR, PAYING AGENT AND CONVERSION AGENT.

The Company shall maintain an office or agency where Securities may be presented for registration of transfer or for exchange (“**Registrar**”), an office or agency where Securities may be presented for payment (“**Paying Agent**”) and an office or agency where Securities may be presented for conversion (“**Conversion Agent**”). The Registrar shall keep a register of the Securities and of their transfer and exchange. The Company may appoint or change one or more co-registrars, one or more additional paying agents and one or more additional conversion agents without notice and may act in any such capacity on its own behalf. The term “Registrar” includes any co-registrar; the term “**Paying Agent**” includes any additional paying agent; and the term “**Conversion Agent**” includes any additional conversion agent.

The Company shall enter into an appropriate agency agreement with any Agent not a party to this Indenture. The agreement shall implement the provisions of this Indenture that relate to such Agent. The Company shall notify the Trustee of the name and address of any

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Agent not a party to this Indenture. If the Company fails to maintain a Registrar, Paying Agent or Conversion Agent, the Trustee shall act as such.

The Company initially appoints the Trustee as Paying Agent, Registrar and Conversion Agent.

## 2.04 PAYING AGENT TO HOLD MONEY IN TRUST.

Each Paying Agent shall hold in trust for the benefit of the Securityholders or the Trustee all moneys held by the Paying Agent for the payment of the Securities, and shall notify the Trustee of any default by the Company in making any such payment. While any such default continues, the Trustee may require a Paying Agent to pay all money held by it to the Trustee. The Company at any time may require a Paying Agent to pay all money held by it to the Trustee. Upon payment over to the Trustee, the Paying Agent shall have no further liability for the money. If the Company acts as Paying Agent, it shall segregate and hold as a separate trust fund all money held by it as Paying Agent.

## 2.05 SECURITYHOLDER LISTS.

The Trustee shall preserve in as current a form as is reasonably practicable the most recent list available to it of the names and addresses of Securityholders. If the Trustee is not the Registrar, the Company shall furnish to the Trustee on or before each interest payment date and at such other times as

the Trustee may request in writing a list, in such form and as of such date as the Trustee may reasonably require, of the names and addresses of Securityholders.

## 2.06 TRANSFER AND EXCHANGE.

Subject to **Sections 2.15** and **2.16** hereof, where Securities are presented to the Registrar with a request to register their transfer or to exchange them for an equal principal amount of Securities of other authorized denominations, the Registrar shall register the transfer or make the exchange if its requirements for such transaction are met. To permit registrations of transfer and exchanges, the Trustee shall authenticate Securities at the Registrar's request. The Company or the Trustee, as the case may be, shall not be required (a) to issue, authenticate, register the transfer of or exchange any Security during a period beginning at the opening of business 15 days before the mailing of a notice of redemption of the Securities selected for redemption under **Section 3.04** and ending at the close of business on the day of such mailing or (b) to register the transfer of or exchange any Security so selected for redemption in whole or in part, except the unredeemed portion of Securities being redeemed in part.

No service charge shall be made for any transfer, exchange or conversion of Securities, but the Company may require payment of a sum sufficient to cover any tax or other governmental charge that may be imposed in connection with any transfer, exchange or conversion of Securities, other than exchanges pursuant to **Sections 2.10, 3.07, 3.08, 9.05** or **10.02** not involving any transfer.

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## 2.07 REPLACEMENT SECURITIES.

If the Holder of a Security claims that the Security has been mutilated, lost, destroyed or wrongfully taken, the Company shall issue and the Trustee shall authenticate a replacement Security if the Trustee's requirements are met and, in the case of a mutilated Security, such mutilated Security is surrendered to the Trustee. In the case of lost, destroyed or wrongfully taken Securities, if required by the Trustee, an indemnity bond must be provided by the Holder that is sufficient in the judgment of the Trustee to protect the Company, the Trustee or any Agent from any loss which any of them may suffer if a Security is replaced. The Trustee may charge for its expenses in replacing a Security.

In case any such mutilated, lost, destroyed or wrongfully taken Security has become or is about to become due and payable, the Company in its discretion may, instead of issuing a new Security, pay such Security when due.

Every replacement Security is an additional obligation of the Company only as provided in **Section 2.08**.

The provisions of this **Section 2.07** are exclusive and shall preclude (to the extent lawful) all other rights and remedies with respect to the replacement or payment of mutilated, destroyed, lost or stolen Securities.

## 2.08 OUTSTANDING SECURITIES.

Securities outstanding at any time are all the Securities authenticated by the Trustee except for those converted, those cancelled by it, those delivered to it for cancellation and those described in this **Section 2.08** as not outstanding. A Security does not cease to be outstanding because the Company or one of its subsidiaries or Affiliates holds the Security.

If a Security is replaced pursuant to **Section 2.07**, it ceases to be outstanding unless the Trustee receives proof satisfactory to it, or a court holds, that the replaced Security is held by a protected purchaser.

If the Paying Agent (other than the Company) holds on a redemption date or Maturity Date money sufficient to pay Securities payable on that date, then on and after that date, such Securities shall be deemed to be no longer outstanding and interest on them shall cease to accrue. If a security is converted in accordance with **Article X**, then from and after the time of conversion, such Security shall cease to be outstanding and interest on such Security shall cease to accrue.

## 2.09 SECURITIES HELD BY THE COMPANY OR AN AFFILIATE.

In determining whether the Holders of the required aggregate principal amount of Securities have concurred in any direction, waiver or consent, Securities owned by the Company or any of its subsidiaries or an Affiliate shall be considered as though not outstanding, except that for the purposes of determining whether the Trustee shall be protected in relying on any such direction, waiver or consent, only Securities which the Trustee knows are so owned shall be so disregarded.

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## 2.10 TEMPORARY SECURITIES.

Until definitive Securities are ready for delivery, the Company may prepare and the Trustee shall authenticate upon Company Order temporary Securities. Temporary Securities shall be substantially in the form of definitive Securities but may have variations that the Company considers appropriate for temporary Securities. Without unreasonable delay, the Company shall prepare and the Trustee shall authenticate upon Company Order definitive Securities in exchange for temporary Securities.

## 2.11 CANCELLATION.

The Company at any time may deliver Securities to the Trustee for cancellation. The Registrar, Paying Agent and Conversion Agent shall forward to the Trustee any Securities surrendered to them for transfer, exchange, payment or conversion. The Trustee shall cancel all Securities surrendered for transfer, exchange, payment, conversion or cancellation and all cancelled Securities held by the Trustee shall be disposed of by the Trustee in accordance with the Trustee's customary procedure. The Company may not issue new Securities to replace Securities that it has paid or delivered to the Trustee for cancellation or that any Securityholder has converted pursuant to **Article X**.

#### 2.12 DEFAULTED INTEREST.

If and to the extent the Company defaults in a payment of interest on the Securities, the Company shall pay the defaulted interest in any lawful manner plus, to the extent not prohibited by applicable statute or case law, interest payable on the defaulted interest at the rate provided in the Securities. The Company may pay the defaulted interest to the persons who are Securityholders on a subsequent special record date. The Company shall fix such record date and payment date. At least 15 days before the record date, the Company shall mail to Securityholders a notice that states the record date, payment date and amount of interest to be paid.

#### 2.13 CUSIP NUMBERS.

The Company in issuing the Securities may use one or more "CUSIP" numbers, and if so, the Trustee shall use the CUSIP numbers in notices of redemption or exchange as a convenience to Holders; *provided, however*, that no representation is hereby deemed to be made by the Trustee as to the correctness or accuracy of the CUSIP numbers printed in the notice or on the Securities, and that reliance may be placed only on the other identification numbers printed on the Securities. The Company shall promptly notify the Trustee of any change in the CUSIP numbers.

#### 2.14 DEPOSIT OF MONEYS.

Prior to 11:00 A.M., New York City time, on each interest payment date, Maturity Date, redemption date and Repurchase Date, the Company shall have deposited with the Paying Agent in immediately available funds money or Common Stock or a combination thereof, if applicable, sufficient to make such payments, if any, due on such interest payment date, Maturity Date, redemption date and Repurchase Date, as the case may be, in a timely manner which permits the

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Paying Agent to remit payment to the Holders on such interest payment date, Maturity Date, redemption date and Repurchase Date, as the case may be.

#### 2.15 BOOK-ENTRY PROVISIONS FOR GLOBAL SECURITIES.

(A) The Global Securities initially shall (i) be registered in the name of the Depositary or the nominee of such Depositary, (ii) be delivered to the Trustee as custodian for such Depositary and (iii) bear legends as set forth in **Section 2.17**.

Members of, or participants in, the Depositary ("**Participants**") shall have no rights under this Indenture with respect to any Global Security held on their behalf by the Depositary, or the Trustee as its custodian, or under the Global Security, and the Depositary may be treated by the Company, the Trustee and any agent of the Company or the Trustee as the absolute owner of the Global Security for all purposes whatsoever. Notwithstanding the foregoing, nothing herein shall prevent the Company, the Trustee or any agent of the Company or the Trustee from giving effect to any written certification, proxy or other authorization furnished by the Depositary or impair, as between the Depositary and Participants, the operation of customary practices governing the exercise of the rights of a Holder of any Security.

(B) Transfers of Global Securities shall be limited to transfers in whole, but not in part, to the Depositary, its successors or their respective nominees. Physical Securities shall be transferred to all beneficial owners in exchange for their beneficial interests in Global Securities if (i) the Depositary notifies the Company that it is unwilling or unable to continue as Depositary for any Global Security and a successor Depositary is not appointed by the Company within 90 days of such notice or (ii) an Event of Default has occurred and is continuing and the Registrar has received a written request from the Depositary to issue Physical Securities.

(C) In connection with any transfer or exchange of a portion of the beneficial interest in a Global Security to beneficial owners pursuant to **Section 2.15(B)**, the Registrar shall (if one or more Physical Securities are to be issued) reflect on its books and records the date and a decrease in the aggregate principal amount of such Global Security in an amount equal to the aggregate principal amount of the beneficial interest in the Global Security to be transferred, and the Company shall execute and the Trustee shall authenticate and deliver, one or more Physical Securities of authorized denominations in an aggregate principal amount equal to the aggregate principal amount of the beneficial interest in the Global Security so transferred.

(D) In connection with the transfer of a Global Security in its entirety to beneficial owners pursuant to **Section 2.15(B)**, such Global Security shall be deemed to be surrendered to the Trustee for cancellation, and the Company shall execute, and the Trustee shall upon Company Order authenticate and deliver, to each beneficial owner identified by the Depositary in exchange for its beneficial interest in such Global Security, an equal aggregate principal amount of Physical Securities of authorized denominations.

(E) Any Physical Security constituting a Restricted Security delivered in exchange for an interest in a Global Security pursuant to **Section 2.15(B)** or (C) shall, except as otherwise provided by **Section 2.16**, bear the Private Placement Legend (as defined herein).

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(F) The Holder of any Global Security may grant proxies and otherwise authorize any Person, including Participants and Persons that may hold interests through Participants, to take any action which a Holder is entitled to take under this Indenture or the Securities.

## 2.16 SPECIAL TRANSFER PROVISIONS.

(A) **Transfers to Non-U.S. Persons.** The following provisions shall apply with respect to the registration of any proposed transfer of a Restricted Security to any Non-U.S. Person:

(i) the Registrar shall register the transfer of any Restricted Security, whether or not such Security bears the Private Placement Legend, if (x) the requested transfer is after the second anniversary of the issue date for the Securities; *provided, however*, that neither the Company nor any of its Affiliates has held any beneficial interest in such Security, or portion thereof, at any time on or prior to the second anniversary of the issue date for the Securities or (y) in the case of a transfer to a Non-U.S. Person, the proposed transferor has delivered to the Registrar certificates substantially in the form of **Exhibit C-1** and **Exhibit C-2** hereto;

(ii) if the proposed transferee is a Participant and the Notes to be transferred consist of Physical Securities which after transfer are to be evidenced by an interest in the Global Security, upon receipt by the Registrar of (x) written instructions given in accordance with the Depository's and the Registrar's procedures and (y) the appropriate certificates and other documents, if any, required by clause (y) of paragraph (i) above, the Registrar shall register the transfer and reflect on its books and records the date and an increase in the aggregate principal amount of the Global Security in an amount equal to the aggregate principal amount of Physical Securities to be transferred, and the Trustee shall cancel the Physical Securities so transferred; and

(iii) if the proposed transferor is a Participant seeking to transfer an interest in one Global Security to a transferee who will hold such interest in another Global Security, upon receipt by the Registrar of (x) written instructions given in accordance with the Depository's and the Registrar's procedures and (y) the appropriate certificates and other documents, if any, required by clause (y) of paragraph (i) above, the Registrar shall register the transfer and reflect on its books and records the date and (A) a decrease in the aggregate principal amount of the Global Security through which the transferor held such interest in an amount equal to the aggregate principal amount of the Securities to be transferred and (B) an increase in the aggregate principal amount of the Global Security through which the transferee proposes to hold such interest, in an amount equal to the aggregate principal amount of the Securities to be transferred.

(B) **Transfers to QIBs.** The following provisions shall apply with respect to the registration of any proposed transfer of a Restricted Security to a QIB:

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(i) the Registrar shall register the transfer of any Restricted Security, whether or not such Security bears the Private Placement Legend, if (x) the requested transfer is after the second anniversary of the issue date for the Securities; *provided, however*, that neither the Company nor any of its Affiliates has held any beneficial interest in such Security, or portion thereof, at any time on or prior to the second anniversary of the issue date for the Securities or (y) such transfer is being made by a proposed transferor who has checked the box provided for on the form of Security stating, or has otherwise advised the Company and the Registrar in writing, that the sale has been made in compliance with the provisions of Rule 144A to a transferee who has signed the certification provided for on the form of Security stating, or has otherwise advised the Company and the Registrar in writing, that it is purchasing the Security for its own account or an account with respect to which it exercises sole investment discretion and that it and any such account is a QIB within the meaning of Rule 144A, and is aware that the sale to it is being made in reliance on Rule 144A and acknowledges that it has received such information regarding the Company as it has requested pursuant to Rule 144A or has determined not to request such information and that it is aware that the transferor is relying upon its foregoing representations in order to claim the exemption from registration provided by Rule 144A;

(ii) if the proposed transferee is a Participant and the Securities to be transferred consist of Physical Securities which after transfer are to be evidenced by an interest in the Global Security, upon receipt by the Registrar of written instructions given in accordance with the Depository's and Registrar's procedures, the Registrar shall register the transfer and reflect on its books and records the date and an increase in the principal amount of the Global Security in an amount equal to the principal amount of Physical Securities to be transferred, and the Trustee shall cancel the Physical Securities so transferred; and

(iii) if the proposed transferor is a Participant seeking to transfer an interest in one Global Security to a transferee who will hold such interest in another Global Security, upon receipt by the Registrar of (x) written instructions given in accordance with the Depository's and the Registrar's procedures and (y) the appropriate certificates and other documents, if any, required by clause (y) of paragraph (i) above, the Registrar shall register the transfer and reflect on its books and records the date and (A) a decrease in the aggregate principal amount of the Global Security through which the transferor held such interest in an amount equal to the aggregate principal amount of the Securities to be transferred and (B) an increase in the aggregate principal amount of the Global Security through which the transferee proposes to hold such interest, in an amount equal to the aggregate principal amount of the Securities to be transferred.

(C) **Restrictions on Transfer and Exchange of Global Securities.** Notwithstanding any other provisions of this Indenture, a Global Security may not be transferred except as a whole by the Depository to a nominee of the Depository or by a nominee of the Depository to the Depository or another nominee of the Depository or by the Depository or any such nominee to a successor Depository or a nominee of such successor Depository.

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(D) **Private Placement Legend.** Upon the transfer, exchange or replacement of Securities not bearing the Private Placement Legend, the Registrar or co-Registrar shall deliver Securities that do not bear the Private Placement Legend. Upon the transfer, exchange or replacement of Securities bearing the Private Placement Legend, the Registrar or co-Registrar shall deliver only Securities that bear the Private Placement Legend unless (i) the requested transfer is after the second anniversary of the issue date for the Securities (*provided, however*, that neither the Company nor any of its Affiliates has held any beneficial interest in such Security, or portion thereof, at any time prior to or on the second anniversary of the issue date) for the Securities, (ii) there is



delivered to the Trustee an opinion of counsel reasonably satisfactory to the Company to the effect that neither such legend nor the related restrictions on transfer are required in order to maintain compliance with the provisions of the Securities Act or (iii) such Security has been sold pursuant to an effective registration statement under the Securities Act and the Holder selling such Securities has delivered to the Registrar or co-Registrar a notice in the form of **Exhibit D** hereto. Upon the effectiveness of the Shelf Registration Statement (as defined in the Registration Rights Agreement), the Company shall deliver to the Trustee a notice of effectiveness, a Security or Securities, an authentication order in accordance with **Section 2.02** and, if required by the Depository, the Company shall deliver to the Depository a letter of representations in a form reasonably acceptable to the Depository.

(E) **General.** By its acceptance of any Security bearing the Private Placement Legend, each Holder of such a Security acknowledges the restrictions on transfer of such Security set forth in this Indenture and in the Private Placement Legend and agrees that it will transfer such Security only as provided in this Indenture.

The Registrar shall retain copies of all letters, notices and other written communications received pursuant to **Section 2.15** or this **Section 2.16**. The Company shall have the right to inspect and make copies of all such letters, notices or other written communications at any reasonable time upon the giving of reasonable written notice to the Registrar.

(F) **Transfers of Securities Held by Affiliates.** Any certificate (i) evidencing a Security that has been transferred to an Affiliate of the Company within two years after the issue date for the Securities, as evidenced by a notation on the assignment form for such transfer or in the representation letter delivered in respect thereof or (ii) evidencing a Security that has been acquired from an Affiliate (other than by an Affiliate) in a transaction or a chain of transactions not involving any public offering, shall, until two years after the last date on which the Company or any Affiliate of the Company was an owner of such Security, in each case, bear the Private Placement Legend, unless otherwise agreed by the Company (with written notice thereof to the Trustee).

## 2.17 RESTRICTIVE LEGENDS.

Each Global Security and Physical Security that constitutes a Restricted Security shall bear the legend (the "**Private Placement Legend**") as set forth in **Exhibit B-1** on the face thereof until after the second anniversary of the later of (i) the issue date for the Securities and (ii) the last date on which the Company or any Affiliate of the Company was the owner of such Security (or any predecessor security) (or such shorter period of time as permitted by Rule 144(k) under the Securities Act or any successor provision thereunder) (or such longer period of

time as may be required under the Securities Act or applicable state securities laws in the opinion of counsel for the Company, unless otherwise agreed between the Company and the Holder thereof).

Each Global Security shall also bear the legend as set forth in **Exhibit B-2**.

## III. REDEMPTION

### 3.01 RIGHT OF REDEMPTION.

Redemption of the Securities, as permitted by any provision of this Indenture, shall be made in accordance with **paragraph 6** of the Securities and this **Article III**.

(A) The Securities may be redeemed at the election of the Company, as a whole or in parts from time to time, at any time prior to May 3, 2005 (a "**Provisional Redemption**"), at a redemption price equal to \$1,000 per \$1,000 principal amount of the Securities redeemed (such amount, together with the Make-Whole Payment (as defined below) the "**Provisional Redemption Price**"), on the date of redemption (the "**Provisional Redemption Date**") specified in the notice of Provisional Redemption if (1) the closing price of the Common Stock on the NNM (or other United States national securities exchange where the Company's Common Stock is traded) has exceeded 150% of the then current conversion price for at least 20 trading days within a period of any 30 consecutive trading days ending on the trading day prior to the date of mailing of the notice of Provisional Redemption (the "**Notice Date**"), and (2) a shelf registration statement covering resales of the Securities and the Common Stock issuable upon conversion thereof is effective and available for use and is expected to remain effective and available for use for the 30 days following the Provisional Redemption Date, unless registration is no longer required.

Upon any such Provisional Redemption, the Company shall make an additional payment (the "**Make-Whole Payment**") with respect to the Securities called for redemption to holders on the Provisional Redemption Date in an amount equal to the total value of the aggregate amount of interest that would have been payable on the Securities from the last day through which interest was paid on the Securities (or May 1, 2002 if no interest has been paid) through May 1, 2005 (or May 2005 if the Provisional Redemption Date is May 2, 2005). The Company may make the Make-Whole Payment, at its option, either in cash or Common Stock or a combination thereof. Payments made in Common Stock will be valued at 95% of the average closing sales prices of the Common Stock on the NNM (or other United States national securities exchange where the Common Stock is traded) for the five trading days ending on the day prior to the Provisional Redemption Date. The Company shall make the Make-Whole Payment on all Securities called for Provisional Redemption, including those Securities converted into Common Stock between the Notice Date and the Provisional Redemption Date.

The Company will comply with all federal and state securities laws in connection with any offer to sell or solicitations of offers to buy Common Stock pursuant to this **Section 3.01(A)**.

(B) On or after May 3, 2005, the Company will have the right to redeem all or any part of the Securities at the Redemption Prices specified in **paragraph 6** therein under the

caption "Redemption Price," in cash, in each case including accrued and unpaid interest, if any, to, but excluding, the redemption date.

### 3.02 NOTICES TO TRUSTEE.

If the Company elects to redeem Securities pursuant to **paragraph 6** of the Securities, it shall notify the Trustee by a Company Order at least 45 days prior to the redemption date (unless a shorter notice period shall be satisfactory to the Trustee) of the redemption date, the aggregate principal amount of Securities to be redeemed, the Redemption Price and the Provisional Redemption Price, if applicable, per \$1,000 principal of Securities.

### 3.03 SELECTION OF SECURITIES TO BE REDEEMED.

If less than all the Securities are to be redeemed, the Trustee shall select the Securities to be redeemed in compliance with the requirements of the principal exchange or market, if any, on which the Securities are listed, or, if the Securities are not so listed, on a *pro rata* basis or by such other method as the Trustee shall deem fair and equitable. The Trustee shall make the selection from Securities outstanding not previously called for redemption. The Trustee may select for redemption portions of the principal of Securities that have denominations larger than \$1,000 principal amount. Securities and portions of them it selects shall be in amounts of \$1,000 principal amount or positive integral multiples of \$1,000 principal amount. The Trustee shall promptly notify the Company in writing of the Securities selected for redemption and the principal amount thereof to be redeemed.

The Registrar need not transfer or exchange any Securities selected for redemption, except the unredeemed portion of the Securities redeemed in part. Also, the Registrar need not transfer or exchange any Securities for a period of 15 days before selecting Securities to be redeemed.

### 3.04 NOTICE OF REDEMPTION.

At least 30 days but not more than 60 days before a redemption date, the Company shall mail by first-class mail a notice of redemption to each Holder whose Securities are to be redeemed.

The notice shall identify the Securities and the aggregate principal amount thereof to be redeemed and shall state:

- (i) the redemption date;
- (ii) the Redemption Price or the Provisional Redemption Price, if applicable, plus the amount of accrued and unpaid interest to be paid on the Securities called for redemption;
- (iii) the then current conversion rate and conversion price and any adjustments to the conversion price;

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- (iv) the name and address of the Paying Agent and the Conversion Agent;
  - (v) the date on which the right to convert the principal of the Securities called for redemption will terminate and the place or places where such Securities may be surrendered for conversion;
  - (vi) that Holders who want to convert Securities must satisfy the requirements in **Article X**;
  - (vii) the paragraph of the Securities pursuant to which the Securities are to be redeemed;
  - (viii) that Securities called for redemption must be surrendered to the Paying Agent to collect the Redemption Price or the Provisional Redemption Price, if applicable;
  - (ix) that unless the Company shall default in the payment of the Redemption Price or the Provisional Redemption Price, if applicable, interest on Securities called for redemption ceases to accrue on and after the redemption date and that the Securities will cease to be convertible after the close of business on the business day immediately preceding the redemption date;
  - (x) if fewer than all of the outstanding Securities are to be redeemed, the certificate numbers, if any, and principal amount of the particular Securities to be redeemed;
  - (xi) the type of consideration for the Make-Whole Payment, if applicable; and
  - (xii) the CUSIP number or numbers, as the case may be, of the Securities.

The date on which the right to convert the principal of the Securities called for redemption will terminate shall be at the close of business on the business day immediately preceding the redemption date.

At the Company's request, upon reasonable prior notice, the Trustee shall give the notice of redemption in the Company's name and at the Company's expense; provided that the form and content of such notice shall be prepared by the Company.

### 3.05 EFFECT OF NOTICE OF REDEMPTION.

Once notice of redemption is mailed, Securities called for redemption become due and payable on the redemption date at the Redemption Price or the Provisional Redemption Price, if applicable, per \$1,000 principal amount stated in the notice plus accrued and unpaid interest to the date of redemption, and, on and after such date (unless the Company shall default in the payment of the Redemption Price or the Provisional Redemption Price, if applicable), such

Securities shall cease to bear interest. Upon surrender to the Paying Agent, such Securities shall be paid at the Redemption Price or the Provisional Redemption Price, if applicable, per \$1,000 principal amount stated in the notice plus accrued interest to the redemption date, unless the redemption date is an interest payment date, in which case the accrued interest will be paid in the ordinary course.

### 3.06 DEPOSIT OF REDEMPTION PRICE.

On or before 11:00 a.m. New York City time on the redemption date, the Company shall deposit with the Paying Agent money or with respect to the Make-Whole Payment, at the Company's option, money or Common Stock or a combination thereof, in funds immediately available on the redemption date sufficient to pay the Redemption Price or the Provisional Redemption Price, if applicable, of and accrued interest on all Securities to be redeemed on that date other than Securities or portions of Securities called for redemption which on or prior thereto have been delivered by the Company to the Trustee for cancellation or have been converted. The Paying Agent shall return to the Company, as soon as practicable, any money not required for that purpose.

### 3.07 SECURITIES REDEEMED IN PART.

Upon surrender of a Security that is redeemed in part, the Company shall execute and the Trustee shall authenticate for the Holder a new Security or Securities in an aggregate principal amount equal to the unredeemed portion of the Security surrendered.

If any Security selected for partial redemption is converted in part, the converted portion of such Security shall be deemed (so far as may be) to be the portion selected for redemption.

### 3.08 REPURCHASE AT OPTION OF HOLDER UPON A CHANGE IN CONTROL.

Upon any Change in Control (as defined below) with respect to the Company, each Holder of Securities shall have the right (the "**Repurchase Right**"), at the Holder's option, to require the Company to repurchase all of such Holder's Securities, or a portion thereof which is \$1,000 or any positive integral multiple thereof, on the date (the "**Repurchase Date**") specified in the Change in Control Notice (as defined below), which date shall be no later than 30 business days after the date of such Change in Control Notice, at the Repurchase Price plus accrued and unpaid interest, if any, to the Repurchase Date.

Within 30 business days after the occurrence of a Change in Control of the Company, the Company is obligated to mail to all Holders of record of the Securities a notice (the "**Change in Control Notice**") of the occurrence of such Change in Control and the Repurchase Right arising as a result thereof. The Company shall deliver a copy of the Change in Control Notice to the Trustee and shall cause a copy to be published at the expense of the Company in **THE NEW YORK TIMES** and in **THE WALL STREET JOURNAL** or another newspaper of national circulation.

Each Change in Control Notice shall state:

- (i) the events causing the Change in Control;

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- (ii) the date of such Change in Control;

- (iii) the Repurchase Date;

- (iv) the date by which the Repurchase Right must be exercised;

- (v) the Repurchase Price, plus the amount of accrued interest to be paid on the Securities to be repurchased;

- (vi) the name and address of the Paying Agent and the Conversion Agent;

- (vii) a description of the procedure which a Holder must follow to exercise a Repurchase Right;

(viii) that, in order to exercise the Repurchase Right, the Securities must be surrendered to the Paying Agent to collect payment of the Repurchase Price;

(ix) that Holders will be entitled to withdraw their election if the Company (if acting as its own Paying Agent), or the Paying Agent receives, not later than the close of business on the second business day prior to the Repurchase Date, or such longer period as may be required by law, a letter or telegram, telex or facsimile transmission (receipt of which is confirmed and promptly followed by a letter) setting forth the name of the Holder, the principal amount of Securities the Holder delivered for purchase and a statement that such Holder is withdrawing his election to have such Securities repurchased, the certificate numbers of such Securities being withdrawn, if applicable, and the principal amount, if any, of the Securities that remain subject to a Change in Control Notice;

(x) the then existing conversion rate and conversion price for conversion of Securities, any adjustments to the conversion rate and the place or places where such Securities may be surrendered for conversion;

- (xi) the CUSIP number or numbers, as the case may be, of the Securities; and

(xii) that Securities with respect to which the Holder thereof has duly delivered an Option of Holder To Elect Purchase Notice in accordance with this **Section 3.08** may be converted into Common Stock, if otherwise so convertible as provided herein, only if such Holder duly withdraws its election in accordance with this **Section 3.08**.

No failure of the Company to give the foregoing notice shall limit any Holder's right to exercise a Repurchase Right.

To exercise a Repurchase Right, a Holder shall deliver to the Company (if it is acting as its own Paying Agent), or to a Paying Agent designated by the Company for such purpose in the Change in Control Notice (i) no later than the close of business on the third business day

immediately preceding the Repurchase Date, the Option of Holder To Elect Purchase Notice on the back of the Securities with respect to which the Repurchase Right is being exercised, duly completed and signed, with appropriate signature guarantee, and (ii) at any time after such delivery of such Option of Holder to Elect Purchase Notice, such Securities with respect to which the Repurchase Right is being exercised, duly endorsed for transfer to the Company. Upon so delivering such Option of Holder To Elect Purchase Notice and such Securities, the Holder of such Securities shall be entitled to receive from the Company (if it is acting as its own Paying Agent), or such Paying Agent, a nontransferable receipt of deposit evidencing such deposit.

In the event a Repurchase Right shall be exercised in accordance with the terms hereof, the Company shall pay or cause to be paid the applicable Repurchase Price (plus accrued and unpaid interest) with respect to the Securities as to which the Repurchase Right shall have been exercised to the Holder on the later of (i) the Repurchase Date and (ii) the time such Holder has duly delivered the Securities with respect to which the Repurchase Right is being exercised in accordance with the immediately preceding paragraph.

On or prior to 11:00 a.m. New York City time on a Repurchase Date, the Company shall deposit with the Trustee or with a Paying Agent (or, if the Company is acting as its own Paying Agent, segregate and hold in trust in accordance with **Section 2.04**) an amount of money (to be available on the Repurchase Date) sufficient to pay the aggregate Repurchase Price (plus accrued and unpaid interest) of all of the Securities which are to be repurchased on that date.

Both the Change in Control Notice and the Option of Holder To Elect Purchase Notice having been given as specified in this **Section 3.08**, the Securities so to be repurchased shall, on the Repurchase Date, become due and payable at the Repurchase Price applicable thereto (plus accrued and unpaid interest) and from and after such date (unless there shall be a default in the payment of the Repurchase Price plus accrued and unpaid interest to the Repurchase Date) such Securities shall cease to bear interest and shall cease to be convertible. Upon surrender of any such Security for repurchase in accordance with said notice, such Security shall be paid by the Company at the Repurchase Price (plus accrued and unpaid interest).

If any Security shall not be paid upon surrender thereof for repurchase, the principal shall, until paid, bear interest from the Repurchase Date at the rate borne by such Security on the principal amount of such Security and shall continue to be convertible.

Any Security which is to be submitted for repurchase only in part shall be delivered pursuant to this **Section 3.08** (with, if the Company or the Trustee so requires, due endorsement by, or a written instrument of transfer in form satisfactory to the Company and the Trustee duly executed by the Holder thereof or its attorney duly authorized in writing), and the Company shall execute, and the Trustee shall upon Company Order authenticate and make available for delivery to the Holder of such Security without service charge, a new Security or Securities, of any authorized denomination as requested by such Holder, of the same tenor and in aggregate principal amount equal to the portion of such Security not submitted for repurchase.

Notwithstanding anything herein to the contrary, if the option granted to Securityholders to require the repurchase of the Securities upon the occurrence of a Change in Control is

determined to constitute a tender offer, the Company will comply with all applicable tender offer rules, including Rules 13e-4 and 14e-1 under the Exchange Act, and file Schedule TO or any other schedules required under the Exchange Act.

As used in this **Section 3.08** of the Indenture and in the Securities:

A “**Change in Control**” of the Company means:

- (i) the acquisition by any “person,” entity or “group” within the meaning of Section 13(d)(3) or 14(d)(2) of the Exchange Act of beneficial ownership (within the meaning of Rule 13d-3 promulgated under the Exchange Act) of 50% or more of the voting power of the total outstanding Common Stock or other capital stock into which the Common Stock is hereafter reclassified or changed;
- (ii) persons who constitute the Board of Directors (the “**Incumbent Board**”) as of the date of the Indenture, cease for any reason to constitute at least a majority of the Board of Directors, provided that any person subsequently becoming a director whose election by the Board of Directors, or nomination for election by stockholders, was approved by a vote of at least a majority of the directors then comprising the Incumbent Board shall be considered as though such person were a member of the Incumbent Board; or
- (iii) the sale, lease or transfer of all or substantially all of the assets and property of the Company to any “person,” entity or “group” within the meaning of Section 13(d) or 14(d) of the Exchange Act, including any group acting for the purpose of acquiring, holding or disposing of securities within the meaning of Rule 13d-5(b)(1) under the Exchange Act.

Notwithstanding anything to the contrary set forth in this **Section 3.08**, a Change in Control will not be deemed to have occurred if either:

- (i) the last sale price of the Common Stock for any five trading days during the ten trading days immediately preceding the Change in Control is at least equal to 105% of the conversion price in effect on such trading day; or

(ii) in the case of a merger or consolidation, all or substantially all of the consideration (excluding cash payments for fractional shares and cash payments pursuant to dissenters' appraisal rights) in the merger or consolidation constituting the Change in Control consists of common stock quoted traded on a United States national securities exchange or on the NNM (or which will be so traded or quoted when issued or exchanged in connection with such Change in Control) and as a result of such transaction or transactions the Securities become convertible solely into such common stock.

### 3.09 CONVERSION ARRANGEMENT ON CALL FOR REDEMPTION.

In connection with any redemption of Securities, the Company may arrange, in lieu of redemption, for the purchase and conversion of any Securities called for redemption by an agreement with one or more investment bankers or other purchasers to purchase all or a portion

of such Securities by paying to the Trustee in trust for the Holders whose Securities are to be so purchased, on or before the close of business on the redemption date, an amount that, together with any amounts deposited with the Trustee by the Company for redemption of such Securities, is not less than the Redemption Price or the Provisional Redemption Price, if applicable, together with interest, if any, accrued to the redemption date, of such Securities. Notwithstanding anything to the contrary contained in this **Article III**, the obligation of the Company to pay the Redemption Price or the Provisional Redemption Price, if applicable, of such Securities, including all accrued interest, if any, shall be deemed to be satisfied and discharged to the extent such amount is so paid by such purchasers, but no such agreement shall relieve the Company of its obligation to pay such Redemption Price or the Provisional Redemption Price, if applicable, and such accrued interest, if any. If such an agreement is entered into, any Securities not duly surrendered for conversion by the Holders thereof may, at the option of the Company, be deemed, to the fullest extent permitted by law, acquired by such purchasers from such Holders and (notwithstanding anything to the contrary contained in **Article X**) surrendered by such purchasers for conversion, all as of immediately prior to the close of business on the redemption date, subject to payment of the above amount as aforesaid. The Trustee shall hold and pay to the Holders whose Securities are selected for redemption any such amount paid to it for purchase and conversion in the same manner as it would moneys deposited with it by the Company for the redemption of Securities. Without the Trustee's prior written consent, no arrangement between the Company and such purchasers for the purchase and conversion of any Securities shall increase or otherwise affect any of the powers, duties, responsibilities or obligations of the Trustee as set forth in this Indenture, and the Company agrees to indemnify the Trustee from, and hold it harmless against, any loss, liability or expense arising out of or in connection with any such arrangement for the purchase and conversion of any Securities between the Company and such purchasers, including the costs and expenses incurred by the Trustee in the defense of any claim or liability arising out of or in connection with the exercise or performance of any of its powers, duties, responsibilities or obligations under this Indenture except to the extent arising from its bad faith, willful misconduct or negligence.

## IV. COVENANTS

### 4.01 PAYMENT OF SECURITIES.

The Company shall pay all amounts due with respect to the Securities on the dates and in the manner provided in the Securities. Any amount of cash or shares of Common Stock to be given to the Trustee or Paying Agent shall be deposited by the Company with the Trustee or Paying Agent prior to 11:00 a.m. New York City time. All such amounts shall be considered paid on the date due if the Paying Agent holds (or, if the Company is acting as Paying Agent, if the Company has segregated and holds in trust in accordance with **Section 2.04**) on that date money or Common Stock, as the case may be in accordance with this Indenture, sufficient to pay the amount then due with respect to the Securities.

The Company shall pay interest on any overdue amount (including, to the extent permitted by applicable law, overdue interest) at the rate borne by the Securities.

### 4.02 MAINTENANCE OF OFFICE OR AGENCY.

The Company will maintain in the Borough of Manhattan, the City of New York, an office or agency (which may be an office of the Trustee or an affiliate of the Trustee, Registrar or co-Registrar) where Securities may be surrendered for registration of transfer or exchange or conversion and where notices and demands to or upon the Company in respect of the Securities and this Indenture may be served. The Company will give prompt written notice to the Trustee of the location, and any change in the location, of such office or agency. If at any time the Company shall fail to maintain any such required office or agency or shall fail to furnish the Trustee with the address thereof, such presentations, surrenders, notices and demands may be made or served at the Corporate Trust Office of the Trustee.

The Company may also from time to time designate one or more other offices or agencies where the Securities may be presented or surrendered for any or all such purposes and may from time to time rescind such designations; *provided, however*, that no such designation or rescission shall in any manner relieve the Company of its obligation to maintain an office or agency in the Borough of Manhattan, the City of New York for such purposes. The Company will give prompt written notice to the Trustee of any such designation or rescission and of any change in the location of any such other office or agency.

The Company hereby designates the Corporate Trust Office of the Trustee as an agency of the Company in accordance with **Section 2.03**.

### 4.03 REPORTS.

(A) The Company (at its own expense) will deliver to the Trustee within 15 days after the filing of the same with the Commission, copies of the quarterly and annual reports and of the information, documents and other reports, if any, which the Company may be required to file with the Commission pursuant to Section 13 or 15(d) of the Exchange Act or which the Company furnishes to its stockholders. In the event the Company is at any time no longer subject to the reporting requirements of Section 13 or 15(d) of the Exchange Act, it shall continue to provide the Trustee with reports containing substantially the same information as would have been required to be filed with the SEC had the Company continued to have been subject to such reporting requirements. In such event, such reports shall be provided at the times the Company would have been required to provide reports had it continued to have been subject to such reporting requirements. Delivery of such reports, information and documents to the Trustee is for informational purposes only and the Trustee's receipt of such shall not constitute constructive notice of any information contained therein or determinable from information contained therein, including the Company's compliance with any of its covenants hereunder (as to which the Trustee is entitled to rely exclusively on the Officers' Certificate).

(B) Notwithstanding that the Company may not be subject to the reporting requirements of Section 13 or 15(d) of the Exchange Act, for so long as any Securities remain outstanding the Company will promptly provide the information required by Rule 144A(d)(4) to any Holder or beneficial owner of Securities that so requests.

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(C) In addition, if and when this Indenture becomes subject to the TIA, the Company will file a copy of all such information required by **clauses (A) and (B)** of this **Section 4.03** with the Commission for public availability (unless the Commission will not accept such a filing) and make such information available to investors who request it in writing.

(D) The Company will comply with the provisions of TIA § 314(a).

#### 4.04 COMPLIANCE CERTIFICATE.

The Company shall deliver to the Trustee within 120 days after the end of each fiscal year of the Company an Officers' Certificate stating whether or not the signers know of any Default or Event of Default by the Company in performing any of its obligations under this Indenture or the Securities. If they do know of any such Default or Event of Default, the certificate shall describe the Default or Event of Default and its status.

#### 4.05 STAY, EXTENSION AND USURY LAWS.

The Company covenants (to the extent that it may lawfully do so) that it will not at any time insist upon, plead, or in any manner whatsoever claim or take the benefit or advantage of, any stay, extension or usury law wherever enacted, now or at any time hereafter in force, which may affect the covenants or the performance of this Indenture; and the Company (in each case, to the extent that it may lawfully do so) hereby expressly waives all benefit or advantage of any such law, and covenants that it will not, by resort to any such law, hinder, delay or impede the execution of any power herein granted to the Trustee, but will suffer and permit the execution of every such power as though no such law has been enacted.

#### 4.06 CORPORATE EXISTENCE.

Subject to **Article V**, the Company will do or cause to be done all things necessary to preserve and keep in full force and effect its corporate existence and the corporate existence of each of its subsidiaries in accordance with the respective organizational documents of each subsidiary and the rights (charter and statutory), licenses and franchises of the Company and its subsidiaries; *provided, however*, that Company shall not be required to preserve any such right, license or franchise, or the corporate existence of any subsidiary, if in the judgment of the Board of Directors (i) the failure to preserve such right, license or franchise, or maintain such corporate existence, would not have a material adverse impact on the conduct of business of the Company and (ii) the loss of such right, license or franchise or the dissolution of such subsidiary does not have a material adverse impact on the Holders.

#### 4.07 NOTICE OF DEFAULT.

In the event that any Default under **Section 6.01** hereof shall occur, the Company will give prompt written notice of such Default to the Trustee.

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## V. SUCCESSORS

#### 5.01 WHEN COMPANY MAY MERGE, ETC.

The Company shall not consolidate with or merge into, or convey, transfer or lease all or substantially all of its properties and assets to, another person unless such other person is a corporation, a limited liability company or other limited liability entity organized and existing under the laws of the United States, any State thereof or the District of Columbia, provided, that this condition will not apply if independent tax counsel experienced in such matters delivers an Opinion of Counsel stating that, under then existing laws, there would be no adverse tax consequences to the Holders in the event that this condition is not satisfied, and such person assumes by supplemental indenture all the obligations of the Company, under the Securities and this Indenture, and immediately after giving effect to the transaction, no Default or Event of Default shall exist.

The Company shall deliver to the Trustee prior to the consummation of the proposed transaction an Officers' Certificate to the foregoing effect and an Opinion of Counsel, which may rely upon such Officers' Certificate as to the absence of Defaults and Events of Default, stating that the proposed transaction and such supplemental indenture will, upon consummation of the proposed transaction, comply with this Indenture.

#### 5.02 SUCCESSOR SUBSTITUTED.

Upon any consolidation or merger or transfer or lease of all or substantially all of the assets of the Company in accordance with **Section 5.01**, the successor person formed by such consolidation or into which the Company is merged or to which such transfer or lease is made shall succeed to, and, except in the case of a lease, be substituted for, and may exercise every right and power of, and shall assume every duty and obligation of, the Company under this Indenture with the same effect as if such successor had been named as the Company herein. When the successor assumes all obligations of the Company hereunder, except in the case of a lease, all obligations of the predecessor shall terminate.

## VI. DEFAULTS AND REMEDIES

### 6.01 EVENTS OF DEFAULT.

An “**Event of Default**” occurs if:

- (i) the Company defaults in the payment of interest or liquidated damages on any Security when the same becomes due and payable and the default continues for a period of 30 days, whether or not such payment shall be prohibited by the provisions of **Article XI** hereof;
- (ii) the Company defaults in the payment of the principal or Repurchase Price or Redemption Price or Provisional Redemption Price, if applicable, of any Security when the same becomes due and payable on the

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Maturity Date, upon redemption or otherwise, whether or not such payment shall be prohibited by the provisions of **Article XI** hereof;

- (iii) the Company fails to comply with any of its other agreements in the Securities or this Indenture and the default continues for the period and after the Notice of Default specified below;
- (iv) the Company pursuant to or within the meaning of any Bankruptcy Law:
  - (A) commences a voluntary case,
  - (B) consents to the entry of an order for relief against it in an involuntary case,
  - (C) consents to the appointment of a Custodian of it or for all or substantially all of its property, or
  - (D) makes a general assignment for the benefit of its creditors; or
  - (v) a court of competent jurisdiction enters an order or decree under any Bankruptcy Law that:
    - (A) is for relief against the Company in an involuntary case or proceeding, or adjudicates the Company insolvent or bankrupt,
    - (B) appoints a Custodian of the Company for all or substantially all of the property of the Company, or
    - (C) orders the winding up or liquidation of the Company,

and the order or decree remains unstayed and in effect for 90 consecutive days.

The term “**Bankruptcy Law**” means Title 11, U.S. Code or any similar Federal or State law for the relief of debtors. The term “**Custodian**” means any receiver trustee, assignee, liquidator or similar official under any Bankruptcy Law.

A default under **clause (iii)** is not an Event of Default until the Trustee or the Holders of at least 25% in aggregate principal amount of the Securities then outstanding notify the Company and the Trustee of the default and the default is not cured within 60 days after receipt of the notice. The notice must specify the default, demand that it be remedied and state that the notice is a “**Notice of Default**”. If the Holders of 25% in aggregate principal amount of the outstanding Securities request the Trustee to give such notice on their behalf, the Trustee shall do so. When a default is cured, it ceases.

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### 6.02 ACCELERATION.

If an Event of Default (other than an Event of Default specified in **Section 6.01(iv)** or **(v)** with respect to the Company) as to which the Trustee has received notice pursuant to **Section 4.07** occurs and is continuing, the Trustee by notice to the Company or the Holders of at least 25% in principal amount of the Securities then outstanding by notice to the Company and the Trustee may declare the Securities to be due and payable. Upon such declaration such principal and interest shall be due and payable immediately. If an Event of Default specified in **Section 6.01(iv)** or **(v)** with respect to the Company occurs, the principal of and accrued interest on all the Securities shall *ipso facto* become and be immediately due and payable without any declaration or other act on the part of the Trustee or any Securityholder. The Holders of a majority in aggregate principal amount of the Securities then outstanding by written notice to the Trustee may rescind an acceleration and its consequences if the rescission would not conflict with any order or decree and if all existing Events of Default have been cured or waived except nonpayment of principal or interest that has become due solely because of the acceleration and if all amounts due to the Trustee under **Section 7.07** have been paid. No such rescission shall affect any subsequent Default or impair any right consequent thereto.

### 6.03 OTHER REMEDIES.

Notwithstanding any other provision of this Indenture, if an Event of Default occurs and is continuing, the Trustee may pursue any available remedy by proceeding at law or in equity to collect the payment of amounts due with respect to the Securities or to enforce the performance of any provision of the Securities or this Indenture.

The Trustee may maintain a proceeding even if it does not possess any of the Securities or does not produce any of them in the proceeding. A delay or omission by the Trustee or any Securityholder in exercising any right or remedy accruing upon an Event of Default shall not impair the right or remedy or constitute a waiver of or acquiescence in the Event of Default. All remedies are cumulative.

#### 6.04 WAIVER OF PAST DEFAULTS.

Subject to **Sections 6.07** and **9.02**, the Holders of a majority in aggregate principal amount of the Securities then outstanding by notice to the Trustee may waive any past Default or Event of Default and its consequences. When a Default or an Event of Default is waived, it is cured and ceases for every purpose of this Indenture, but no such waiver shall extend to a subsequent or other Default or impair any consequential right.

#### 6.05 CONTROL BY MAJORITY.

The Holders of a majority in aggregate principal amount of the Securities then outstanding may direct the time, method and place of conducting any proceeding for any remedy available to the Trustee or exercising any trust or power conferred on it. However, the Trustee may refuse to follow any direction that conflicts with law or this Indenture, is unduly prejudicial to the rights of other Securityholders or would involve the Trustee in personal liability; provided that the Trustee may take any other action deemed proper by the Trustee which is not

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inconsistent with such direction and, if required, the Trustee is to be indemnified to its satisfaction pursuant to **Section 7.07**.

#### 6.06 LIMITATION ON SUITS.

Except as provided in **Section 6.07**, a Securityholder may pursue a remedy with respect to this Indenture or the Securities only if:

- (i) the Holder gives to the Trustee written notice of a continuing Event of Default;
- (ii) the Holders of at least 25% in aggregate principal amount of the Securities then outstanding make a written request to the Trustee to pursue the remedy;
- (iii) such Holder or Holders offer and if requested provide to the Trustee indemnity satisfactory to the Trustee against any loss, liability or expense;
- (iv) the Trustee does not comply with the request within 60 days after receipt of the request and the offer of indemnity; and
- (v) during such 60-day period the Holders of a majority in aggregate principal amount of the Securities then outstanding do not give the Trustee a direction inconsistent with the request.

A Securityholder may not use this Indenture to prejudice the rights of another Securityholder or to obtain a preference or priority over another Securityholder.

#### 6.07 RIGHTS OF HOLDERS TO RECEIVE PAYMENT.

Notwithstanding any other provision of this Indenture, the right of any Holder to receive payment of all amounts due with respect to the Securities, on or after the respective due dates expressed in the Securities, or to bring suit for the enforcement of any such payment on or after such respective dates, shall not be impaired or affected without the consent of the Holder.

Notwithstanding any other provision of this Indenture, the right of any Holder to bring suit for the enforcement of the right to convert the Security shall not be impaired or affected without the consent of the Holder.

#### 6.08 COLLECTION SUIT BY TRUSTEE.

If an Event of Default specified in **Section 6.01(i)** or **(ii)** occurs and is continuing, the Trustee may recover judgment in its own name and as trustee of an express trust against the Company for the whole amount due with respect to the Securities including any unpaid and accrued interest and the amounts provided for in **Section 7.07**.

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#### 6.09 TRUSTEE MAY FILE PROOFS OF CLAIM.



The Trustee may file such proofs of claim and other papers or documents as may be necessary or advisable in order to have the claims of the Trustee, any predecessor Trustee and the Securityholders allowed in any judicial proceedings relative to the Company or its creditors or properties.

The Trustee may collect and receive any moneys or other property payable or deliverable on any such claims and to distribute the same, and any custodian, receiver, assignee, trustee, liquidator, sequestrator or similar official in any judicial proceeding is hereby authorized by each Holder to make such payments to the Trustee and, in the event that the Trustee shall consent to the making of such payments directly to the Holders, to pay the Trustee any amount due it for the reasonable compensation, expenses, disbursements and advances of the Trustee, its agents and counsel, and any other amounts due the Trustee under **Section 7.07**.

Nothing herein contained shall be deemed to authorize the Trustee to authorize or consent to or accept or adopt on behalf of any Holder any plan of reorganization, arrangement, adjustment or composition affecting the Securities or the rights of any Holder thereof, or to authorize the Trustee to vote in respect of the claim of any Holder in any such proceeding.

#### 6.10 PRIORITIES.

If the Trustee collects any money pursuant to this **Article VI**, it shall pay out the money in the following order:

First: to the Trustee for amounts due under **Section 7.07**;

Second: to holders of Senior Indebtedness to the extent required by **Article XI**;

Third: to Securityholders for all amounts due and unpaid on the Securities, without preference or priority of any kind, according to the amounts due and payable on the Securities; and

Fourth: to the Company.

The Trustee, upon prior written notice to the Company may fix a record date and payment date for any payment by it to Securityholders pursuant to this **Section 6.10**.

#### 6.11 UNDERTAKING FOR COSTS.

In any suit for the enforcement of any right or remedy under this Indenture or in any suit against the Trustee for any action taken or omitted by it as Trustee, a court in its discretion may require the filing by any party litigant in the suit other than the Trustee of an undertaking to pay the costs of the suit, and the court in its discretion may assess reasonable costs, including reasonable attorneys' fees, against any party litigant in the suit, having due regard to the merits and good faith of the claims or defenses made by the party litigant. This **Section 6.11** does not

apply to a suit by the Trustee, a suit by a Holder pursuant to **Section 6.07** or a suit by Holders of more than 10% in aggregate principal amount of the outstanding Securities.

## VII. TRUSTEE

#### 7.01 DUTIES OF TRUSTEE.

(A) If an Event of Default has occurred and is continuing, the Trustee shall exercise such of the rights and powers vested in it by this Indenture, and use the same degree of care and skill in their exercise, as a prudent person would exercise or use under the circumstances in the conduct of his or her own affairs.

(B) Except during the continuance of an Event of Default:

(i) the Trustee need perform only those duties that are specifically set forth in this Indenture and no others; and

(ii) in the absence of bad faith, willful misconduct or negligence on its part, the Trustee may conclusively rely, as to the truth of the statements and the correctness of the opinions expressed therein, upon certificates or opinions furnished to the Trustee and conforming to the requirements of this Indenture; but in the case of any such certificates or opinions which by any provision hereof are specifically required to be furnished to the Trustee, the Trustee shall examine the certificates and opinions to determine whether or not they conform to the requirements of this Indenture.

(C) The Trustee may not be relieved from liability for its own negligent action, its own negligent failure to act or its own willful misconduct, except that:

(i) the Trustee shall not be liable for any error of judgment made in good faith by a Trust Officer, unless it is proved that the Trustee was negligent in ascertaining the pertinent facts; and

(ii) the Trustee shall not be liable with respect to any action it takes or omits to take in good faith in accordance with a direction received by it pursuant to **Section 6.05**.

(D) The Trustee may refuse to perform any duty or exercise any right or power unless it receives indemnity reasonably satisfactory to it against any loss, liability or expense.

(E) Every provision of this Indenture that in any way relates to the Trustee is subject to the provisions of this **Section 7.01**.

(F) The Trustee shall not be liable for interest on any money received by it except as the Trustee may agree in writing with the Company. Money held in trust by the Trustee need not be segregated from other funds except to the extent required by law.

## 7.02 RIGHTS OF TRUSTEE.

(A) The Trustee may rely and shall be protected in acting or refraining from acting upon any written resolution, certificate, statement, instrument, opinion, report, notice, request, direction, consent order, bond, debenture, note, other evidence of indebtedness or other prepared document believed by it to be genuine and to have been signed or presented by the proper person. The Trustee need not investigate any fact or matter stated in the document; if, however, the Trustee shall determine to make such further inquiry or investigation, it shall be entitled during normal business hours to examine the relevant books, records and premises of the Company, personally or by agent or attorney upon reasonable prior notice.

(B) Before the Trustee acts or refrains from acting, it may require an Officers' Certificate and/or an Opinion of Counsel. The Trustee shall not be liable for any action it takes or omits to take in good faith in reliance on such Officers' Certificate or Opinion of Counsel.

(C) Any request or direction of the Company mentioned herein shall be sufficiently evidenced by a Company Request or Company Order and any resolution of the Board of Directors shall be sufficiently evidenced by a Board Resolution.

(D) The Trustee may consult with counsel selected by it (such counsel to be reasonably acceptable to the Company) and the written advice of such counsel or any Opinion of Counsel shall be full and complete authorization and protection in respect of any action taken, suffered or omitted by it hereunder in good faith and in reliance thereon.

(E) The Trustee may act through agents or attorneys and shall not be responsible for the misconduct or negligence of any agent or attorney appointed with due care.

(F) The Trustee shall not be liable for any action it takes or omits to take in good faith which it believes to be authorized or within its discretion, rights or powers hereunder.

(G) Except with respect to **Section 6.01**, the Trustee shall have no duty to inquire as to the performance of the Company with respect to the covenants contained in **Article IV** or make any investigation into the facts or matters stated in any written resolution, certificate, statement, instrument, opinion, report, notice, request, direction, consent order, bond, debenture, note, other evidence of indebtedness or other prepared document. In addition, the Trustee shall not be deemed to have knowledge of an Event of Default except (i) any Default or Event of Default occurring pursuant to **Sections 6.01(i)** and **6.01(ii)** or (ii) any Default or Event of Default of which the Trustee shall have received written notification or obtained actual knowledge. Delivery of reports, information and documents to the Trustee under **Article IV** (other than **Sections 4.04** and **4.07**) is for informational purposes only and the Trustee's receipt of the foregoing shall not constitute constructive notice of any information contained therein or determinable from information contained therein, including the Company's compliance with any of its covenants hereunder (as to which the Trustee is entitled to rely conclusively on Officers' Certificates).

## 7.03 INDIVIDUAL RIGHTS OF TRUSTEE.

The Trustee in its individual or any other capacity may become the owner or pledgee of Securities and may otherwise deal with the Company or any of its Affiliates with the same rights it would have if it were not Trustee. Any Agent may do the same with like rights. The Trustee, however, must comply with **Sections 7.10** and **7.11**.

## 7.04 TRUSTEE'S DISCLAIMER.

The Trustee makes no representation as to the validity or adequacy of this Indenture or the Securities; it shall not be accountable for the Company's use of the proceeds from the Securities; and it shall not be responsible for any statement in the Securities (other than its certificate of authentication), in any offering statement or in the Indenture or in the determination as to which beneficial owners are entitled to receive any notices hereunder.

## 7.05 NOTICE OF DEFAULTS.

If a Default or Event of Default occurs and is continuing as to which the Trustee has received notice pursuant to **Section 4.07**, the Trustee shall mail to each Securityholder a notice of the Default or Event of Default within 30 days after it is known to the Trustee unless such Default or Event of Default has been cured or waived. Except in the case of a Default or Event of Default in payment of any amounts due with respect to any Security, the Trustee may withhold the notice if and so long as it in good faith determines that withholding the notice is in the interests of Securityholders. The Trustee shall not be deemed to have knowledge of a Default or Event of Default unless an officer of the Trustee has received written notice or obtained actual knowledge of such Default or Event of Default.

## 7.06 REPORTS BY TRUSTEE TO HOLDERS.

Within 60 days after each May 15 beginning with May 15, 2002, the Trustee shall mail to each Securityholder if required by TIA § 313(a) a brief report dated as of such May 15 that complies with TIA § 313(c). In such event, the Trustee also shall comply with TIA § 313(b).

A copy of each report at the time of its mailing to Securityholders shall be mailed to the Company and filed by the Trustee with the SEC and each stock exchange, if any, on which the Securities are listed. The Company shall promptly notify the Trustee when the Securities are listed on any stock exchange.

## 7.07 COMPENSATION AND INDEMNITY.

The Company shall pay to the Trustee from time to time such compensation for its services as shall be agreed upon in writing. The Trustee's compensation shall not be limited by any law on compensation of a trustee of an express trust. The Company shall reimburse the Trustee upon request for all reasonable out-of-pocket expenses incurred by it. Such expenses shall include the reasonable compensation and out-of-pocket expenses of the Trustee's agents and counsel.

The Company shall indemnify the Trustee and hold it harmless against any loss or liability or expense (including the reasonable fees and expenses of counsel) incurred by it in connection with the acceptance or administration of this trust and the performance of its duties hereunder, including the reasonable costs and expenses of defending itself against any claim or liability in connection with the exercise or performance of any of its powers and duties hereunder. The Company need not pay for any settlement made without its consent. The Trustee shall notify the Company promptly of any claim for which it may seek indemnification. The Company need not reimburse any expense or indemnify against any loss or liability incurred by the Trustee through the Trustee's negligence, bad faith or willful misconduct.

To secure the Company's payment obligations in this **Section 7.07**, the Trustee shall have a lien prior to the Securities on all money or property held or collected by the Trustee, except that held in trust to pay amounts due on particular Securities.

The indemnity obligations of the Company with respect to the Trustee provided for in this **Section 7.07** shall survive any resignation or removal of the Trustee and the discharge of this Indenture.

When the Trustee incurs expenses or renders services after an Event of Default specified in **Section 6.01(iv)** or **(v)** occurs, the expenses and the compensation for the services are intended to constitute expenses of administration under any Bankruptcy Law, insolvency or similar law now or hereafter in effect.

#### 7.08 **REPLACEMENT OF TRUSTEE.**

A resignation or removal of the Trustee and appointment of a successor Trustee shall become effective only upon the successor Trustee's acceptance of appointment as provided in this **Section 7.08**.

The Trustee may resign by so notifying the Company in writing 30 business days prior to such resignation. The Holders of a majority in aggregate principal amount of the Securities then outstanding may remove the Trustee by so notifying the Trustee and the Company in writing and may appoint a successor Trustee with the Company's consent. The Company may remove the Trustee if:

- (i) the Trustee fails to comply with **Section 7.10**;
- (ii) the Trustee is adjudged a bankrupt or an insolvent;
- (iii) a receiver or other public officer takes charge of the Trustee or its property; or
- (iv) the Trustee becomes incapable of acting.

If the Trustee resigns or is removed or if a vacancy exists in the office of Trustee for any reason, the Company shall promptly appoint a successor Trustee. Within one year after the successor Trustee takes office, the Holders of a majority in aggregate principal amount of the

Securities then outstanding may appoint a successor Trustee to replace the successor Trustee appointed by the Company.

If a successor Trustee does not take office within 30 days after the retiring Trustee resigns or is removed, the retiring Trustee, the Company or the Holders of at least 10% in aggregate principal amount of the outstanding Securities may petition any court of competent jurisdiction for the appointment of a successor Trustee.

If the Trustee fails to comply with **Section 7.10**, any Holder may petition any court of competent jurisdiction for the removal of the Trustee and the appointment of a successor Trustee.

A successor Trustee shall deliver a written acceptance of its appointment to the retiring Trustee and to the Company. Thereupon the resignation or removal of the retiring Trustee shall become effective, and the successor Trustee shall have all the rights, powers and duties of the Trustee under this Indenture. The successor Trustee shall mail a notice of its succession to Securityholders. The retiring Trustee shall promptly transfer all property held by it as Trustee to the successor Trustee, subject to the lien provided for in **Section 7.07**.

#### 7.09 **SUCCESSOR TRUSTEE BY MERGER, ETC.**

If the Trustee consolidates with, merges or converts into, or transfers all or substantially all of its corporate trust business to, another corporation, the successor corporation without any further act shall be the successor Trustee, if such successor corporation is otherwise eligible hereunder.

7.10 **ELIGIBILITY; DISQUALIFICATION.**

This Indenture shall always have a Trustee who satisfies the requirements of TIA § 310(a)(1). The Trustee shall always have or be a member of a Bank Holding Company having a combined capital and surplus of at least \$50,000,000 as set forth in its most recent published annual report of condition. The Trustee shall comply with TIA § 310(b).

7.11 **PREFERENTIAL COLLECTION OF CLAIMS AGAINST COMPANY.**

The Trustee shall comply with TIA § 311(a), excluding any creditor relationship listed in TIA § 311(b). A Trustee who has resigned or been removed shall be subject to TIA § 311(a) to the extent indicated.

**VIII. DISCHARGE OF INDENTURE**

8.01 **TERMINATION OF THE OBLIGATIONS OF THE COMPANY.**

The Company may terminate all of its obligations under this Indenture if all Securities previously authenticated and delivered (other than mutilated, destroyed, lost or stolen Securities which have been replaced or paid as provided in **Section 2.07**) have been delivered to the Trustee for cancellation or if:

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(i) the Securities mature within one year or all of them are to be called for redemption within one year under arrangements reasonably satisfactory to the Trustee for giving the notice of redemption;

(ii) the Company irrevocably deposits in trust with the Trustee money or U.S. Government Obligations, or Common Stock with respect to any Make-Whole Payment, sufficient to pay the principal or Redemption Price or Provisional Redemption Price, if applicable, of and any unpaid and accrued interest on the Securities to maturity or redemption, as the case may be. Immediately after making the deposit, the Company shall give notice of such event to the Securityholders;

(iii) the Company has paid or caused to be paid all sums then payable by the Company to the Trustee hereunder as of the date of such deposit; and

(iv) the Company has delivered to the Trustee an Opinion of Counsel and an Officers' Certificate stating that all conditions precedent provided for herein relating to the satisfaction and discharge of this Indenture have been complied with. The Company may make the deposit only during the one-year period and only if **Article XI** permits it.

However, the Company's obligations in **Sections 2.02, 2.03, 2.04, 2.05, 2.06, 2.07, 2.08, 2.15, 2.16, 2.17, 4.01, 4.02, 7.07 and 7.08 and Article VIII and Article X** shall survive until the Securities are no longer outstanding. Thereafter the obligations of the Company in **Sections 7.07 and 8.03** shall survive.

After a deposit pursuant to this **Section 8.01**, the Trustee upon request shall acknowledge in writing the discharge of the obligations of the Company under the Securities and this Indenture except for those surviving obligations specified above.

In order to have money available on a payment date to pay the principal or Redemption Price or Provisional Redemption Price, if applicable, of and any unpaid and accrued interest on the Securities, the U.S. Government Obligations shall be payable as to principal and any unpaid and accrued interest on or before such payment date in such amounts as will provide the necessary money.

"**U.S. Government Obligations**" means direct non-callable obligations of, or non-callable obligations guaranteed by, the United States of America for the payment of which the full faith and credit of the United States of America is pledged.

8.02 **APPLICATION OF TRUST MONEY.**

The Trustee shall hold in trust money or U.S. Government Obligations deposited with it pursuant to **Section 8.01**. It shall apply the deposited money and the money from U.S. Government Obligations through the Paying Agent and in accordance with this Indenture to the payment of the principal or Redemption Price or Provisional Redemption Price, if applicable, of and any unpaid and accrued interest on the Securities. Money and securities so held in trust are not subject to the subordination provisions of **Article XI**.

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8.03 **REPAYMENT TO COMPANY.**

The Trustee and the Paying Agent shall promptly notify the Company of, and pay to the Company upon the written request of the Company, any excess money or securities held by them at any time. The Trustee and the Paying Agent shall pay to the Company upon the written request of the Company any money held by them for the payment of the principal or Redemption Price or Provisional Redemption Price, if applicable, of and any unpaid and accrued interest that remains unclaimed for two years or such shorter period under applicable state escheat laws; *provided, however*, that the Trustee or such Paying Agent, before being required to make any such repayment, may, at the expense and request of the Company, cause to be published once in a newspaper of general circulation in the City of New York or cause to be mailed to each Holder, notice stating that such money remains and that, after a date specified therein,

which shall not be less than 30 days from the date of such publication or mailing, any unclaimed balance of such money then remaining will be repaid to the Company. After payment to the Company, Securityholders entitled to the money must look to the Company for payment as general creditors unless an applicable abandoned property law designates another person.

#### 8.04 REINSTATEMENT.

If the Trustee or Paying Agent is unable to apply any money or U.S. Government Obligations in accordance with **Sections 8.01** and **8.02** by reason of any legal proceeding or by reason of any order or judgment of any court or governmental authority enjoining, restraining or otherwise prohibiting such application, the obligations of the Company under this Indenture and the Securities shall be revived and reinstated as though no deposit had occurred pursuant to **Sections 8.01** and **8.02** until such time as the Trustee or Paying Agent is permitted to apply all such money or U.S. Government Obligations in accordance with **Sections 8.01** and **8.02**; *provided, however*, that if the Company has made any payment of amounts due with respect to any Securities because of the reinstatement of its obligations, the Company shall be subrogated to the rights of the Holders of such Securities to receive such payment from the money or U.S. Government Obligations held by the Trustee or Paying Agent.

### IX. AMENDMENTS

#### 9.01 WITHOUT CONSENT OF HOLDERS.

The Company, with the consent of the Trustee, may amend or supplement this Indenture or the Securities without notice to or the consent of any Securityholder:

- (i) to cure any ambiguity, defect, omission or inconsistency that does not adversely affect the rights of any Securityholder;
- (ii) to comply with **Sections 5.01** and **10.12**;
- (iii) to make any changes or modifications to this Indenture necessary in connection with the registration of the Securities under the Securities Act and the qualification of the Indenture under the TIA;

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- (iv) to provide for uncertificated Securities in addition to certificated Securities;
- (v) to secure the obligations of the Company in respect of the Securities;
- (vi) to add to the covenants of the Company for the benefit of the Holders or to surrender any right or power conferred upon the Company; or
- (vii) to make any change that does not adversely affect the rights of any Securityholder.

#### 9.02 WITH CONSENT OF HOLDERS.

The Company, with the consent of the Trustee, may amend or supplement this Indenture or the Securities without notice to any Securityholder but with the written consent of the Holders of at least a majority in aggregate principal amount of the outstanding Securities. Subject to **Section 6.07**, the Holders of a majority in aggregate principal amount of the outstanding Securities may waive compliance by the Company with any provision of this Indenture or the Securities without notice to any other Securityholder. However, without the consent of each Securityholder affected, an amendment, supplement or waiver, including a waiver pursuant to **Section 6.04**, may not:

- (i) reduce the principal amount of Securities whose Holders must consent to an amendment, supplement or waiver under this Indenture or to the waiver of defaults or compliance hereunder;
- (ii) reduce the rate of accrual of interest or change the time for payment of interest on any Security;
- (iii) reduce the principal, Redemption Price, Provisional Redemption Price, if applicable, or Repurchase Price of or change the fixed maturity of any Security (including, without limitation, the optional redemption provisions);
- (iv) make any Security payable in currency or securities other than as stated in such Security;
- (v) waive a default in the payment of any amount due with respect to any Security;
- (vi) make any change in **Section 6.04**, **6.07** or **9.02**; or
- (vii) change the right to convert, or receive payment with respect to, any Security or the right to institute suit for the enforcement of any payment with respect to, or conversion of, any Security or the right to require the Company to repurchase any of the Securities upon a Change in Control.

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An amendment under this **Section 9.02** may not make any change that adversely affects the rights under **Article XI** of any holder of Senior Indebtedness unless the holders of such Senior Indebtedness pursuant to its terms consent to the change.

Promptly after an amendment under this **Section 9.02** becomes effective, the Company shall mail to Securityholders a notice briefly describing the amendment. Any failure of the Company to mail such notice shall not in any way impair or affect the validity of such amendment, supplement or waiver.

It shall not be necessary for the consent of the Holders under this **Section 9.02** to approve the particular form of any proposed amendment or supplement, but it shall be sufficient if such consent approves the substance thereof.

#### 9.03 **COMPLIANCE WITH TRUST INDENTURE ACT.**

Every amendment, waiver or supplement to this Indenture or the Securities shall comply with the TIA as then in effect.

#### 9.04 **REVOCATION AND EFFECT OF CONSENTS.**

Until an amendment, supplement or waiver becomes effective, a consent to it by a Holder is a continuing consent by the Holder and every subsequent Holder of a Security or portion of a Security that evidences the same debt as the consenting Holder's Security, even if notation of the consent is not made on any Security. However, any such Holder or subsequent Holder may revoke the consent as to its Security or portion of a Security if the Trustee receives the notice of revocation before the date the amendment, supplement or waiver becomes effective. An amendment, supplement or waiver becomes effective in accordance with its terms and thereafter binds every Securityholder.

After an amendment, supplement or waiver becomes effective with respect to the Securities, it shall bind every Securityholder unless it makes a change described in **Section 9.02**. In that case, the amendment, supplement or waiver shall bind each Holder of a Security who has consented to it and, provided that notice of such amendment, supplement or waiver is reflected on a Security that evidences the same debt as the consenting Holder's Security, every subsequent Holder of a Security or portion of a Security that evidences the same debt as the consenting Holder's Security.

#### 9.05 **NOTATION ON OR EXCHANGE OF SECURITIES.**

If an amendment, supplement or waiver changes the terms of a Security, the Trustee may require the Holder of the Security to deliver it to the Trustee. The Trustee may place an appropriate notation on the Security as directed and prepared by the Company about the changed terms and return it to the Holder. Alternatively, if the Company so determines, the Company in exchange for the Security shall issue and the Trustee shall authenticate a new Security that reflects the changed terms.

#### 9.06 **TRUSTEE PROTECTED.**

The Trustee need not sign any amendment, supplement or waiver authorized pursuant to this **Article IX** that adversely affects the Trustee's rights, duties, liabilities or responsibilities, unless the Trustee receives indemnity reasonably satisfactory to it against any loss, liability or expense. The Trustee shall be entitled to receive and be protected in relying upon an Opinion of Counsel and an Officers' Certificate stating that any supplemental indenture, amendment or waiver complies with the Indenture.

#### 9.07 **EFFECT OF SUPPLEMENTAL INDENTURE.**

Upon execution of any supplemental indenture under this **Article IX**, this Indenture shall be modified in accordance therewith, and such supplemental indenture shall form a part of this Indenture for all purposes and every Holder of Securities theretofore or thereafter authenticated and delivered hereunder shall be bound thereto.

### X. **CONVERSION**

#### 10.01 **CONVERSION PRIVILEGE; RESTRICTIVE LEGENDS.**

A Holder of a Security may convert such Security into Common Stock at any time during the period stated in **paragraph 9** of the Securities. The initial conversion rate is stated in **paragraph 9** of the Securities. The conversion rate is subject to adjustment in accordance with **Sections 10.06** through **10.12**.

A Holder may convert a portion of the principal of such Security if the portion is \$1,000 principal amount or a positive integral multiple of \$1,000 principal amount. Provisions of this Indenture that apply to conversion of all of a Security also apply to conversion of a portion of it.

Any shares issued upon conversion of a Security shall bear the Private Placement Legend until after the second anniversary of the later of the issue date for the Securities and the last date on which the Company or any Affiliate of the Company was the owner of such shares or the Security (or any predecessor security) from which such shares were converted (or such shorter period of time as permitted by Rule 144(k) under the Securities Act or any successor provision thereunder) (or such longer period of time as may be required under the Securities Act or applicable state securities laws in the Opinion of Counsel for the Company, unless otherwise agreed by the Company and the Holder thereof).

#### 10.02 **CONVERSION PROCEDURE.**

To convert a Security, a Holder must satisfy the requirements in **paragraph 9** of the Securities. The "conversion date" is the first business day on which the Holder satisfies all those requirements. As soon as practicable after the conversion date, the Company shall deliver to the Holder through the Conversion Agent a certificate for the number of full shares of Common Stock issuable upon the conversion and a check in lieu of any fractional share determined in accordance with **Section 10.03**. The person in whose name the certificate is registered shall be treated as a stockholder of record on and after the conversion date.

Except as described below, no payment or adjustment will be made for accrued interest on, or liquidated damages with respect to, a converted Security or for dividends on any Common Stock issued on or prior to conversion. If any Holder surrenders a Security for conversion after the close of business on the record date for the payment of an installment of interest and prior to the opening of business on the next interest payment date, then, notwithstanding such conversion, the interest payable on such interest payment date shall be paid to the Holder of such Security on such record date; *provided, however*, that such Security, when surrendered for conversion, must be accompanied by payment to the Trustee on behalf of the Company of an amount equal to the interest payable on such interest payment date on the portion so converted; *provided further, however*, that such payment to the Trustee described in the immediately preceding proviso shall not be required in connection with any conversion of a Security that occurs on or after the date that the Company has issued a notice of redemption pursuant to **Section 3.04** hereof and prior to the date of such redemption.

If a Holder converts more than one Security at the same time, the number of full shares issuable upon the conversion shall be based on the total principal amount of the Securities converted.

Upon surrender of a Security that is converted in part, the Company shall execute and the Trustee shall authenticate for and deliver to the Holder a new Security in an authorized denomination equal in principal amount to the unconverted portion of the Security surrendered.

If the last day on which a Security may be converted is not a business day or is a Legal Holiday in a place where a Conversion Agent is located, the Security may be surrendered to that Conversion Agent on the next succeeding business day that is not a Legal Holiday.

#### 10.03 FRACTIONAL SHARES.

The Company will not issue fractional shares of Common Stock upon conversion of Securities and instead will deliver a check in an amount equal to the value of such fraction computed on the basis of the last sale price of the Common Stock as reported on the NNM (or if not listed for trading thereon, then on the principal securities exchange or on the principal automated quotation system on which the Common Stock is listed or admitted to trading) at the close of business on the date of conversion or if no such sale takes place on such day, the last sale price for such day shall be the average of the closing bid and asked prices regular way on the NNM (or if not listed for trading thereon, on the principal securities exchange or on the principal automated quotation system on which the Common Stock is listed or admitted to trading) for such day. If on the date of conversion, the Common Stock is not quoted by any such organization, the fair value of such Common Stock on such day, as reasonably determined in good faith by the Board of Directors shall be used.

#### 10.04 TAXES ON CONVERSION.

If a Holder converts its Security, the Company shall pay any documentary, stamp or similar issue or transfer tax due on the issue of shares of Common Stock upon the conversion. However, the Holder shall pay any such tax which is due because the shares are issued in a name other than the Holder's name.

#### 10.05 COMPANY TO PROVIDE STOCK.

The Company shall prior to the issuance of any Securities reserve out of its authorized but unissued Common Stock or Common Stock held in its treasury enough shares of Common Stock to permit the conversion of all of the Securities.

All shares of Common Stock which may be issued upon conversion of the Securities shall be duly authorized, validly issued, fully paid and non-assessable, and shall be free from preemptive rights and free of any liens and adverse claims.

The Company will endeavor to comply with all securities laws regulating the offer and delivery of shares of Common Stock upon conversion of Securities and will endeavor to list such shares on each national securities exchange or automated quotation system on which the Common Stock is listed.

#### 10.06 ADJUSTMENT OF CONVERSION RATE.

The conversion rate shall be subject to adjustment from time to time as follows:

(a) In case the Company shall (1) pay a dividend in shares of Common Stock to all holders of Common Stock, (2) make a distribution in shares of Common Stock to all holders of Common Stock, (3) subdivide the outstanding shares of Common Stock into a greater number of shares of Common Stock or (4) combine the outstanding shares of Common Stock into a smaller number of shares of Common Stock, the conversion rate in effect immediately prior to such action shall be adjusted so that the holder of any Security thereafter surrendered for conversion shall be entitled to receive the number of shares of Common Stock which he would have owned immediately following such action had such Securities been converted immediately prior thereto. Any adjustment made pursuant to this **Section 10.06(a)** shall become effective immediately after the record date in the case of a dividend or distribution and shall become effective immediately after the effective date in the case of a subdivision or combination.

(b) In case the Company shall issue rights or warrants to all holders of Common Stock, entitling them (for a period commencing no earlier than the record date for the determination of Holders of Common Stock entitled to receive such rights or warrants and expiring not more than 60 days after such record date) to subscribe for or purchase shares of Common Stock (or securities convertible into Common Stock), at a price per share less than the then current market price (as determined pursuant to **Section 10.06(f)** below) of Common Stock on such record date, the conversion rate shall be increased by multiplying the conversion rate in effect immediately prior to such record date by a fraction of which the numerator shall be the number of shares of Common Stock, outstanding on such record date, plus the number of shares of Common Stock so offered for subscription or

purchase and the denominator of which shall be the number of shares of Common Stock outstanding at the close of business on such record date plus the number of shares of Common Stock which the aggregate of the offering price of the total

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number of shares of Common Stock so offered for subscription or purchase would purchase at such current market price. Such adjustments shall become effective immediately after such record date.

(c) In case the Company shall distribute to all holders of Common Stock shares of capital stock of the Company other than Common Stock, evidences of indebtedness or other assets (other than cash dividends out of current or retained earnings), or shall distribute to substantially all holders of Common Stock rights or warrants to subscribe for securities (other than those referred to in **Section 10.06(b)** above), then in each such case the conversion rate shall be increased by multiplying the conversion rate in effect immediately prior to the close of business on the record date for the determination of shareholders entitled to such distribution by a fraction of which the numerator shall be the current market price of Common Stock (determined as provided in **subsection (f)** below), on such date and the denominator shall be such current market price less the fair market value (as determined by the Board of Directors whose determination shall be conclusive and described in a Board Resolution) on such date of the portion of the evidences of indebtedness, shares of capital stock, cash and other assets to be distributed or of such subscription rights or warrants applicable to one share of Common Stock such increase to become effective immediately prior to the opening of business on the day following such record date. Notwithstanding the foregoing, in the event that the Company shall distribute rights or warrants (other than those referred to in **Section 10.06(b)** above) ("**Rights**") *pro rata* to holders of Common Stock, the Company may, in lieu of making any adjustment pursuant to this **Section 10.06(c)**, make proper provision so that each Holder of a Security who converts such Security (or any portion thereof) after the record date for such distribution and prior to the expiration or redemption of the Rights shall be entitled to receive upon such conversion, in addition to the shares of Common Stock issuable upon such conversion (the "**Conversion Shares**"), a number of Rights to be determined as follows: (i) if such conversion occurs on or prior to the date for the distribution to the holders of Rights of separate certificates evidencing such Rights (the "**Distribution Date**"), the same number of Rights to which a holder of a number of shares of Common Stock equal to the number of shares of Conversion Shares is entitled at the time of such conversion in accordance with the terms and provisions of and applicable to the Rights; and (ii) if such conversion occurs after the Distribution Date, the same number of Rights to which a holder of the number of shares of Common Stock into which the principal amount of the Security so converted was convertible immediately prior to the Distribution Date would have been entitled on the Distribution Date in accordance with the terms and provisions of and applicable to the Rights; *provided, however*, that in the event such fair market value on such record date of the portion of the distributed evidences of indebtedness, shares of capital stock and other assets or subscription rights or warrants so applicable to one share of Common Stock is equal to or greater than such current market price of the Common Stock on such record date, in lieu of the foregoing adjustment, adequate provision shall be made so that each Holder shall have the right to receive upon conversion of a Security (or any portion thereof) the amount of distributed

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evidences of indebtedness, shares of capital stock and other assets or subscription rights or warrants such Holder would have received had such Holder converted such Security (or any portion thereof) immediately prior to such record date. In the event that such dividend or distribution is not so paid or made, the conversion rate shall again be adjusted to be the conversion rate which would then be in effect if such dividend or distribution had not been declared.

(d) In case the Company shall, by dividend or otherwise, at any time make a distribution (the "**Triggering Distribution**," and the amount of the Triggering Distribution, together with the sum of (w) and (x) below, the "**Combined Amount**") to all or substantially all holders of its Common Stock of cash (including any distributions of cash out of current or retained earnings of the Company, but excluding any cash that is distributed as part of a distribution requiring a conversion rate adjustment pursuant to this **subsection (d)**) in an aggregate amount that, together with the sum of (w) the aggregate amount of any cash and the fair market value (as determined in good faith by the Board of Directors, whose determination shall be conclusive thereof and described in a Board Resolution), as of the expiration of the tender or exchange offer referred to below, of any other consideration payable in respect of any tender or exchange offer by the Company or a subsidiary of the Company for all or any portion of the Common Stock consummated within the 12 months preceding the date of payment of the Triggering Distribution and in respect of which no conversion rate adjustment has been made pursuant to this **Section 10.06**, and (x) the aggregate amount of all other cash distributions to all or substantially all holders of Common Stock made within the 12 months preceding the date of payment of the Triggering Distribution and in respect of which no conversion rate adjustment has been made pursuant to this **Section 10.06**, exceeds 10% of the product of the current market price per share (as determined in accordance with **subsection (f)** of this **Section 10.06**) of the Common Stock on the close of business, New York City time, on the business day (the "**Distribution Declaration Date**") immediately preceding the day on which the Triggering Distribution is declared by the Company and the number of shares of Common Stock outstanding on the Distribution Declaration Date (excluding shares held in the treasury of the Company), the conversion rate shall be adjusted by multiplying the conversion rate in effect immediately prior to the effectiveness of the conversion rate adjustment contemplated by this **subsection (d)** by a fraction (y) which denominator is such current market price per share of Common Stock less a quotient which dividend is the Combined Amount and which divisor is such number of shares of Common Stock outstanding, and (z) which numerator is such current market price per share of Common Stock. Such adjustment shall become effective immediately prior to the opening of business on the day following the Distribution Declaration Date.

(e) In case a tender or exchange offer made by the Company or any subsidiary of the Company for all or any portion of the Common Stock shall expire and such tender or exchange offer (as amended through the expiration thereof) shall involve the payment of aggregate consideration in an amount



(determined as the sum of the aggregate amount of cash consideration and the aggregate fair market value (as determined in good faith by the Board of Directors, whose determination shall be conclusive thereof and described in a Board Resolution), as of the last time (the “**Expiration Time**,” and the date of the Expiration Time, the “**Expiration Date**”) tenders or exchanges may have been made pursuant to such tender or exchange offer (as it may be amended), of any other consideration) that, together with the sum of (u) the aggregate amount of any cash and the fair market value (as determined in good faith by the Board of Directors, whose determination shall be conclusive thereof and described in a Board Resolution), as of the expiration of the other tender or exchange offer referred to below, of any other consideration payable in respect of any other tender or exchange offer by the Company or a subsidiary of the Company for all or any portion of the Common Stock consummated within the 12 months preceding the Expiration Date and in respect of which no conversion rate adjustment has been made pursuant to this **Section 10.06** and (v) the aggregate amount of other all-cash distributions to all or substantially all holders of Common Stock made within the 12 months preceding the Expiration Date and in respect of which no conversion rate adjustment has been made pursuant to this **Section 10.06**, exceeds 10% of the product of the current market price per share (as determined in accordance with **subsection (f)** of this **Section 10.06**) of the Common Stock on the close of business, New York City time, on the Expiration Date and the number of shares of Common Stock outstanding at the Expiration Time (including any tendered or exchanged shares but excluding shares held in the treasury of the Company), the conversion rate shall be adjusted by multiplying the conversion rate in effect immediately prior to the effectiveness of the conversion rate adjustment contemplated by this **subsection (e)** by a fraction which numerator is the sum of (w) the amount of the aggregate consideration (determined as aforesaid) payable to stockholders based on the acceptance (up to any maximum specified in the terms of the tender or exchange offer) of all shares validly tendered or exchanged and not withdrawn as of the Expiration Time (the shares deemed so accepted, up to any such maximum, the “**Purchased Shares**”) and (x) the product of such number of shares of Common Stock outstanding less the number of Purchased Shares, and the current market price per share (as determined in accordance with **subsection (f)** of this **Section 10.06**) of Common Stock on the close of business, New York City time, on the trading day next succeeding the Expiration Date, and which denominator is the product of (y) such number of shares of Common Stock outstanding and (z) the current market price per share (as determined in accordance with **subsection (f)** of this **Section 10.06**) of Common Stock on the close of business, New York City time, on the trading day next succeeding the Expiration Date. Such adjustment shall become effective immediately prior to the opening of business on the day following the Expiration Date. If the Company is obligated to purchase shares pursuant to any such tender or exchange offer, but the Company is permanently prevented by applicable law from effecting any or all such purchases, or any or all such purchases are rescinded, then the conversion rate shall again be adjusted to be the conversion rate that would have been in effect based upon the number of shares actually

purchased. If the application of this **subsection (e)** to any tender or exchange offer would result in a decrease in the conversion rate, then no adjustment shall be made for such tender or exchange offer under this **subsection (e)**.

(f) For the purpose of any computation under **subsections (a), (b), (c), (d)** and **(e)** above of this **Section 10.06**, the current market price per share of Common Stock on the date fixed for determination of the stockholders entitled to receive the issuance or distribution requiring such computation (the “**Determination Date**”) shall be deemed to be the average of the Daily Market Prices for the ten consecutive trading days immediately preceding the Determination Date; *provided, however*, that (i) if the “ex” date for any event (other than the issuance or distribution requiring such computation) that requires an adjustment to the conversion rate pursuant to **subsection (a), (b), (c), (d)** or **(e)** above occurs on or after the tenth trading day prior to the Determination Date and prior to the “ex” date for the issuance or distribution requiring such computation, the Daily Market Price for each trading day prior to the “ex” date for such other event shall be adjusted by multiplying such Daily Market Price by the reciprocal of the fraction by which the conversion rate is so required to be adjusted as a result of such other event, (ii) if the “ex” date for any event (other than the issuance or distribution requiring such computation) that requires an adjustment to the conversion rate pursuant to **subsection (a), (b), (c), (d)** or **(e)** above occurs on or after the “ex” date for the issuance or distribution requiring such computation and on or prior to the Determination Date, the Daily Market Price for each business day on and after the “ex” date for such other event shall be adjusted by multiplying such Daily Market Price by the same fraction by which the conversion rate is so required to be adjusted as a result of such other event, and (iii) if the “ex” date for the issuance or distribution requiring such computation is on or prior to the Determination Date, after taking into account any adjustment required pursuant to clause (i) or (ii) of this proviso, the Daily Market Price for each trading day on and after the “ex” date shall be adjusted by adding thereto the amount of any cash and the fair market value (as determined by the Board of Directors in a manner consistent with any determination of such value for the purposes of this **Section 10.06**, whose determination shall be conclusive and described in a Resolution of the Board of Directors) of the evidences of indebtedness, shares of capital stock or other securities or assets being distributed (in the distribution requiring such computation) applicable to one share of Common Stock as of the close of business on the day before such “ex” date. For the purpose of any computation under **subsection (e)** of this **Section 10.06**, the current market price per share of Common Stock at the expiration time for the tender offer requiring such computation shall be deemed to be the average of the Daily Market Price for the ten consecutive trading days commencing on the business day immediately following the expiration time of such tender offer (the “**Commencement Date**”); *provided, however*, that if the “ex” date for any event (other than the tender offer requiring such computation) that requires an adjustment to the conversion rate pursuant to **subsection (a), (b), (c), (d)** or **(e)** above occurs on or after the expiration time for the tender offer requiring such computation and prior to the day in question, the Daily Market Price for each

trading day on or after to the “ex” date for such other event shall be adjusted by multiplying such Daily Market Price by the same fraction by which the conversion rate is so required to be adjusted as a result of such other event. For purposes of this **subsection**, the term “ex” date, (i) when used with respect to any issuance or distribution, means the first date on which the Common Stock trades regular way on the relevant exchange or in the relevant market from which the Daily Market Price was obtained without the right to receive such issuance or distribution, (ii) when used with respect to any subdivision or combination of shares of Common Stock, means the first date on which the Common Stock trades regular way on such exchange or in such market after the time at which such subdivision or combination becomes effective, and (iii) when used with respect to any tender offer means the first date on which the Common Stock trades regular way on such exchange or in such market after the expiration time of such tender offer (as it may be amended or extended).

(g) In addition to the foregoing adjustments in subsections (a), (b), (c), (d) and (e) above, the Company, from time to time and to the extent permitted by law, may increase the conversion rate by any amount for at least 20 business days, if the Board of Directors of the Company has made a determination, which determination shall be conclusive, that such increase would be in the best interest of the Company. The Company shall give notice to the Trustee and cause such notice of such increase to be mailed to each Holder of Securities at such Holder’s address as the same appears on the registry books of the Registrar, at least 15 days prior to the date on which such increase commences.

#### 10.07 NO ADJUSTMENT.

No adjustment in the conversion rate shall be required until cumulative adjustments amount to 1% or more of the conversion rate as last adjusted; *provided, however*, that any adjustments which by reason of this **Section 10.07** are not required to be made shall be carried forward and taken into account in any subsequent adjustment. All calculations under this **Article X** shall be made to the nearest cent or to the nearest one-hundredth of a share, as the case may be. No adjustment need be made for rights to purchase Common Stock pursuant to a Company plan for reinvestment of dividends or interest. No adjustment need be made for a change in the par value of the Common Stock.

If any rights, options or warrants issued by the Company as described in **Section 10.06** are only exercisable upon the occurrence of certain triggering events, then the conversion rate will not be adjusted as provided in **Section 10.06** until the earliest of such triggering event occurs. Upon the expiration or termination of any rights, options or warrants without the exercise of such rights, options or warrants, the conversion rate then in effect shall be adjusted immediately to the conversion rate which would have been in effect at the time of such expiration or termination had such rights, options or warrants, to the extent outstanding immediately prior to such expiration or termination, never been issued.

No adjustment need be made for a transaction referred to in this **Article X** if Securityholders are to participate in the transaction without conversion on a basis and with notice

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that the Board of Directors determines to be fair and appropriate in light of the basis and notice on which holders of Common Stock participate in the transaction.

#### 10.08 OTHER ADJUSTMENTS.

In the event that, as a result of an adjustment made pursuant to **Section 10.06** hereof, the Holder of any Security thereafter surrendered for conversion shall become entitled to receive any shares of Capital Stock other than shares of Common Stock, thereafter the conversion rate of such other shares so receivable upon conversion of any Security shall be subject to adjustment from time to time in a manner and on terms as nearly equivalent as practicable to the provisions with respect to Common Stock contained in this **Article X**.

#### 10.09 ADJUSTMENTS FOR TAX PURPOSES.

The Company may make such increases in the conversion rate, in addition to those required by **Section 10.06** hereof, as the Board of Directors may determine to be advisable in order that any stock dividend, subdivision of shares, distribution or rights to purchase stock or securities or distribution of securities convertible into or exchangeable for stock made by the Company or to its stockholders will not be taxable to the recipients thereof.

#### 10.10 NOTICE OF ADJUSTMENT.

Whenever the conversion rate is adjusted, the Company shall promptly mail to Holders at the addresses appearing on the Registrar’s books a notice of the adjustment and file with the Trustee an Officers’ Certificate briefly stating the facts requiring the adjustment and the manner of computing it. The certificate shall be conclusive evidence of the correctness of such adjustment.

#### 10.11 NOTICE OF CERTAIN TRANSACTIONS.

In the event that:

- (1) the Company takes any action which would require an adjustment in the conversion rate;
- (2) the Company takes any action that would require a supplemental indenture pursuant to **Section 10.12**; or
- (3) there is a dissolution or liquidation of the Company;

a Holder of a Security may wish to convert such Security into shares of Common Stock prior to the record date for or the effective date of the transaction so that he may receive the rights, warrants, securities or assets which a holder of shares of Common Stock on that date may receive. Therefore, the Company shall mail to Holders at the addresses appearing on the Registrar’s books and file with the Trustee and the Conversion Agent a notice stating the proposed record or effective date, as the case may be, of any transaction referred to in **clause (1), (2) or (3)** of this **Section 10.11**. The Company shall mail such notice at least 15 days before such

date; however, failure to mail such notice or any defect therein shall not affect the validity of any transaction referred to in **clause (1), (2) or (3)** of this **Section 10.11**.

#### 10.12 EFFECT OF RECLASSIFICATIONS, CONSOLIDATIONS, MERGERS, BINDING SHARE EXCHANGES OR SALES ON CONVERSION PRIVILEGE.

If any of the following shall occur, namely: (i) any reclassification or change in the Common Stock issuable upon conversion of Securities (other than a change in par value, or from par value to no par value, or from no par value to par value, or as a result of a subdivision or combination), (ii) any consolidation, merger or binding share exchange to which the Company is a party other than a merger in which the Company is the continuing corporation and which does not result in any reclassification of, or change (other than a change in name, or par value, or from par value to no par value, or from no par value to par value or as a result of a subdivision or combination) in, the Common Stock, or (iii) any sale or conveyance of all or substantially all of the property or business of the Company as an entirety, then the Company or such successor or purchasing corporation, as the case may be, shall, as a condition precedent to such reclassification, change, consolidation, merger, binding share exchange, sale or conveyance, execute and deliver to the Trustee a supplemental indenture in form reasonably satisfactory to the Trustee providing that the Holder of each Security then outstanding shall have the right to convert such Security into the kind and amount of shares of stock and other securities and property (including cash) receivable upon such reclassification, change, consolidation, merger, binding share exchange, sale or conveyance by a holder of the number of shares of Common Stock, deliverable upon conversion of such Security immediately prior to such reclassification, change, consolidation, merger, binding share exchange, sale or conveyance. Such supplemental indenture shall provide for adjustments of the conversion rate which shall be as nearly equivalent as may be practicable to the adjustments of the conversion rate provided for in this **Article X**. The foregoing, however, shall not in any way affect the right a Holder of a Security may otherwise have, pursuant to **clause (ii)** of the last sentence of **subsection (c)** of **Section 10.06** hereof, to receive Rights upon conversion of a Security. If, in the case of any such consolidation, merger, binding share exchange, sale or conveyance, the stock or other securities and property (including cash) receivable thereupon by a holder of Common Stock includes shares of stock or other securities and property of a corporation other than the successor or purchasing corporation, as the case may be, in such consolidation, merger, binding share exchange, sale or conveyance, then such supplemental indenture shall also be executed by such other corporation and shall contain such additional provisions to protect the interests of the Holders of the Securities as the Board of Directors shall reasonably consider necessary by reason of the foregoing. The provision of this **Section 10.12** shall similarly apply to successive consolidations, mergers, binding share exchange, sales or conveyances.

In the event the Company shall execute a supplemental indenture pursuant to this **Section 10.12**, the Company shall promptly file with the Trustee an Officers' Certificate briefly stating the reasons therefor, the kind or amount of shares of stock or securities or property (including cash) receivable by Holders of the Securities upon the conversion of their Securities after any such reclassification, change, consolidation, merger, binding share exchange, sale or conveyance and any adjustment to be made with respect thereto.

#### 10.13 TRUSTEE'S DISCLAIMER.

The Trustee has no duty to determine when an adjustment under this **Article X** should be made, how it should be made or what such adjustment should be, but may accept as conclusive evidence of the correctness of any such adjustment, and shall be protected in relying upon the Officers' Certificate with respect thereto which the Company is obligated to file with the Trustee pursuant to **Section 10.10** hereof. The Trustee makes no representation and shall not be accountable as to the validity or value of any securities or assets issued upon conversion of Securities, and the Trustee shall not be responsible for the failure by the Company to comply with any provisions of this **Article X**. Each Conversion Agent shall have the same protection under this **Section 10.13** as the Trustee.

The Trustee has no duty to determine whether a supplemental indenture under **Section 10.12** is needed and shall not be under any responsibility to determine the correctness of any provisions contained in any supplemental indenture executed pursuant to **Section 10.12**, but may accept as conclusive evidence of the correctness thereof, and shall be protected in relying upon, the Officers' Certificate with respect thereto which the Company is obligated to file with the Trustee pursuant to **Section 10.12** hereof.

### XI. SUBORDINATION

#### 11.01 AGREEMENT TO SUBORDINATE.

The Company agrees, and each Securityholder by accepting a Security agrees, that the payment of all amounts due with respect to the Securities is subordinated in right of payment, to the extent and in the manner provided in this **Article XI**, to the prior payment in full of all Senior Indebtedness and that the subordination is for the benefit of the holders of Senior Indebtedness.

Money and securities held in trust pursuant to **Article VIII** are not subject to the subordination provisions of this **Article XI**.

#### 11.02 CERTAIN DEFINITIONS.

"**Indebtedness**" means, with respect to any person, the principal of, and premium, if any, and interest on (a) all indebtedness of such person for borrowed money (including all indebtedness evidenced by notes, bonds, debentures or other securities sold by such person for money), (b) all obligations incurred by such person in the acquisition (whether by way of purchase, merger, consolidation or otherwise and whether by such person or another person) of any business, real property or other assets (except inventory and related items acquired in the ordinary course of the conduct of the acquiror's usual business), (c) direct or indirect guarantees or similar agreements by such person of indebtedness described in clause (a), (b), (e), (f), (g) or (h) of another person, (d) all

renewals, extensions, refundings, deferrals, restructurings, amendments, supplements and modifications of any such indebtedness, obligation or guarantee, (e) all reimbursement obligations and other liabilities, contingent or otherwise, of such person with respect to letters of credit, bankers' acceptances or similar facilities issued for the account of such person, (f) all capital lease obligations of such person, (g) all obligations of such person under interest rate swap, currency exchange or similar agreements of such person and (h) all

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obligations and other liabilities, contingent or otherwise, under any lease or related document, including a purchase agreement, conditional sale or other title retention agreement, in connection with the lease of real property or improvements thereon (or any personal property included as part of any such lease) which provides that such person is contractually obligated to purchase or cause a third party to purchase the leased property or pay an agreed upon residual value of the leased property, including such person's obligations under such lease or related document to purchase or cause a third party to purchase such leased property or pay an agreed upon residual value of the leased property to the lessor.

**"Representative"** means the indenture trustee or other trustee, agent or representative for an issue of Senior Indebtedness.

**"Senior Indebtedness"** means all Indebtedness of the Company outstanding at any time except Indebtedness that by its terms is subordinate in right of payment to the Securities or Indebtedness that is not otherwise senior in right of payment to the Securities. Senior Indebtedness does not include Indebtedness of the Company to any of its subsidiaries.

#### 11.03 LIQUIDATION; DISSOLUTION; BANKRUPTCY.

Upon any distribution of assets to creditors of the Company in a liquidation, winding up or dissolution of the Company, or in a bankruptcy, reorganization, insolvency, receivership or similar proceeding relating to the Company or its properties:

(i) holders of Senior Indebtedness shall be entitled to receive payment in full of the principal of and interest (including interest accruing after the commencement of any such proceeding) to the date of payment on the Senior Indebtedness before Securityholders shall be entitled to receive any payment from the Company of amounts due with respect to the Securities (other than cash payments due upon conversion in lieu of fractional shares in accordance with **Section 10.03**); and

(ii) until the Senior Indebtedness is paid in full, any distribution to which Securityholders would be entitled from the Company but for this **Article XI** shall be made to holders of Senior Indebtedness, as their interests may appear, except the Securityholders may receive securities that are subordinated to Senior Indebtedness to at least the same extent as the Securities and payments made pursuant to **Sections 8.01** and **8.02**.

#### 11.04 COMPANY NOT TO MAKE PAYMENTS WITH RESPECT TO SECURITIES IN CERTAIN CIRCUMSTANCES.

No payment of amounts due on the Securities may be made by the Company, directly or indirectly, with respect to the Securities (including any repurchase pursuant to the exercise of the Repurchase Right) or to acquire any of the Securities at any time if a default in payment of the principal of or premium, if any, or interest on Senior Indebtedness exists, unless and until such default shall have been cured or waived or shall have ceased to exist. During the continuance of any event of default with respect to any Senior Indebtedness as such event of default is defined under any such Senior

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Indebtedness or in any agreement pursuant to which any Senior Indebtedness has been issued (other than default in payment of the principal of or premium, if any, or interest on any Senior Indebtedness), permitting the holders thereof to accelerate the maturity thereof, no payment may be made by the Company, directly or indirectly, of any amount due with respect to the Securities (a **"Payment Blockage"**) for 180 days following written notice (a **"Payment Blockage Notice"**) to the Company from any holder or holders thereof or its representative or representatives or the trustee or trustees under any indenture under which any instrument evidencing any such Senior Indebtedness may have been issued, that such an event of default has occurred and is continuing. Only one Payment Blockage Notice with respect to the same event of default may be given during any period of 360 consecutive days unless such event of default has been cured or waived for a period of not less than 90 consecutive days; provided, that in no event shall there be more than one interest payment in respect of the Securities blocked during any such 360-day period. No new Payment Blockage Notice of non-payment may be given by the holders of such Senior Indebtedness during any period of 360 consecutive days unless all events of defaults which triggered the preceding Payment Blockage have been cured or waived. However, if the maturity of such Senior Indebtedness is accelerated, no payment may be made by the Company on the Securities until such Senior Indebtedness that has matured has been paid or such acceleration has been cured or waived.

Regardless of anything to the contrary herein, nothing shall prevent (a) any payment by the Trustee to the Securityholders of amounts deposited with it pursuant to **Article VIII** or (b) any payment by the Trustee or the Paying Agent as permitted by **Section 11.12**. Nothing contained in this **Article XI** will limit the right of the Trustee or the Securityholders to take any action to accelerate the maturity of the Securities pursuant to **Section 6.02** or to pursue any rights or remedies hereunder. Nothing in this **Section 11.04** shall apply to claims of or payments to the Trustee under or pursuant to **Section 7.07**.

#### 11.05 ACCELERATION OF SECURITIES.

If payment of the Securities is accelerated because of an Event of Default, the Company shall promptly notify holders of Senior Indebtedness of the acceleration.

#### 11.06 WHEN DISTRIBUTION MUST BE PAID OVER.

In the event that the Company shall make any payment to the Trustee with respect to the Securities at a time when such payment is prohibited by **Section 11.03** or **11.04**, such payment shall be held by the Trustee, in trust for the benefit of, and shall be paid forthwith over and delivered to, the holders of Senior Indebtedness (*pro rata* as to each of such holders on the basis of the respective amounts of Senior Indebtedness held by them) or their Representative or the trustee under the indenture or other agreement (if any) pursuant to which Senior Indebtedness may have been issued, as their respective interests may appear, for application to the payment of all Senior Indebtedness remaining unpaid to the extent necessary to pay all Senior Indebtedness in full in accordance with its terms, after giving effect to any concurrent payment or distribution to or for the holders of Senior Indebtedness.

If a distribution is made to Securityholders, that because of this **Article XI** should not have been made to them, the Securityholders who receive the distribution shall hold it in trust for holders of Senior Indebtedness and pay it over to them as their interests may appear.

#### 11.07 NOTICE BY COMPANY.

The Company shall promptly notify the Trustee and the Paying Agent in writing of any facts known to the Company that would cause a payment of any amount due with respect to the Securities to violate this **Article XI**, but failure to give such notice shall not affect the subordination of the Securities to the Senior Indebtedness provided in this **Article XI**.

#### 11.08 SUBROGATION.

After all Senior Indebtedness is paid in full and until the Securities are paid in full, Securityholders shall be subrogated (equally and ratably with all other Indebtedness of the Company ranking *pari passu* with the Securities) to the rights of holders of Senior Indebtedness to receive distributions applicable to Senior Indebtedness to the extent that distributions otherwise payable to the Securityholders have been applied to the payment of Senior Indebtedness. A distribution made under this **Article XI** to holders of Senior Indebtedness which otherwise would have been made to Securityholders is not, as between the Company and Securityholders, a payment by the Company on Senior Indebtedness.

#### 11.09 RELATIVE RIGHTS.

This **Article XI** defines the relative rights of Securityholders and holders of Senior Indebtedness. Nothing in this Indenture shall:

- (i) impair, as between the Company, on the one hand, and Securityholders, on the other hand, the obligation of the Company, which is absolute and unconditional, to pay all amounts due with respect to the Securities in accordance with their terms;
- (ii) affect the relative rights of Securityholders and creditors of the Company other than holders of Senior Indebtedness; or
- (iii) prevent the Trustee or any Securityholder from exercising its available remedies upon a Default or Event of Default, subject to the rights of holders of Senior Indebtedness to receive distributions otherwise payable to Securityholders.

#### 11.10 SUBORDINATION MAY NOT BE IMPAIRED BY COMPANY.

No right of any holder of Senior Indebtedness to enforce the subordination of the indebtedness evidenced by the Securities shall be impaired by any act or failure to act by the Company or by the failure of the Company to comply with this Indenture.

#### 11.11 DISTRIBUTION OR NOTICE TO REPRESENTATIVE.

Whenever a distribution is to be made or a notice given to holders of Senior Indebtedness, the distribution may be made and the notice given to their Representatives.

#### 11.12 RIGHTS OF TRUSTEE AND PAYING AGENT.

The Trustee or Paying Agent may continue to make payments on the Securities until it receives written notice of facts that would cause a payment of amounts due with respect to the Securities to violate this **Article XI**. Only the Company or a Representative or a holder of an issue of Senior Indebtedness that has no Representative may give the notice.

The Trustee shall be entitled to rely on the delivery to it of a written notice by a person representing himself to be a holder of Senior Indebtedness (or a Representative on behalf of such holder) to establish that such notice has been given by a holder of Senior Indebtedness or a Representative on behalf of any such holder. In the event that the Trustee determines in good faith that further evidence is required with respect to the right of any person who is a holder of Senior Indebtedness to participate in any payment or distribution pursuant to this **Article XI**, the Trustee may request such person to furnish evidence to the reasonable satisfaction of the Trustee as to the amount of Senior Indebtedness held by such person, the extent to which such person is entitled to participate in such payment or distribution and any other facts pertinent to the rights of such person under this **Article XI**, and if such evidence is not furnished the Trustee may defer any payment to such person pending judicial determination as to the right of such person to receive such payment or until such time as the Trustee shall be otherwise satisfied as to the right of such person to receive such payment.

The Trustee in its individual or any other capacity may hold Senior Indebtedness with the same rights it would have if it were not Trustee. Any Agent may do the same with like rights.

The Trustee shall not be deemed to owe any fiduciary duty to the holders of Senior Indebtedness and shall not be liable to any such holder if it shall mistakenly pay over or distribute to Securityholders or the Company or any other person money or assets to which any holders of Senior Indebtedness shall be entitled by virtue of this **Article XI** or otherwise.

#### 11.13 OFFICERS' CERTIFICATE.

If there occurs an event referred to in **Section 11.03** or **11.04**, the Company shall promptly give to the Trustee an Officers' Certificate (on which the Trustee may conclusively rely) identifying all holders of Senior Indebtedness or their Representatives and the principal amount of Senior Indebtedness then outstanding held by each such holder and stating the reasons why such Officers' Certificate is being delivered to the Trustee.

#### 11.14 OBLIGATION OF COMPANY UNCONDITIONAL.

Nothing contained in this **Article XI** or elsewhere in this Indenture or in any Security is intended to or shall impair, as between the Company, its creditors other than holders of Senior Indebtedness and the Holders of the Securities, the obligation of the Company, which is absolute and unconditional, to pay to the Holders of the Securities all amounts due with respect to the Securities as and when the same shall become due and payable in accordance with their terms, or is intended to or shall affect the relative rights of the Holders of the Securities and creditors of the Company, other than the holders of the Senior Indebtedness, nor shall anything herein or therein prevent the Trustee or the Holder of any Security from exercising all remedies otherwise permitted by applicable law upon default under this Indenture, subject to the rights, if any, under

this **Article XI** of the holders of Senior Indebtedness in respect of cash, property or securities of the Company received upon the exercise of any such remedy. Upon any distribution of assets of the Company referred to in this **Article XI**, the Trustee, subject to the provisions of **Sections 7.01** and **7.02**, and the Holders of the Securities shall be entitled to rely upon any order or decree by any court of competent jurisdiction in which such dissolution, winding up, liquidation or reorganization proceedings are pending, or a certificate of the liquidating trustee or agent or other person making any distribution to the Trustee or the Holders of the Securities, for the purpose of ascertaining the persons entitled to participate in such distribution, the holders of the Senior Indebtedness and other indebtedness of the Company, the amount thereof or payable thereon, the amount or amounts paid or distributed thereon and all other facts pertinent thereto or to this **Article XI**. Nothing contained in this **Article XI** or elsewhere in this Indenture or in any Security is intended to or shall affect the obligation of the Company to make, or prevent the Company from making, at any time except during the pendency of any dissolution, winding up, liquidation or reorganization proceeding, and except during the continuance of any default specified in **Section 11.04** (not cured or waived), payments at any time of all amounts due with respect to the Securities.

#### 11.15 NOT TO PREVENT EVENTS OF DEFAULT.

The failure to make any payment due with respect to the Securities by reason of any provision of this **Article XI** shall not be construed as preventing the occurrence of an Event of Default under **Section 6.01**.

## XII. MISCELLANEOUS

#### 12.01 TRUST INDENTURE ACT CONTROLS.

If any provision of this Indenture limits, qualifies or conflicts with another provision which is required to be included in this Indenture by the TIA, the required provision of the TIA shall control.

#### 12.02 NOTICES.

Any notice or communication by the Company or the Trustee to one or both of the others is duly given if in writing and delivered in person, mailed by first-class mail or by express delivery to the other parties' addresses stated in this **Section 12.02**. The Company or the Trustee by notice to the others may designate additional or different addresses for subsequent notices or communications.

Any notice or communication to a Securityholder shall be mailed to its address shown on the register kept by the Registrar. Failure to mail a notice or communication to a Securityholder or any defect in it shall not affect its sufficiency with respect to other Securityholders.

If a notice or communication is mailed in the manner provided above, it is duly given, whether or not the addressee receives it.

If the Company mails a notice or communication to Securityholders, it shall mail a copy to the other and to the Trustee and each Agent at the same time.

All notices or communications shall be in writing.

The Company's address is:

ISIS Pharmaceuticals, Inc.  
2292 Faraday Avenue  
Carlsbad, CA 92008  
(760) 931-9200  
Attention: B. Lynne Parshall

The Trustee's address is:

Wells Fargo Bank Minnesota, National Association  
Corporate Trust Services  
MAC N9303-110  
Sixth and Marquette  
Minneapolis, MN 55479  
Attention: Michael T. Lechner

**12.03 COMMUNICATION BY HOLDERS WITH OTHER HOLDERS.**

Securityholders may communicate pursuant to TIA § 312(b) with other Securityholders with respect to their rights under this Indenture or the Securities. The Company, the Trustee, the Registrar and anyone else shall have the protection of TIA § 312(c).

**12.04 CERTIFICATE AND OPINION AS TO CONDITIONS PRECEDENT.**

Upon any request or application by the Company to the Trustee to take any action under this Indenture, the Company shall furnish to the Trustee:

- (i) an Officers' Certificate stating that, in the opinion of the signers, all conditions precedent, if any, provided for in this Indenture relating to the proposed action have been complied with; and
- (ii) an Opinion of Counsel stating that, in the opinion of such counsel, all such conditions precedent have been complied with.

Each signer of an Officers' Certificate or an Opinion of Counsel may (if so stated) rely, effectively, upon an Opinion of Counsel as to legal matters and an Officers' Certificate as to factual matters if such signer reasonably and in good faith believes in the accuracy of the document relied upon.

**12.05 STATEMENTS REQUIRED IN CERTIFICATE OR OPINION.**

Each Officers' Certificate or Opinion of Counsel with respect to compliance with a condition or covenant provided for in this Indenture shall include:

- (i) a statement that the person making such certificate or opinion has read such covenant or condition;
- (ii) a brief statement as to the nature and scope of the examination or investigation upon which the statements or opinions contained in such certificate or opinion are based;
- (iii) a statement that, in the opinion of such person, he or she has made such examination or investigation as is necessary to enable him or her to express an informed opinion as to whether or not such covenant or condition has been complied with; and
- (iv) a statement as to whether or not, in the opinion of such person, such condition or covenant has been complied with.

**12.06 RULES BY TRUSTEE AND AGENTS.**

The Trustee may make reasonable rules for action by or at a meeting of Securityholders. The Registrar, Paying Agent or Conversion Agent may make reasonable rules and set reasonable requirements for their respective functions.

**12.07 LEGAL HOLIDAYS.**

A "Legal Holiday" is a Saturday, a Sunday or a day on which banking institutions are not required to be open in the City of New York, in the State of New York or in the city in which the Trustee administers its corporate trust business. If a payment date is a Legal Holiday at a place of payment, payment may be made at that place on the next succeeding day that is not a Legal Holiday, and no interest shall accrue on that payment for the intervening period.

A "business day" is a day other than a Legal Holiday.

**12.08 NO RECOURSE AGAINST OTHERS.**

No past, present or future director, officer, employee, incorporator or stockholder of the Company, as such, shall have any liability for any obligations of the Company under the Securities or this Indenture or for any claim based on, in respect of, or by reason of, such obligations or their creation. Each Holder by accepting a Security waives and releases all such liability. The waiver and release are part of the consideration for the issuance of the Securities.

**12.09 DUPLICATE ORIGINALS.**

The parties may sign any number of copies of this Indenture. Each signed copy shall be an original, but all of them together represent the same agreement. Delivery of an executed

counterpart by facsimile shall be effective as delivery of a manually executed counterpart thereof.

**12.10 GOVERNING LAW.**

The laws of the State of New York, without regard to principles of conflicts of law, shall govern this Indenture and the Securities.

**12.11 NO ADVERSE INTERPRETATION OF OTHER AGREEMENTS.**

This Indenture may not be used to interpret another indenture, loan or debt agreement of the Company or any of its subsidiaries. Any such indenture, loan or debt agreement may not be used to interpret this Indenture.

**12.12 SUCCESSORS.**

All agreements of the Company in this Indenture and the Securities shall bind their respective successors. All agreements of the Trustee in this Indenture shall bind its successors.

**12.13 SEPARABILITY.**

In case any provision in this Indenture or in the Securities shall be invalid, illegal or unenforceable, the validity, legality and enforceability of the remaining provisions shall not in any way be affected or impaired thereby and a Holder shall have no claim therefor against any party hereto.

**12.14 TABLE OF CONTENTS, HEADINGS, ETC.**

The Table of Contents, Cross-Reference Table and headings of the Articles and Sections of this Indenture have been inserted for convenience of reference only, are not to be considered a part hereof and shall in no way modify or restrict any of the terms or provisions hereof.

**IN WITNESS WHEREOF**, the parties hereto have caused this Indenture to be duly executed as of the date first above written.

ISIS PHARMACEUTICALS, INC.

By: /s/ B. Lynne Parshall

Name:

Title:

WELLS FARGO BANK MINNESOTA, NATIONAL  
ASSOCIATION

By: /s/ Michael T. Lechner

Name:

Title:

[Face of Security]

**ISIS PHARMACEUTICALS, INC.**

[INSERT PRIVATE PLACEMENT LEGEND AND GLOBAL SECURITY LEGEND AS REQUIRED]

EXHIBIT A



5 ½% Convertible Subordinated Note due 2009  
CUSIP No. \_\_\_\_\_

**ISIS PHARMACEUTICALS, INC.**, a Delaware corporation (herein called the "**Company**"), for value received, hereby promises to pay to Cede & Co. or registered assigns, the principal sum of \_\_\_\_\_ Dollars (\$\_\_\_\_\_) on May 1, 2009, and to pay interest thereon, as provided on the reverse hereof, until the principal and any unpaid and accrued interest is paid or duly provided for. The right to payment of the principal and all other amounts due with respect hereto is subordinated to the rights of Senior Indebtedness as set forth in the Indenture referred to on the reverse side hereof.

Interest Payment Dates: May 1 and November 1, with the first payment to be made on November 1, 2002.

Record Dates: April 15 and October 15.

The provisions on the back of this certificate are incorporated as if set forth on the face hereof.

**IN WITNESS WHEREOF, ISIS PHARMACEUTICALS, INC.** has caused this instrument to be duly signed.

ISIS PHARMACEUTICALS, INC.

By: \_\_\_\_\_

Name:

Title:

Dated: \_\_\_\_\_

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TRUSTEE'S CERTIFICATE OF AUTHENTICATION

This is one of the Securities referred to in the within-mentioned Indenture.

WELLS FARGO BANK MINNESOTA, NATIONAL ASSOCIATION, as Trustee

By: \_\_\_\_\_

Authorized Signatory

Dated: \_\_\_\_\_

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[REVERSE OF SECURITY]

**ISIS PHARMACEUTICALS, INC.**

5 ½% Convertible Subordinated Note due 2009

1. **Interest.** **ISIS PHARMACEUTICALS, INC.**, a Delaware corporation (the "**Company**"), promises to pay interest on the principal amount of this Security at the rate *per annum* shown above. The **Company** will pay interest semi-annually on May 1 and November 1 of each year, with the first payment to be made on November 1, 2002. Interest on the Securities will accrue on the principal amount from the most recent date to which interest has been paid or, if no interest has been paid, from May 1, 2002. Interest will be computed on the basis of a 360-day year of twelve 30-day months.

2. **Maturity.** The Notes will mature on May 1, 2009.

3. **Method of Payment.** The **Company** will pay interest on the Securities (except defaulted interest) to the persons who are registered Holders of Securities at the close of business on the record date set forth on the face of this Security next preceding the applicable interest payment date. Holders must surrender Securities to a Paying Agent to collect the principal, Redemption Price, Provisional Redemption Price, if applicable, Make-Whole Payment, if applicable, or Repurchase Price of the Securities. The **Company** will pay all amounts due with respect to the Securities in money of the United States that at the time of payment is legal tender for payment of public and private debts. However, the **Company** may, at its option, pay all amounts due with respect to the Securities held other than by the Depository by check payable in such money. It may mail an interest check to a Holder's registered address.

4. **Paying Agent, Registrar, Conversion Agent.** Initially, Wells Fargo Bank Minnesota, National Association (the “Trustee”) will act as Paying Agent, Registrar and Conversion Agent. The Company may change any Paying Agent, Registrar or Conversion Agent without notice. The Company may act in any such capacity.

5. **Indenture.** The Company issued the Securities under an Indenture dated as of May 1, 2002 (the “Indenture”) between the Company and the Trustee. The terms of the Securities include those stated in the Indenture and those made part of the Indenture by reference to the Trust Indenture Act of 1939 (15 U.S. Code §§ 77aaa-77bbb) (the “Act”) as in effect on the date of the Indenture. The Securities are subject to all such terms, and Securityholders are referred to the Indenture and the Act for a statement of such terms. The Securities are general unsecured senior subordinated obligations of the Company limited to \$125,000,000 aggregate principal amount (\$143,750,000 if the Initial Purchasers (as defined in the Indenture) have elected to exercise their over-allotment option to purchase an additional \$18,750,000 of the Securities), except as otherwise provided in the Indenture (except for Securities issued in substitution for destroyed, mutilated, lost or stolen Securities). Terms used herein which are defined in the Indenture have the meanings assigned to them in the Indenture.

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6. **Provisional and Optional Redemption.** The Securities will be redeemable prior to maturity at the option of the Company, in whole or in part, at any time on or after May 3, 2005, in cash, at the following redemption prices (expressed as percentages of the principal amount thereof), if redeemed during the periods commencing on the dates set forth below, in each case together with accrued and unpaid interest, if any, to the redemption date:

Date	Redemption Price
May 3, 2005 to April 30, 2006	103.143%
May 1, 2006 to April 30, 2007	102.357%
May 1, 2007 to April 30, 2008	101.571%
May 1, 2008 through May 1, 2009 inclusive	100.786%

The Securities may be redeemed at the election of the Company, as a whole or in parts from time to time, at any time prior to May 3, 2005 (a “Provisional Redemption”), at a redemption price equal to \$1,000 per \$1,000 principal amount of the Securities redeemed (such amount, together with the Make-Whole Payment (as defined below) the “Provisional Redemption Price”), on the date of redemption (the “Provisional Redemption Date”) specified in the notice of Provisional Redemption if (1) the closing price of the Common Stock on the NNM (or other United States national securities exchange where the Company’s Common Stock is traded) has exceeded 150% of the then current conversion price for at least 20 trading days within a period of any 30 consecutive trading days ending on the trading day prior to the date of mailing of the notice of Provisional Redemption (the “Notice Date”), and (2) a shelf registration statement covering resales of the Securities and the Common Stock issuable upon conversion thereof is effective and available for use and is expected to remain effective and available for use for the 30 days following the Provisional Redemption Date, unless registration is no longer required.

Upon any such Provisional Redemption, the Company shall make an additional payment (the “Make-Whole Payment”) with respect to the Securities called for redemption to holders on the Provisional Redemption Date in an amount equal to the total value of the aggregate amount of interest that would have been payable on the Securities from the last day through which interest was paid on the Securities (or May 1, 2002 if no interest has been paid) through May 1, 2005 (or May 2, 2005 if the Provisional Redemption is May 2, 2005). The Company may make the Make-Whole Payment, at its option, either in cash or Common Stock or a combination thereof. Payments made in Common Stock will be valued at 95% of the average closing sales prices of the Common Stock on the NNM (or other United States national securities exchange where the Common Stock is traded) for the five trading days ending on the day prior to the

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Provisional Redemption Date. The Company shall make the Make-Whole Payment on all Securities called for sProvisional Redemption, including those Securities converted into Common Stock between the Notice Date and the Provisional Redemption Date.

7. **Notice of Redemption.** Notice of redemption will be mailed at least 30 days but not more than 60 days before the redemption date to each Holder of Securities to be redeemed at its registered address. Securities in denominations larger than \$1,000 principal amount may be redeemed in part but only in positive integral multiples of \$1,000 principal amount. On and after the redemption date interest ceases to accrue on Securities or portions of them called for redemption.

8. **Repurchase at Option of Holder.** In the event of a Change in Control with respect to the Company, then each Holder of the Securities shall have the right, at the Holder’s option, subject to the rights of the holders of Senior Indebtedness under **Article XI** of the Indenture, to require the Company to repurchase such Holder’s Securities including any portion thereof which is \$1,000 in principal amount or any positive integral multiple thereof on a business day (the “Repurchase Date”) that is no later than 30 business days after the date of the Change in Control Notice, unless otherwise required by applicable law, at a price equal to 100% of the outstanding principal amount of such Security, plus accrued and unpaid interest to the Repurchase Date.

Within 30 business days after the occurrence of the Change in Control, the Company is obligated to give notice of the occurrence of such Change in Control to each Holder. Such notice shall include, among other things, the date by which Holder must notify the Company of such Holder’s intention to exercise the Repurchase Right and of the procedure which such Holder must follow to exercise such right. To exercise a Repurchase Right, a Holder shall deliver to the Company (if it is acting as its own Paying Agent), or to a Paying Agent designated by the Company for such purpose in the Change in Control Notice, (i) no later than the close of business on the third business day immediately preceding the Repurchase Date, the Option of Holder To Elect Purchase Notice on the back of the Securities with respect to which the Repurchase Right is being exercised, duly completed and signed, with appropriate signature guarantee, and (ii) at any time after such delivery of such Option of Holder To Elect Purchase Notice, such Securities with respect to which the Repurchase Right is being exercised, duly endorsed for transfer to the Company. Upon so delivering such Option of Holder To Elect Purchase Notice and such Securities,

the Holder of such Securities shall be entitled to receive from the Company (if it is acting as its own Paying Agent), or such Paying Agent, a nontransferable receipt of deposit evidencing such deposit.

A “**Change in Control**” of the Company means:

(i) the acquisition by any “person,” entity or “group” within the meaning of Section 13(d)(3) or 14(d)(2) of the Exchange Act of beneficial ownership (within the meaning of Rule 13d-3 promulgated under the Exchange Act) of 50% or more of the voting power of the total outstanding Common Stock or other capital stock into which the Common Stock is hereafter reclassified or changed;

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(ii) persons who constitute the Board of Directors (the “**Incumbent Board**”) as of the date of the indenture, cease for any reason to constitute at least a majority of the Board of Directors, provided that any person subsequently becoming a director whose election, or nomination for election by stockholders, was approved by a vote of at least a majority of the directors then comprising the Incumbent Board shall be considered as though such person were a member of the Incumbent Board; or

(iii) the sale, lease or transfer of all or substantially all of the assets and property of the Company to any “person,” entity or “group” within the meaning of Section 13(d) or 14(d) of the Exchange Act.

However, a Change in Control will not be deemed to have occurred if either:

(i) the last sale price of the Common Stock for any five trading days during the ten trading days immediately preceding the Change in Control is at least equal to 105% of the conversion price in effect on such trading day; or

(ii) in the case of a merger or consolidation, all or substantially all of the consideration (excluding cash payments for fractional shares and cash payments pursuant to dissenters’ appraisal rights) in the merger or consolidation constituting the Change in Control consists of common stock quoted traded on a United States national securities exchange or on the NNM (or which will be so traded or quoted when issued or exchanged in connection with such Change in Control) and as a result of such transaction or transactions the Securities become convertible solely into such common stock.

9. **Conversion.** A Holder may convert his or her Security into Common Stock of the Company at any time prior to the close of business on May 1, 2009, or, (x) if the Security is called for redemption by the Company, the Holder may convert it at any time before the close of business on the business day immediately preceding the date fixed for such redemption, or (y) if the Security is to be repurchased by the Company pursuant to **paragraph 8** hereof, the Holder may convert it at any time before the close of business on the business day immediately preceding the Repurchase Date. The initial conversion rate is 60.1504 shares of Common Stock per \$1,000 principal amount of Securities, or an effective initial conversion price of approximately \$16.625 per share, subject to adjustment in the event of certain circumstances as specified in the Indenture. The Company will deliver a check in lieu of any fractional share. On conversion no payment or adjustment for any unpaid and accrued interest, or liquidated damages with respect to, the Securities will be made. If a Holder surrenders a Security for conversion between the record date for the payment of interest and the next interest payment date, such Security, when surrendered for conversion, must be accompanied by payment of an amount equal to the interest thereon which the registered Holder on such record date is to receive, unless the Securities have been called for redemption as described in the Indenture.

To convert a Security, a Holder must (1) complete and sign the Conversion Notice, with appropriate signature guarantee, on the back of the Security, (2) surrender the Security to a Conversion Agent, (3) furnish appropriate endorsements and transfer documents if required by the Registrar or Conversion Agent, (4) pay the amount of interest, if any, the Holder may be paid

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as provided in the last sentence of the above paragraph and (5) pay any transfer or similar tax if required. A Holder may convert a portion of a Security if the portion is \$1,000 principal amount or a positive integral multiple of \$1,000 principal amount.

Any shares issued upon conversion of a Security shall bear the Private Placement Legend until after the second anniversary of the later of the issue date for the Securities and the last date on which the Company or any Affiliate of the Company was the owner of such shares or the Security (or any predecessor security) from which such shares were converted (or such shorter period of time as permitted by Rule 144(k) under the Securities Act or any successor provision thereunder) (or such longer period of time as may be required under the Securities Act or applicable state securities laws in the Opinion of Counsel for the Company, unless otherwise agreed by the Company and the Holder thereof).

10. **Subordination.** The Securities are subordinated in right of payment, in the manner and to the extent set forth in the Indenture, to the prior payment in full of all Senior Indebtedness. Each Holder by accepting a Security agrees to such subordination and authorizes the Trustee to give it effect.

11. **Denominations, Transfer, Exchange.** The Securities are in registered form without coupons in denominations of \$1,000 principal amount and positive integral multiples of \$1,000 principal amount. The transfer of Securities may be registered and Securities may be exchanged as provided in the Indenture. The Registrar may require a Holder, among other things, to furnish appropriate endorsements and transfer documents. No service charge shall be made for any such registration of transfer or exchange, but the Company may require payment of a sum sufficient to cover any tax or other governmental charge payable in connection therewith. The Registrar need not exchange or register the transfer of any Security selected for redemption in whole or in part, except the unredeemed portion of Securities to be redeemed in part. Also, it need not exchange or register the transfer of any Securities for a period of 15 days before the mailing of a notice of redemption of the Securities selected to be redeemed.

12. **Persons Deemed Owners.** The registered Holder of a Security may be treated as the owner of such Security for all purposes.

13. **Merger or Consolidation.** The Company shall not consolidate with, or merge into, or transfer or lease all or substantially all of its properties or assets to, any person unless the person is a corporation, limited liability company or other limited liability entity organized under the laws of the United States, any State thereof or the District of Columbia, provided that this condition will not apply if independent tax counsel experienced in such matters delivers an Opinion of Counsel stating that, under then existing laws, there would be no adverse tax consequences to the Holders in the event that this condition is not satisfied, and such person assumes by supplemental indenture all the obligations of the Company under the Securities and the Indenture and immediately after giving effect to the transaction no Default or Event of Default exists.

14. **Amendments, Supplements and Waivers.** Subject to certain exceptions, the Indenture or the Securities may be amended or supplemented with the consent of the Holders of at least a majority in aggregate principal amount of the Securities then outstanding, and any

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existing Default or Event of Default may be waived with the consent of the Holders of a majority in aggregate principal amount of the Securities then outstanding. Without notice to or the consent of any Securityholder, the Indenture or the Securities may be amended or supplemented to cure any ambiguity, omission, defect or inconsistency, to provide for uncertificated Securities in addition to certificated Securities, to comply with **Sections 5.01** and **10.12** of the Indenture or to make any change that does not adversely affect the rights of any Securityholder.

15. **Defaults and Remedies.** An Event of Default includes the occurrence of any of the following: default in payment of principal at maturity, upon redemption or exercise of a Repurchase Right or otherwise; default for 30 days in payment of interest or other amounts due; failure by the Company for 60 days after notice to it to comply with any of its other agreements in the Indenture or the Securities; and certain events of bankruptcy or insolvency. If any Event of Default occurs and is continuing, the Trustee or the Holders of at least 25% in aggregate principal amount of the Securities then outstanding may declare all the Securities to be due and payable immediately, except as provided in the Indenture. If an Event of Default specified in **Section 6.01(iv)** or **(v)** of the Indenture with respect to the Company occurs, the principal of and accrued interest on all the Securities shall *ipso facto* become and be immediately due and payable without any declaration or other act on the part of the Trustee or any Securityholder. Securityholders may not enforce the Indenture or the Securities except as provided in the Indenture. The Trustee may require indemnity satisfactory to it before it enforces the Indenture or the Securities. Subject to certain limitations, Holders of a majority in principal amount of the Securities then outstanding may direct the Trustee in its exercise of any trust or power. The Trustee may withhold from Securityholders notice of any continuing Default or Event of Default (except a Default or Event of Default in payment) if it determines that withholding notice is in the interests of the Securityholders. The Company must furnish an annual compliance certificate to the Trustee.

16. **Registration Rights.** The Holders are entitled to registration rights as set forth in the Registration Rights Agreement (as defined in the Indenture). The Holders shall be entitled to receive liquidated damages in certain circumstances, all as set forth in the Registration Rights Agreement.

17. **Trustee Dealings with the Company.** The Trustee under the Indenture, or any banking institution serving as successor Trustee thereunder, in its individual or any other capacity, may make loans to, accept deposits from, and perform services for the Company or its Affiliates, and may otherwise deal with the Company or its Affiliates, as if it were not Trustee.

18. **No Recourse Against Others.** No past, present or future director, officer, employee, consultant or stockholder, as such, of the Company shall have any liability for any obligations of the Company under the Securities or the Indenture or for any claim based on, in respect of or by reason of such obligations or their creation. Each Securityholder by accepting a Security waives and releases all such liability. The waiver and release are part of the consideration for the issue of the Securities.

19. **Authentication.** This Security shall not be valid until authenticated by the manual signature of the Trustee or an authenticating agent.

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20. **Abbreviations.** Customary abbreviations may be used in the name of a Securityholder or an assignee, such as: TEN COM (= tenants in common), TEN ENT (= tenants by the entirety), JT TEN (= joint tenants with right of survivorship and not as tenants in common), CUST (= Custodian), and U/G/M/A (Uniform Gifts to Minors Act).

THE COMPANY WILL FURNISH TO ANY SECURITYHOLDER UPON WRITTEN REQUEST AND WITHOUT CHARGE A COPY OF THE INDENTURE. REQUESTS MAY BE MADE TO:

ISIS Pharmaceuticals, Inc.  
2292 Faraday Avenue  
Carlsbad, CA 92008  
Attention: Corporate Secretary

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[FORM OF ASSIGNMENT]

I or we assign to

PLEASE INSERT SOCIAL SECURITY OR OTHER IDENTIFYING NUMBER

(please print or type name and address)

the within Security and all rights thereunder, and hereby irrevocably constitutes and appoints

attorney to transfer the Security on the books of the Company with full power of substitution in the premises.

Dated: \_\_\_\_\_

NOTICE: The signature on this assignment must correspond with the name as it appears upon the face of the within Security in every particular way without alteration or enlargement or any change whatsoever and be guaranteed by a guarantor institution participating in the Securities Transfer Agents Medallion Program or in such other guarantee program acceptable to the Trustee.

Signature Guarantee: \_\_\_\_\_

In connection with any transfer of this Security occurring prior to the date which is the earlier of (i) the date of the declaration by the Commission of the effectiveness of a registration statement under the Securities Act of 1933, as amended (the "Securities Act") covering resales of this Security (which effectiveness shall not have been suspended or terminated at the date of the transfer) and (ii) the Resale Restriction Termination Date, the undersigned confirms that it has not utilized any general solicitation or general advertising in connection with transfer:

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[Check One]

- (1) \_\_\_\_\_ to the Company or any subsidiary thereof; or
- (2) \_\_\_\_\_ pursuant to and in compliance with Rule 144A under the Securities Act of 1933, as amended; or
- (3) \_\_\_\_\_ outside the United States to a person other than a "U.S. person" in compliance with Rule 904 of Regulation S under the Securities Act of 1933, as amended; or
- (4) \_\_\_\_\_ pursuant to the exemption from registration provided by Rule 144 under the Securities Act of 1933, as amended; or
- (5) \_\_\_\_\_ pursuant to an effective registration statement under the Securities Act of 1933, as amended.

and unless the box below is checked, the undersigned confirms that such Security is not being transferred to an "affiliate" of the Company as defined in Rule 144 under the Securities Act of 1933, as amended (an "Affiliate"):

The transferee is an Affiliate of the Company.

(If the Security is transferred to an Affiliate, the restrictive legend must remain on the Security for two years following the date of the transfer).

Unless one of the items is checked, the Trustee will refuse to register any of the Securities evidenced by this certificate in the name of any person other than the registered Holder thereof; provided, however, that if item (4) is checked, the Company or the Trustee may require, prior to registering any such transfer of the Securities, in their sole discretion, such written legal opinions, certifications and other information as the Trustee or the Company have reasonably requested to confirm that such transfer is being made pursuant to an exemption from, or in a transaction not subject to, the registration requirements of the Securities Act of 1933, as amended.

If none of the foregoing items are checked, the Trustee or Registrar shall not be obligated to register this Security in the name of any person other than the Holder hereof unless and until the conditions to any such transfer of registration set forth herein and in Section 2.16 of the Indenture shall have been satisfied.

Dated: \_\_\_\_\_

Signed: \_\_\_\_\_

(Sign exactly as name appears on the other side of this Security)

Signature Guarantee: \_\_\_\_\_

TO BE COMPLETED BY PURCHASER IF (2) ABOVE IS CHECKED

The undersigned represents and warrants that it is purchasing this Security for its own account or an account with respect to which it exercises sole investment discretion and that

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it and any such account is a "qualified institutional buyer" within the meaning of Rule 144A under the Securities Act of 1933, as amended, and is aware that the sale to it is being made in reliance on Rule 144A and acknowledges that it has received such information regarding the Company as the undersigned has requested pursuant to Rule 144A or has determined transferor is relying upon the undersigned's foregoing representations in order to claim the exemption from registration provided by Rule 144A.

Dated: \_\_\_\_\_

NOTICE: To be executed by an executive officer

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CONVERSION NOTICE

To convert this Security into Common Stock of the, check the box:

To convert only part of this Security, state the principal amount to be converted (must be in multiples of \$1,000):

\$ \_\_\_\_\_

If you want the stock certificate made out in another person's name, fill in the form below:

(Insert other person's soc. sec. or tax I.D. no.)

\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

(Print or type other person's name, address and zip code)

Date: \_\_\_\_\_ Signature(s): \_\_\_\_\_

(Sign exactly as your name(s) appear(s) on the other side of this Security)

Signature(s) guaranteed by:

\_\_\_\_\_  
(All signatures must be guaranteed by a guarantor institution participating in the Securities Transfer Agents Medallion Program or in such other guarantee program acceptable to the Trustee.)

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OPTION OF HOLDER TO ELECT PURCHASE NOTICE

Certificate No. of Security: \_\_\_\_\_

If you want to elect to have this Security purchased by the Company pursuant to **Section 3.08** of the Indenture, check the box:

If you want to elect to have only part of this Security purchased by the Company pursuant to **Section 3.08** of the Indenture, state the principal amount:

\$ \_\_\_\_\_

(in an integral multiple of \$1,000)

Date: \_\_\_\_\_ Signature(s): \_\_\_\_\_

(Sign exactly as your name(s) appear(s) on the other side of this Security)

**SCHEDULE A****SCHEDULE OR EXCHANGES OF INTERESTS IN THE GLOBAL SECURITY.**

The following exchanges of a part of this Global Security for an interest in another Global Security or for Securities in certificated form have been made:

<b>Date of Exchange</b>	<b>Amount of decrease in Principal amount of this Global Security</b>	<b>Amount of increase in Principal amount of this Global Security</b>	<b>Principal amount of this Global Security following such decrease (or increase)</b>	<b>Signature or authorized signatory of Trustee or Note Custodian</b>
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<sup>a</sup> This is included in Global notes only.

**EXHIBIT B-1****FORM OF PRIVATE PLACEMENT LEGEND**

THIS SECURITY HAS NOT BEEN REGISTERED UNDER THE SECURITIES ACT OF 1933, AS AMENDED (THE "SECURITIES ACT"), OR THE SECURITIES LAWS OF ANY STATE OR OTHER JURISDICTION. NEITHER THIS SECURITY NOR ANY INTEREST OR PARTICIPATION HEREIN MAY BE REOFFERED, SOLD, ASSIGNED, TRANSFERRED, PLEDGED, ENCUMBERED OR OTHERWISE DISPOSED OF IN THE ABSENCE OF SUCH REGISTRATION OR UNLESS SUCH TRANSACTION IS EXEMPT FROM, OR NOT SUBJECT TO, SUCH REGISTRATION. THE HOLDER HEREOF MAY NOT ENGAGE IN HEDGING TRANSACTIONS WITH RESPECT TO THIS SECURITY UNLESS SUCH TRANSACTIONS ARE IN COMPLIANCE WITH THE SECURITIES ACT.

THE HOLDER OF THIS SECURITY BY ITS ACCEPTANCE HEREOF AGREES TO OFFER, SELL OR OTHERWISE TRANSFER SUCH SECURITY, PRIOR TO THE DATE (THE "RESALE RESTRICTION TERMINATION DATE") WHICH IS THE LATER OF (X) TWO YEARS AFTER THE LATER OF THE ORIGINAL ISSUE DATE HEREOF AND THE LAST DATE ON WHICH THE COMPANY OR ANY AFFILIATE OF THE COMPANY WAS THE OWNER OF THIS SECURITY (OR ANY PREDECESSOR OF SUCH SECURITY), AND (Y) SUCH LATER DATE, IF ANY, AS MAY BE REQUIRED BY APPLICABLE LAW ONLY (A) TO THE COMPANY OR ANY SUBSIDIARY OF THE COMPANY, (B) PURSUANT TO A REGISTRATION STATEMENT THAT HAS BEEN DECLARED EFFECTIVE UNDER THE SECURITIES ACT, (C) FOR SO LONG AS THE SECURITIES ARE ELIGIBLE FOR RESALE PURSUANT TO RULE 144A UNDER THE SECURITIES ACT, TO A PERSON IT REASONABLY BELIEVES IS A "QUALIFIED INSTITUTIONAL BUYER" AS DEFINED IN RULE 144A UNDER THE SECURITIES ACT THAT PURCHASES FOR ITS OWN ACCOUNT OR FOR THE ACCOUNT OF A QUALIFIED INSTITUTIONAL BUYER TO WHOM NOTICE IS GIVEN THAT THE TRANSFER IS BEING MADE IN RELIANCE ON RULE 144A UNDER THE SECURITIES ACT OR (D) PURSUANT TO OFFERS AND SALES THAT OCCUR OUTSIDE THE UNITED STATES IN ACCORDANCE WITH REGULATION S UNDER THE SECURITIES ACT, SUBJECT TO THE COMPANY'S AND THE TRUSTEE'S RIGHT PRIOR TO ANY SUCH OFFER, SALE OR TRANSFER PURSUANT TO THIS CLAUSE (D) TO REQUIRE THE DELIVERY OF AN OPINION OF COUNSEL, CERTIFICATION AND/OR OTHER INFORMATION SATISFACTORY TO EACH OF THEM. THIS LEGEND WILL BE REMOVED UPON THE REQUEST OF THE HOLDER AFTER THE RESALE RESTRICTION TERMINATION DATE.

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**EXHIBIT B-2****FORM OF LEGEND FOR GLOBAL SECURITY**

Any Global Security authenticated and delivered hereunder shall bear a legend (which would be in addition to any other legends required in the case of a Restricted Security) in substantially the following form:

THIS SECURITY IS A GLOBAL SECURITY WITHIN THE MEANING OF THE INDENTURE HEREINAFTER REFERRED TO AND IS REGISTERED IN THE NAME OF A DEPOSITARY OR A NOMINEE OF A DEPOSITARY OR A SUCCESSOR DEPOSITARY. THIS SECURITY IS NOT EXCHANGEABLE FOR SECURITIES REGISTERED IN THE NAME OF A PERSON OTHER THAN THE DEPOSITARY OR ITS NOMINEE EXCEPT IN THE LIMITED CIRCUMSTANCES DESCRIBED IN THE INDENTURE, AND NO TRANSFER OF THIS SECURITY (OTHER THAN A TRANSFER OF THIS SECURITY AS A WHOLE BY THE DEPOSITARY TO A NOMINEE OF THE DEPOSITARY OR BY A NOMINEE OF THE DEPOSITARY TO THE DEPOSITARY OR ANOTHER NOMINEE OF THE DEPOSITARY) MAY BE REGISTERED EXCEPT IN THE LIMITED CIRCUMSTANCES DESCRIBED IN THE INDENTURE.

UNLESS THIS CERTIFICATE IS PRESENTED BY AN AUTHORIZED REPRESENTATIVE OF THE DEPOSITORY TRUST COMPANY, A NEW YORK CORPORATION ("DTC"), TO THE COMPANY OR ITS AGENT FOR REGISTRATION OF TRANSFER, EXCHANGE, OR PAYMENT, AND ANY CERTIFICATE ISSUED IS REGISTERED IN THE NAME OF CEDE & CO. OR IN SUCH OTHER NAME AS IS REQUESTED BY AN AUTHORIZED REPRESENTATIVE OF DTC (AND ANY PAYMENT IS MADE TO CEDE & CO. OR TO SUCH OTHER ENTITY AS IS REQUESTED BY AN AUTHORIZED REPRESENTATIVE OF DTC), ANY TRANSFER, PLEDGE OR OTHER USE HEREOF FOR VALUE OR OTHERWISE BY OR TO ANY PERSON IS WRONGFUL INASMUCH AS THE REGISTERED OWNER HEREOF, CEDE & CO., HAS AN INTEREST HEREIN.

TRANSFERS OF THIS GLOBAL SECURITY SHALL BE LIMITED TO TRANSFERS IN WHOLE, BUT NOT IN PART, TO NOMINEES OF CEDE & CO. OR TO A SUCCESSOR THEREOF OR SUCH SUCCESSOR'S NOMINEE AND TRANSFERS OF PORTIONS OF THIS GLOBAL SECURITY SHALL BE LIMITED TO TRANSFERS MADE IN ACCORDANCE WITH THE RESTRICTIONS SET FORTH IN SECTION 2.16 OF THE INDENTURE.

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EXHIBIT C-1

Form of Certificate To Be Delivered  
in Connection with Transfers  
Pursuant to Regulation S

Wells Fargo Bank Minnesota, National Association  
Corporate Trust Services  
MAC N9303-110  
Sixth and Marquette  
Minneapolis, MN 55479

Attention: Corporate Finance

Re: ISIS PHARMACEUTICALS, INC. (the "**Company**") 5 ½% Convertible Subordinated Notes due 2009 (the "**Securities**")

Ladies and Gentlemen:

In connection with our proposed sale of \$\_\_\_\_\_ aggregate principal amount of the Securities, we confirm that such sale has been effected pursuant to and in accordance with Regulation S under the U.S. Securities Act of 1933, as amended (the "**Securities Act**"), and, accordingly, we represent that:

- (1) the offer of the Securities was made in an "offshore transaction" to a person other than a "U.S. person" (as defined in Regulation S);
- (2) either (a) at the time the buy offer was originated, the transferee was outside the United States or we and any person acting on our behalf reasonably believed that the transferee was outside the United States, or (b) the transaction was executed in, on or through the facilities of a designated off-shore securities market and neither we nor any person acting on our behalf knows that the transaction has been pre-arranged with a buyer in the United States;
- (3) no directed selling efforts have been made in the United States in contravention of the requirements of Rule 903(b) or Rule 904(b) of Regulation S, as applicable;
- (4) the transaction is not part of a plan or scheme to evade the registration requirements of the Securities Act;
- (5) we have advised the transferee of the transfer restrictions applicable to the Securities; and

C-1-1

(6) if we are a dealer in securities or have received a selling concession, fee or other remuneration in respect of the Securities, and the transfer is to occur during the restricted period, then the requirements of Rule 904(c)(1) have been satisfied.

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You, the Company and counsel for the Company are entitled to rely upon this letter and are irrevocably authorized to produce this letter or a copy hereof to any interested party in any administrative or legal proceedings or official inquiry with respect to the matters covered hereby. Terms used in this certificate have the meanings set forth in Regulation S.

Very truly yours,

[Name of Transferor]

By: \_\_\_\_\_



Form of Certificate To Be Delivered  
in Connection with Transfers  
Pursuant to Regulation S

Wells Fargo Bank Minnesota, National Association  
Corporate Trust Services  
MAC N9303-110  
Sixth and Marquette  
Minneapolis, MN 55479

Attention: Corporate Finance

Re: ISIS PHARMACEUTICALS, INC. (the "Company") 5 1/2% Convertible Subordinated Notes due 2009 (the "Securities")

Ladies and Gentlemen:

In connection with our proposed purchase of \$\_\_\_\_\_ aggregate principal amount of the Securities, we confirm that such sale has been effected pursuant to and in accordance with Regulation S under the U.S. Securities Act of 1933, as amended (the "Securities Act"), and, accordingly, we represent that:

- (1) the undersigned is not a U.S. person (as defined in Regulation S) and has not acquired the Securities for the account or benefit of any U.S. person;
- (2) the undersigned is not a distributor within the meaning of Regulation S; and
- (3) the undersigned agrees to resell the Securities only in accordance with the provisions of Regulation S, pursuant to registration under the Securities Act, or pursuant to an exemption from registration and agrees not to engage in hedging transactions with regard to the Securities unless in compliance with the Securities Act.

You, the Company and counsel for the Company are entitled to rely upon this letter and are irrevocably authorized to produce this letter or a copy hereof to any interested party in any administrative or legal proceedings or official inquiry with respect to the matters covered hereby. Terms used in this certificate have the meanings set forth in Regulation S.

Very truly yours,

[Name of Transferee]

C-2-1

By: \_\_\_\_\_  
Authorized Signature

C-2-2

Form of Notice of Transfer Pursuant to Registration Statement

ISIS Pharmaceuticals, Inc.  
2292 Faraday Avenue  
Carlsbad, California 92008

Wells Fargo Bank Minnesota, National Association  
Corporate Trust Services  
MAC N9303-110  
Sixth and Marquette  
Minneapolis, MN 55479

Ladies and Gentlemen:

Please be advised that \_\_\_\_\_ has transferred \$\_\_\_\_\_ aggregate principal amount of the Securities or \_\_\_\_\_ shares of the Common Stock, \$0.001 par value per share, of the Company issuable on conversion of the Securities ("Stock") pursuant to an effective Shelf Registration Statement on Form S-3 (File No. 333-\_\_\_\_\_).

We hereby certify that the prospectus delivery requirements, if any, of the Securities Act of 1933 as amended, have been satisfied with respect to the transfer described above and that the above-named beneficial owner of the Securities or Stock is named as a "Selling Security Holder" in the Prospectus dated \_\_\_\_\_, or in amendments or supplements thereto, and that the aggregate principal amount of the Securities, or number of shares of Stock transferred are [a portion of] the Securities or Stock listed in such Prospectus, as amended or supplemented, opposite such owner's name.

Very truly yours,

\_\_\_\_\_  
(Name)

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EXECUTION COPY

\$125,000,000

Isis Pharmaceuticals, Inc.

5 ½% Convertible Subordinated Notes

due 2009

PURCHASE AGREEMENT

April 26, 2002

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PURCHASE AGREEMENT

April 26, 2002

UBS Warburg LLC  
Robertson Stephens, Inc.  
Needham & Company, Inc.  
Roth Capital Partners, LLC  
as Initial Purchasers

c/o UBS Warburg LLC  
299 Park Avenue  
New York, New York 10171

Ladies and Gentlemen:

Isis Pharmaceuticals, Inc., a Delaware corporation, (the "Company"), proposes to issue and sell to the initial purchasers named in Schedule A hereto (the "Initial Purchasers") \$125,000,000 aggregate principal amount of its 5½% Convertible Subordinated Notes due 2009 (the "Firm Notes"). In addition, solely for the purpose of covering over-allotments, the Company proposes to grant to the Initial Purchasers the option to purchase from the Company

up to an additional \$18,750,000 aggregate principal amount of the Company's 5 ½% Convertible Subordinated Notes due 2009 (the "Additional Notes"). The Firm Notes and the Additional Notes are hereinafter collectively sometimes referred to as the "Notes."

The Notes are to be issued pursuant to an indenture (the "Indenture") to be dated as of May 1, 2002, between the Company and Wells Fargo Bank Minnesota, N. A., as trustee (the "Trustee"). Copies of the Indenture, in substantially final form, have been delivered to the Initial Purchasers. The Notes will be convertible in accordance with their terms and the terms of the Indenture into shares of the common stock (the "Common Stock") of the Company, par value \$0.001 per share (the "Shares").

The Notes and the Shares will be offered without being registered under the Securities Act of 1933, as amended, and the rules and regulations thereunder (collectively, the "Act"), to "qualified institutional buyers" in compliance with the exemption from registration provided by Rule 144A under the Act ("Rule 144A") and in offshore transactions in reliance on Regulation S under the Act ("Regulation S").

The Initial Purchasers and their direct and indirect transferees will be entitled to the benefits of a Registration Rights Agreement to be entered into at or prior to the time of purchase (as defined herein) between the Company and the Initial Purchasers (the "Registration Rights Agreement").

In connection with the sale of the Notes, the Company has prepared a preliminary offering memorandum (the "Preliminary Memorandum") and will prepare a final offering memorandum (the "Final Memorandum") and, with the Preliminary Memorandum, each an "Offering Memorandum"), including or incorporating by reference a description of the terms of the Notes and the Shares, the terms of the offering and a description of the Company. As used herein, the terms "Preliminary Memorandum," "Final Memorandum" and "Offering Memorandum" shall include in each case the documents incorporated by reference therein, if any. The terms "supplement," "amendment" and "amend" as used herein with respect to an Offering Memorandum shall include all documents deemed to be incorporated by reference in the Preliminary Memorandum or Final Memorandum, if any, that are filed subsequent to the

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date of such Offering Memorandum, but prior to the completion of the offering of the Notes, with the Securities and Exchange Commission (the "Commission") pursuant to the Securities Exchange Act of 1934, as amended, and the rules and regulations thereunder (collectively, the "Exchange Act").

The Company and the Initial Purchasers agree as follows:

1. Sale and Purchase. Upon the basis of the representations and warranties and subject to the terms and conditions herein set forth, the Company agrees to sell to the Initial Purchasers, and each of the Initial Purchasers, severally and not jointly, agrees to purchase from the Company, the aggregate principal amount of Firm Notes set forth opposite the name of such Initial Purchaser in Schedule A hereto at a purchase price of 97% of the principal amount thereof.

In addition, the Company hereby grants to the several Initial Purchasers the option to purchase, and upon the basis of the representations and warranties and subject to the terms and conditions herein set forth, the Initial Purchasers shall have the right to purchase, severally and not jointly, from the Company all or a portion of the Additional Notes as may be necessary to cover over-allotments made in connection with the offering of the Firm Notes, at a purchase price of 97% of the principal amount thereof, plus accrued interest, if any, from the time of purchase (as hereinafter defined) to the additional time of purchase (as hereinafter defined). This option may be exercised by the Initial Purchasers, at any time and from time to time on or before the 30<sup>th</sup> day following the date hereof by written notice to the Company. Such notice shall set forth the aggregate initial principal amount of Additional Notes as to which the option is being exercised and the date and time when the Additional Notes are to be delivered (such date and time being herein referred to as the "additional time of purchase"); provided, however, that the additional time of purchase shall not be earlier than (i) the time of purchase or (ii) the second business day after the date on which the option shall have been exercised nor later than the tenth business day(1) after the date on which the option shall have been exercised. The principal amount of Additional Notes to be sold to each Initial Purchaser shall be the amount which bears the same proportion to the aggregate amount of Additional Notes being purchased as the principal amount of Firm Notes set forth opposite the name of such Initial Purchaser on Schedule A hereto bears to the total amount of Firm Notes.

2. Payment and Delivery. Payment of the purchase price for the Firm Notes shall be made to the Company by Federal (same day) funds, at the offices of Dewey Ballantine LLP in New York, New York, or at such other place as may be agreed upon by the parties hereto, for the respective accounts of the Initial Purchasers. Such payment and delivery shall be made at 10:00 A.M., New York City time, on May 1, 2002 (unless another time shall be agreed to by you and the Company or unless postponed in accordance with the provisions of Section 9 hereof). The time at which such payment and delivery are actually made is hereinafter sometimes called the "time of purchase."

Payment of the purchase price for the Additional Notes shall be made at the additional time of purchase in the same manner and at the same office as the payment for the Firm Notes.

Certificates for the Notes shall be in definitive form or global form, as specified by you, and registered in such names and in such denominations as you shall specify in writing not later than one full business day prior to the time of purchase or the additional time of purchase, as the case may be. For the purpose of expediting the checking of the certificates for the Notes by you, the Company agrees to

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(1) As used herein "business day" shall mean a day on which the New York Stock Exchange is open for trading.

3. Representations and Warranties of the Company. The Company represents and warrants to each of the Initial Purchasers that:

(a) the Preliminary Memorandum does not contain and the Final Memorandum, as amended or supplemented, as applicable, will not contain an untrue statement of a material fact or omit to state a material fact required to be stated therein or necessary to make the statements therein, in light of the circumstances under which they were made, not misleading; provided, however, that the Company makes no representation or warranty with respect to any statement contained in the Offering Memorandum in reliance upon and in conformity with information concerning the Initial Purchasers furnished in writing by or on behalf of any Initial Purchaser through you to the Company for use in the Offering Memorandum; and neither the Company nor any of its affiliates has distributed any offering material in connection with the offer or sale of the Notes other than the Offering Memorandum or any other materials, if any, permitted by the Act;

(b) the Company's capitalization (i) on December 31, 2001 was in all material respects as set forth under the heading entitled "Actual" in the section of the Offering Memorandum entitled "Capitalization"; and (ii) as of the time of purchase shall be in all material respects as set forth on an as adjusted basis to give effect to the sale of the Firm Notes, as set forth under the heading entitled "As Adjusted" in the section of the Offering Memorandum entitled "Capitalization" (subject to the issuance of shares of Common Stock upon the exercise of stock options disclosed as outstanding and issued under the plans described in the Offering Memorandum and subject to the issuance of shares of Common Stock pursuant to agreements described in the Offering Memorandum); all of the issued and outstanding shares of capital stock of the Company have been duly and validly authorized and issued and are fully paid and non-assessable, have been issued in compliance with all federal and state securities laws and were not issued in violation of any preemptive right, resale right, right of first refusal or similar right;

(c) the Company has been duly incorporated and is validly existing as a corporation in good standing under the laws of the State of Delaware, with the requisite corporate power and authority to own, lease and operate its properties and conduct its business as described in the Offering Memorandum;

(d) the Company is duly qualified to do business as a foreign corporation and is in good standing in each jurisdiction where the ownership or leasing of its properties or the conduct of its business requires such qualification, except where the failure to so qualify would not reasonably be expected to have a material adverse effect on the business, operations, prospects, properties, condition (financial or otherwise) or results of operation of the Company and the Subsidiaries (as hereinafter defined) taken as a whole (a "Material Adverse Effect"). The Company has no subsidiaries (as defined in the Act) other than as listed in Schedule B annexed hereto (the "Subsidiaries") and except for such other inactive subsidiaries that do not possess, individually or in the aggregate, any assets, liabilities or rights that are material to the Company and the Subsidiaries taken as a whole; the Company owns such interest in the Subsidiaries as is set forth in the Offering Memorandum; except for the Subsidiaries or as described in the Offering Memorandum, the Company does not own, directly or indirectly, any long-term debt or any material equity interest in any firm, corporation, partnership, joint venture, association or other entity; complete and correct copies of the certificates of incorporation and of the bylaws of the

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Company and all amendments thereto have been made available to you; each of the Subsidiaries has been duly incorporated and is validly existing as a corporation in good standing under the laws of the jurisdiction of its incorporation, with the requisite corporate power and authority to own, lease and operate its properties and to conduct its business as described in the Offering Memorandum; each of the Subsidiaries is duly qualified to do business as a foreign corporation and is in good standing in each jurisdiction where the ownership or leasing of the properties or the conduct of its business requires such qualification, except where the failure to so qualify would not reasonably be expected to have a Material Adverse Effect; all of the outstanding shares of capital stock of each of the Subsidiaries have been duly authorized and validly issued, are fully paid and non-assessable, have been issued in compliance with all applicable securities laws and were not issued in violation of any preemptive right, resale right, right of first refusal or similar right;

(e) neither the Company nor any of the Subsidiaries is in breach or violation of, or in default under (nor has any event occurred which with notice, lapse of time, or both would result in the Company's or any Subsidiary's breach or violation of, or constitute the Company's or any Subsidiary's default under) (each such breach, violation, default or event of the Company or any of the Subsidiaries, a "Default Event"), (i) its charter, bylaws or other organizational documents, (ii) any obligation, agreement, covenant or condition contained in any license, permit, indenture, mortgage, deed of trust, bank loan or credit agreement or other evidence of indebtedness, or any lease, contract or other agreement or instrument to which the Company or any of the Subsidiaries is a party or by which any of them or any of their properties may be bound or affected, (iii) any federal, state, local or foreign law, regulation or rule or (iv) any decree, judgment or order applicable to the Company, any of the Subsidiaries or any of their respective properties, other than, in the case of clauses (ii) and (iii), such Default Events as would not, individually or in the aggregate, reasonably be expected to have a Material Adverse Effect; and the execution, delivery and performance of this Agreement, the Registration Rights Agreement, the Indenture and the Notes and consummation of the other transactions contemplated hereby and thereby, including the issuance and sale of the Notes and the issuance of the Shares upon conversion of the Notes, does not constitute and will not result in a Default Event under (w) any provisions of the charter, bylaws or other organizational documents of the Company or any of the Subsidiaries, (x) under any provision of any license, permit, indenture, mortgage, deed of trust, bank loan or credit agreement or other evidence of indebtedness, or any lease, contract or other agreement or instrument to which the Company or any of the Subsidiaries or by which any of them or their respective properties may be bound or affected, (y) under any federal, state, local or foreign law, regulation or rule or (z) under any decree, judgment or order applicable to the Company, any of the Subsidiaries or any of their respective properties, except, in the case of clauses (x) and (y), for such Default Events as would not, individually or in the aggregate, reasonably be expected to have a Material Adverse Effect;

(f) this Agreement has been duly authorized, executed and delivered by the Company and is a legal, valid and binding agreement of the Company;

(g) the Registration Rights Agreement has been duly authorized by the Company and when executed and delivered by the Company and the other parties thereto will be a legal, valid and binding agreement of the Company, enforceable against the Company in accordance with its terms except as the enforceability thereof may be limited by bankruptcy, insolvency, fraudulent conveyance, reorganization, moratorium or similar laws affecting creditors' rights generally and general principles of equity and except to the extent the rights to indemnity may be limited by applicable law;

(h) the Notes have been duly authorized by the Company and when executed and delivered by the Company and duly authenticated in accordance with the terms of the Indenture and delivered to and paid for by the Initial Purchasers in accordance with the terms hereof will constitute legal, valid and binding obligations of the Company, enforceable against the Company in accordance with their terms except as the enforceability thereof may be limited by bankruptcy, insolvency, fraudulent conveyance, reorganization, moratorium or similar laws affecting creditors' rights generally and general principles of equity, and will be entitled to the benefits of the Indenture and the Registration Rights Agreement; the Shares initially issuable upon conversion of the Notes have been duly authorized and validly reserved for issuance upon conversion of the Notes, and upon conversion of the Notes in accordance with their terms and the terms of the Indenture will be issued free of statutory and contractual preemptive rights and are sufficient in number to meet the current conversion requirements, and such Shares, when so issued upon such conversion in accordance with the terms of the Indenture, will be duly and validly issued and fully paid and non-assessable;

(i) the Indenture has been duly authorized by the Company and when executed and delivered by the Company and the other parties thereto will be a legal, valid and binding agreement of the Company, enforceable against the Company in accordance with its terms except as the enforceability thereof may be limited by bankruptcy, insolvency, fraudulent conveyance, reorganization, moratorium or similar laws affecting creditors' rights generally and general principles of equity and except to the extent the rights to indemnity may be limited by applicable law;

(j) the terms of the Notes, the Registration Rights Agreement, the Indenture and the capital stock of the Company, including the Shares, conform in all material respects to the description thereof contained in the Offering Memorandum;

(k) no approval, authorization, consent or order of or filing with any national, state, local or other governmental or regulatory commission, board, body, authority or agency is required to be obtained or made by the Company or any of the Subsidiaries in connection with the issuance and sale of the Notes and the Shares as contemplated hereby or the consummation by the Company of the other transactions contemplated hereby other than (i) as may be required (A) under the securities or blue sky laws of the various jurisdictions in which the Notes and the Shares are being offered by the Initial Purchasers, (B) by federal and state securities laws with respect to the Company's obligations under the Registration Rights Agreement, (C) with respect to the Notes, under the applicable listing criteria of the National Association of Securities Dealers, Inc. (the "NASD") for its PORTAL trading market ("PORTAL") and (D) with respect to the Shares, under the applicable listing criteria of the Nasdaq National Market and (ii) as have been made or obtained on or prior to the time of purchase or the additional time of purchase, as the case may be (or, if not required to be made or obtained on or prior to the time of purchase or the additional time of purchase, as the case may be, that will be made or obtained when required);

(l) except as set forth in the Offering Memorandum (i) no person has the right, contractual or otherwise, to cause the Company to issue or sell to it the Notes or the Shares or any shares of Common Stock or shares of any other capital stock or other equity interests of the Company, (ii) no person has any preemptive rights, co-sale rights, rights of first refusal or other rights to purchase the Notes or the Shares or any shares of Common Stock or shares of any other capital stock or other equity interests of the Company and (iii) no person has the right to act as an underwriter, or as a financial advisor to the Company, in connection with the offer and sale

of the Notes and the Shares, in the case of each of the foregoing clauses (i), (ii) and (iii), whether as a result of the sale of the Notes and the Shares as contemplated hereby or otherwise; no person has the right, contractual or otherwise, to cause the Company to register under the Act any shares of Common Stock or shares of any other capital stock or other equity interests of the Company whether as a result of the sale of the Notes and the Shares as contemplated hereby, the transactions contemplated by the Registration Rights Agreement or otherwise, except as disclosed in the Offering Memorandum and except for such rights as have been complied with or waived, or, with respect to the transactions contemplated by the Registration Rights Agreement, except as such rights will be complied with or waived;

(m) Ernst & Young LLP, whose report on the consolidated financial statements of the Company and the Subsidiaries is included in the Offering Memorandum, are independent public accountants as required by the Act;

(n) the Company and each of the Subsidiaries has all necessary licenses, permits, authorizations, consents and approvals and has made all necessary filings required under any federal, state, local or foreign law, regulation or rule (collectively, "Permits"), and has obtained all authorizations, consents and approvals from other persons (collectively, "Approvals") that are necessary in order to conduct its business as described in the Offering Memorandum, other than such Permits and Approvals the failure of which to obtain would not, individually or in the aggregate, reasonably be expected to have a Material Adverse Effect; to its knowledge, neither the Company nor any of the Subsidiaries is in violation of, or any default under, any such Permit or Approval or any federal, state, local or foreign law, regulation or rule or any decree, order or judgment applicable to the Company or any of the Subsidiaries the effect of which would, individually or in the aggregate, reasonably be expected to have a Material Adverse Effect;

(o) all legal or governmental proceedings, related party transactions, contracts, leases or documents of a character required to be filed pursuant to the Exchange Act have been so filed, and all descriptions of such documents contained in the Offering Memorandum are correct in all material respects;

(p) except as disclosed in the Offering Memorandum, there are no actions, suits, claims, investigations or proceedings pending or threatened to which the Company, its directors or officers, any of the Subsidiaries or, to the Company's knowledge, any of the Subsidiaries' directors or officers is a party or of which any of their respective properties is subject at law or in equity, or before or by any federal, state, local or

foreign governmental or regulatory commission, board, body, authority or agency which, if adversely decided, would reasonably be expected to result in a judgment, decree or order having a Material Adverse Effect or prevent consummation of the transactions contemplated hereby;

(q) the financial statements, together with the related schedules and notes, included in the Offering Memorandum present fairly in all material respects the consolidated financial position of the Company and the Subsidiaries as of the dates indicated and the consolidated results of operations and cash flows of the Company and the Subsidiaries for the periods specified and have been prepared in compliance in all material respects with the requirements of the Act and in conformity with generally accepted accounting principles applied on a consistent basis during the periods involved; the other financial and statistical data set forth under "Summary Consolidated Financial Data," "Capitalization," and "Selected Consolidated Financial Data" in the Offering Memorandum are accurately presented in all material respects and

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prepared on a basis consistent with such financial statements and books and records of the Company;

(r) subsequent to the respective dates as of which information is given in the Final Memorandum, there has not been (i) any material adverse change, or any development which could reasonably be expected to result in a material adverse change in the business, operations, properties, condition (financial or otherwise), or results of operations of the Company and the Subsidiaries taken as a whole, (ii) any transaction of the Company or the Subsidiaries which is material to the Company and the Subsidiaries taken as a whole, (iii) any obligation, direct or contingent, which is material to the Company and the Subsidiaries taken as a whole, incurred by the Company or any of the Subsidiaries, or (iv) any dividend or distribution of any kind declared, paid or made on the capital stock of the Company other than accrued, paid in kind dividends for the Company's Series A Convertible Exchangeable 5% Preferred Stock and Series B Convertible Exchangeable 5% Preferred Stock; neither the Company nor any of the Subsidiaries has any material contingent obligation which is not disclosed in the Offering Memorandum;

(s) the Company has obtained for the benefit of the Initial Purchasers the agreement (a "Lock-Up Agreement"), in the form set forth as Exhibit A hereto, of each of its executive officers and directors; the Company will not release or purport to release any of its executive officers or directors from any Lock-Up Agreement without the prior written consent of UBS Warburg LLC;

(t) the Company is not and, after giving effect to the offering and sale of the Notes, will not be an "investment company" or an entity "controlled" by an "investment company," as such terms are defined in the Investment Company Act of 1940, as amended (the "Investment Company Act");

(u) any statistical and market related data included in the Offering Memorandum are based on or derived from sources that the Company believes to be reliable and accurate, and the Company has obtained the written consent to the use of such data from such sources to the extent required;

(v) neither the Company nor any of the Subsidiaries nor, to the Company's knowledge, any of their respective affiliates has taken, directly or indirectly, any action designed to or which has constituted or which might reasonably be expected to cause or result, under the Exchange Act or otherwise, in the stabilization or manipulation of the price of any security of the Company to facilitate the sale or resale of the Notes;

(w) the Company and each of the Subsidiaries maintain insurance of the types and in amounts reasonably adequate for their respective businesses, including, but not limited to, insurance covering real and personal property owned or leased by the Company against theft, damage, destruction, acts of vandalism and other risks customarily insured against, all of which insurance is in full force and effect;

(x) neither the Company nor any of the Subsidiaries has sustained since the date of the latest financial statements included in the Offering Memorandum any losses or interferences with its business from fire, explosion, flood or other calamity, whether or not covered by insurance, or from any labor dispute or court or governmental action, order or decree, otherwise than as set forth or contemplated in the Offering Memorandum or other than any losses

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or interferences which would not, individually or in the aggregate, reasonably be expected to have a Material Adverse Effect;

(y) the Company and each of the Subsidiaries have good title to all personal property owned by them as described in the Offering Memorandum, which to the Company's knowledge is free and clear of all liens, encumbrances and defects except such as (i) are described in the Offering Memorandum, (ii) were incurred in the ordinary course of business and are not material or (iii) would not, individually or in the aggregate, reasonably be expected to have a Material Adverse Effect; except as described in the Offering Memorandum, any real property and buildings held under lease by the Company are held by it under valid, subsisting and enforceable leases with such exceptions as are not material and do not interfere with the use made and presently proposed to be made of such property and buildings by the Company or any of the Subsidiaries, as the case may be;

(z) neither the Company nor, to the Company's knowledge, any of the Subsidiaries has violated any foreign, federal, state or local law or regulation relating to the protection of human health and safety, the environment or hazardous or toxic substances or wastes, pollutants or contaminants, nor any federal or state law relating to discrimination in the hiring, promotion or pay of employees nor any applicable federal or state wages and hours laws, nor any provisions of the Employee Retirement Income Security Act or the rules and regulations promulgated thereunder, which would, individually or in the aggregate, reasonably be expected to result in a Material Adverse Effect;

(aa) the Company and each of the Subsidiaries maintain a system of internal accounting controls sufficient to provide reasonable assurance that (i) transactions are executed in accordance with management's general or specific authorizations; (ii) transactions are recorded as necessary to permit preparation of financial statements in conformity with generally accepted accounting principles and to maintain asset accountability; (iii) access to assets is permitted only in accordance with management's general or specific authorization; and (iv) the recorded accountability for assets is compared with the existing assets at reasonable intervals and appropriate action is taken with respect to any differences;

(bb) except as would not individually or in the aggregate reasonably be expected to have a Material Adverse Effect, all tax returns required to be filed by the Company and each of the Subsidiaries have been filed, other than those filings being contested in good faith, and all taxes, including withholding taxes, penalties and interest, assessments, fees and other charges due pursuant to such returns or pursuant to any assessment received by the Company or any of the Subsidiaries have been paid, other than those being contested in good faith and for which adequate reserves have been provided;

(cc) all documents incorporated by reference by the Offering Memorandum complied in all material respects, as of the date of the Offering Memorandum, with the requirements of the Exchange Act;

(dd) other than as set forth in the Offering Memorandum, or as would not individually or in the aggregate, reasonably be expected to have a Material Adverse Effect, the Company and the Subsidiaries own, possess, license or have other rights to use, all patents, trademarks, servicemarks, trade names, copyrights, trade secrets, information, proprietary rights and processes ("Intellectual Property") necessary for their business as described in the Offering Memorandum, without any known conflict with or infringement of the interests of others. Except

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as described in the Offering Memorandum, the Company is not aware of any options, licenses or agreements of any kind relating to the Intellectual Property of the Company or the Subsidiaries that are outstanding and required to be described in a document incorporated by reference into the Offering Memorandum, and, except as described in the Offering Memorandum, neither the Company nor either of the Subsidiaries is a party to or bound by any options, licenses or agreements with respect to the Intellectual Property of any other person or entity that are required to be described in a document incorporated by reference into the Offering Memorandum; none of the technology employed by the Company and the Subsidiaries has been obtained or is used or proposed to be used by the Company or the Subsidiaries in violation of any contractual obligation binding on the Company or the Subsidiaries or any of their respective directors or executive officers or, to the Company's knowledge, any employees of the Company or the Subsidiaries, other than any violation which would not reasonably be expected to individually or in the aggregate have a Material Adverse Effect; except as described in the Offering Memorandum, to the Company's knowledge neither the Company nor either of the Subsidiaries has violated, infringed or conflicted with, or, by conducting its business as described in the Offering Memorandum and commercializing the products under development described therein, would violate, infringe or conflict with any of the Intellectual Property of any other person or entity other than any such violation, infringement or conflict which would not reasonably be expected to individually or in the aggregate have a Material Adverse Effect;

(ee) the clinical, pre-clinical and other studies and tests conducted by or on behalf of or sponsored by the Company or any Subsidiary or in which the Company, any Subsidiary or their respective products or product candidates have participated that are described in the Offering Memorandum or the results of which are referred to in the Offering Memorandum were and, if still pending, are being conducted in accordance with standard medical and scientific research procedures; except to the extent disclosed in the Offering Memorandum, the Company and each Subsidiary has operated and currently is in compliance in all material respects with all applicable rules, regulations and policies of the U.S. Food and Drug Administration and comparable drug regulatory agencies outside of the United States (collectively, the "Regulatory Authorities"); and except to the extent disclosed in the Offering Memorandum, the Company has not received any notices or other correspondence from the Regulatory Authorities or any other governmental agency requiring the termination or suspension of any clinical or pre-clinical studies or tests that are described in the Offering Memorandum or the results of which are referred to in the Offering Memorandum;

(ff) when the Notes are issued pursuant to this Agreement, the Notes will not be of the same class (within the meaning of Rule 144A) as securities of the Company that are listed on a national securities exchange registered pursuant to Section 6 of the Exchange Act or quoted in a U.S. automated inter-dealer quotation system;

(gg) none of the Company, the Subsidiaries or any affiliate (as defined in Rule 501(b) of Regulation D under the Act, an "Affiliate") of the Company has directly, or through any agent, (i) sold, offered for sale, solicited offers to buy or otherwise negotiated in respect of, any security (as defined in the Act) which is or will be integrated with the sale of the Notes in a manner that would require the registration under the Act of the Notes or (ii) offered, solicited offers to buy or sold the Notes by any form of general solicitation or general advertising (as those terms are used in Regulation D under the Act) or in any manner involving a public offering within the meaning of Section 4(2) of the Act;

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(hh) none of the Company, its Affiliates or any person acting on its or their behalf (other than the Initial Purchasers, for which parties the Company makes no representations), or, to the knowledge of the Company, the Subsidiaries, has engaged or will engage in any directed selling efforts (within the meaning of Regulation S) with respect to any offer or sale of the Notes made in reliance on Regulation S, and the Company and its Affiliates and any person acting on its or their behalf (other than the Initial Purchasers, for which parties the Company makes no representations), and to the knowledge of the Company, the Subsidiaries, have complied and will comply with the offering restrictions requirement of Regulation S with respect to any offer or sale of the Notes made in reliance on Regulation S; and

(ii) it is not necessary in connection with the offer, sale and delivery of the Notes to the Initial Purchasers pursuant to this Agreement to register the Notes under the Act or to qualify the Indenture under the Trust Indenture Act of 1939, as amended.

4. Representations and Warranties of the Initial Purchasers. The Initial Purchasers propose to offer the Notes for sale upon the terms and conditions set forth in this Agreement and the Offering Memorandum, and each Initial Purchaser hereby represents and warrants to and agrees with the Company that:

- (a) It will offer and sell the Notes only: (i) to persons whom it reasonably believes are "qualified institutional buyers" ("QIBs") within the meaning of Rule 144A in transactions meeting the requirements of Rule 144A and (ii) outside the United States to persons other than U.S. persons (as defined in Regulation S) in compliance with Regulation S, who, in each case, in purchasing such Notes, are deemed to have represented and agreed as provided in the Offering Memorandum under the caption "Notice to investors";
- (b) It is a QIB within the meaning of Rule 144A;
- (c) It has not and will not directly or indirectly, solicit offers in the United States for, or offer or sell, the Notes by any form of general solicitation, general advertising (as such terms are used in Regulation D) or in any manner involving a public offering within the meaning of Section 4(2) of the Act; and
- (d) With respect to offers and sales outside the United States:
  - (i) It understands that no action has been or will be taken in any jurisdiction by the Company that would permit a public offering of the Notes, or possession or distribution of the Offering Memorandum or any other offering or publicity material relating to the Notes, in any country or jurisdiction where action for that purpose is required;
  - (ii) The Notes have not been registered under the Act and may not be offered or sold within the United States or to, or for the account or benefit of, U.S. persons except in accordance with Rule 144A or Regulation S or pursuant to another exemption from the registration requirements of the Act; and
  - (iii) It has offered the Notes and will offer and sell the Notes (A) as part of their distribution at any time and (B) otherwise until one year after the later of the commencement of the offering and the time of purchase (or the additional time of purchase, if later) (the "Distribution Compliance Period"), only in accordance with Rule 903 of Regulation S or as otherwise permitted in this Section 4; accordingly, neither it, its

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Affiliates nor any persons acting on its or their behalf have engaged or will engage in any directed selling efforts (within the meaning of Regulation S) with respect to the Notes, and it, its Affiliates and such persons have complied and will comply with the offering restrictions requirement of Regulation S, including, during the Distribution Compliance Period:

- a) no such offer or sale will be made to a U.S. person or for the account or benefit of a U.S. person (other than an Initial Purchaser);
- b) it will not engage in hedging transactions involving the Notes or the Shares unless in compliance with the Act and will include in any information provided to publishers of publicly available databases a statement that the Notes are subject to restrictions under Regulation S and Rule 144A; and
- c) it, its Affiliates and any person acting on its behalf, if selling Notes to another Initial Purchaser, a dealer or a person receiving a selling concession, fee or other remuneration in respect of the Notes, will send a confirmation or other notice to the purchaser stating that the purchaser is subject to the same restrictions on offers and sales as set forth in this Section 4.

5. Certain Covenants of the Company. The Company hereby agrees:

- (a) to prepare the Offering Memorandum in a form approved by the Initial Purchasers and not to make any amendment or supplement to the Final Memorandum which shall reasonably be disapproved by counsel to the Initial Purchasers promptly after reasonable notice thereof;
- (b) to furnish such information as may be required and otherwise to cooperate in qualifying the Notes and the Shares for offering and sale under the securities or blue sky laws of such states as you may designate and to maintain such qualifications in effect so long as required for the distribution of the Notes; provided that the Company shall not be required to qualify as a foreign corporation or to consent to the service of process under the laws of any such state (except service of process with respect to the offering and sale of the Notes); and to promptly advise you of the receipt by the Company of any notification with respect to the suspension of the qualification of the Notes and the Shares for sale in any jurisdiction or the initiation or threat of any proceeding for such purpose;
- (c) to furnish, upon request, to the Initial Purchasers for as long as the Notes are outstanding (i) copies of any reports or other communications which the Company shall send to its stockholders or shall from time to time publish or publicly disseminate, (ii) copies of all annual, quarterly and current reports filed with the Commission on Forms 10-K, 10-Q and 8-K, or such other similar forms, as may be designated by the Commission, (iii) copies of documents or reports filed with any national securities exchange on which any class of securities of the Company is listed and (iv) such other public information as you may reasonably request regarding the Company or any of the Subsidiaries, in each case as soon as reasonably practicable after such reports, communications, documents or information become available;



(d) to furnish the Initial Purchasers with as many copies of the Offering Memorandum, any documents incorporated by reference therein and any amendment or supplement thereto as the Initial Purchasers may from time to time reasonably request, and if, at any time prior to the completion of the resale of the Notes by the Initial Purchasers, any event shall have occurred as a result of which the Offering Memorandum as then amended or supplemented would include an untrue statement of material fact or omit to state a material fact necessary to make the statements therein, in the light of the circumstances under which they were made when such Offering Memorandum is delivered, not misleading, or, if for any other reason it shall be necessary or desirable during such time to amend or supplement the Offering Memorandum, to notify the Initial Purchasers and upon the request of the Initial Purchasers to prepare and furnish, at the Company's expense, to the Initial Purchasers and to any dealer in securities as many copies as the Initial Purchasers may from time to time reasonably request of an amended Offering Memorandum or a supplement to the Offering Memorandum which will correct such statement or omission or effect such compliance;

(e) to furnish to you as early as reasonably practicable prior to the time of purchase and the additional time of purchase, as the case may be but not later than two business days prior thereto, a copy of the latest available unaudited interim consolidated financial statements, if any, of the Company and the Subsidiaries which have been read by the Company's independent certified public accountants, as stated in their letter to be furnished pursuant to Section 7(d) hereof;

(f) at any time when the Company is not subject to Section 13 or 15(d) of the Exchange Act and so long as any of the Notes (or Shares issued upon conversion thereof) are "restricted securities" within the meaning of Rule 144(a)(3) under the Act, for the benefit of holders from time to time of the Notes, to furnish at its expense, upon request, to holders of Notes and prospective purchasers of Notes information satisfying the requirements of subsection (d)(4)(i) of Rule 144A;

(g) to use its best efforts to cause the Notes to be eligible for trading in PORTAL;

(h) to apply the net proceeds from the sale of the Notes in the manner set forth under the caption "Use of proceeds" in the Offering Memorandum;

(i) to reserve and keep available at all times free of preemptive rights, Shares for the purpose of enabling the Company to satisfy any obligations to issue Shares upon conversion of the Notes;

(j) to use its best efforts to list, as promptly as practicable but in no event later than the time that the registration statement is declared effective in accordance with the Registration Rights Agreement, and subject to notice of issuance, the Shares on the Nasdaq National Market;

(k) to pay all costs, expenses, fees and taxes in connection with (i) the preparation of each Preliminary Memorandum, Final Memorandum and any amendments or supplements thereto, and the printing and furnishing of copies of each thereof to the Initial Purchasers and to dealers (including costs of mailing and shipment), (ii) the preparation, issue, execution, authentication, transfer and delivery of the Notes and the Shares, (iii) the printing of this Agreement, the Registration Rights Agreement, the Indenture and any closing documents

(including compilations thereof) and the reproduction and/or printing and furnishing of copies of each thereof to the Initial Purchasers and (except closing documents) to dealers (including costs of mailing and shipment), (iv) the qualification of the Notes and the Shares for offering and sale under state laws and the determination of their eligibility for investment under state law as aforesaid (including associated filing fees and the reasonable legal fees and disbursements of counsel for the Initial Purchasers) and the printing and furnishing of copies of any blue sky surveys or legal investment surveys to the Initial Purchasers and to dealers, (v) any fees payable to investment rating agencies with respect to the rating of the Notes, (vi) the cost and charges of the Trustee and any transfer agent, registrar or depository, (vii) the costs and expenses of the Company relating to presentations or meetings undertaken in connection with the marketing of the offer and sale of the Notes to prospective investors and the Initial Purchasers' sales forces, including, without limitation, expenses associated with the production of road show slides and graphics, fees and expenses of any consultants engaged in connection with the road show presentations, travel, lodging and other expenses incurred by the officers of the Company and any such consultants, and the cost of any aircraft chartered in connection with the road show and (viii) the performance of the other obligations of the Company hereunder;

(l) not to sell, offer or agree to sell, contract to sell, hypothecate, pledge, grant any option to sell or otherwise dispose of, directly or indirectly, any Notes or shares of Common Stock or securities convertible into or exchangeable or exercisable for Common Stock or other rights to purchase Common Stock or any other securities of the Company that are substantially similar to the Notes or the Common Stock, or file or cause to be declared effective a registration statement under the Act relating to the offer and sale of any Notes or shares of Common Stock or securities convertible into or exercisable or exchangeable for Common Stock or other rights to purchase Common Stock or any other securities of the Company that are substantially similar to the Notes or the Common Stock, for a period of ninety (90) days after the date hereof (the "Lock-up Period"), without the prior written consent of UBS Warburg LLC except for (i) the issuance and sale of the Notes pursuant to this Agreement and the issuance of Shares upon conversion of the Notes, (ii) the registration of the offer and sale of the Notes and the Shares pursuant to the Registration Rights Agreement, (iii) issuances of Common Stock upon the exercise of options or warrants or upon the conversion of convertible securities disclosed as outstanding in the Offering Memorandum, (iv) the issuance of stock options not exercisable during the Lock-up Period pursuant to stock option plans described in the Offering Memorandum and (v) the issuance and registration of securities which may be required pursuant to the Company's or the Subsidiaries' currently outstanding agreements which are described in the Offering Memorandum, including without limitation the issuance of Common Stock to Hybridon, Inc. and the registration thereof under the Act. During the first 45 days of the Lock-up Period UBS Warburg LLC may withhold its consent to the actions described in this Section 5(l) for any or no reason. If after the expiration of the first 45 days of the Lock-up Period the average last reported sales price of the Common Stock on the Nasdaq National Market for any five consecutive trading days equals or exceeds \$19.95 per share

(adjusted for any stock split, combination or similar transaction), then UBS Warburg LLC may not thereafter withhold its consent to such actions unreasonably.

(m) not to sell, offer for sale or solicit offers to buy or otherwise negotiate in respect of any security (as defined in the Act), either directly or by an Affiliate, which could be integrated with the sale of the Notes in a manner which would require the registration under the Act of the offer and sale of the Notes;

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(n) not to solicit any offer to buy or offer or sell the Notes or the Shares by means of any form of general solicitation or general advertising (as those terms are used in Regulation D) or in any manner involving a public offering within the meaning of Section 4(2) of the Act;

(o) with respect to those Notes sold in reliance on Regulation S, (i) not to, either directly or by any of its affiliates or any person acting on its or their behalf (other than the Initial Purchasers), engage in any directed selling efforts (within the meaning of Regulation S) and (ii) directly and its affiliates and any person acting on its or their behalf (other than the Initial Purchasers) to comply with the requirements of Regulation S and, during the Distribution Compliance Period, to include in any information provided to publishers of publicly available databases a statement that the Notes are subject to restrictions under Regulation S and Rule 144A;

(p) during the period of two years after the time of purchase or the additional time of purchase, if later, not to directly, nor permit any of its affiliates (as defined in Rule 144 under the Act ("Rule 144")) to, resell any of the Notes or the Shares which constitute "restricted securities" under Rule 144 that have been reacquired by any of them except pursuant to an effective registration statement under the Act;

(q) not to take any action prohibited by Regulation M under the Exchange Act in connection with the distribution of the Notes contemplated hereby; and

(r) to file in a timely manner a Form D with the Securities and Exchange Commission pursuant to Regulation D under the Act relating to the offer and sale of the Notes.

6. Reimbursement of Initial Purchasers' Expenses. If the Notes are not delivered for any reason other than the termination of this Agreement pursuant to the last paragraph of Section 9 hereof or the default by one or more of the Initial Purchasers in its or their respective obligations hereunder, the Company agrees, in addition to paying the amounts described in Section 5(k) hereof, to reimburse the Initial Purchasers for all of their out-of-pocket expenses, including the reasonable fees and disbursements of their counsel.

7. Conditions of Initial Purchasers' Obligations. The several obligations of the Initial Purchasers hereunder are subject to the accuracy of the representations and warranties on the part of the Company on the date hereof and at the time of purchase (and the several obligations of the Initial Purchasers at the additional time of purchase are subject to the accuracy of the representations and warranties on the part of the Company on the date hereof and at the time of purchase (unless previously waived) and at the additional time of purchase, as the case may be), the performance by the Company of its obligations hereunder and to the following additional conditions precedent:

(a) You shall have received, at the time of purchase and at the additional time of purchase, as the case may be, an opinion of Cooley Godward LLP, counsel for the Company, addressed to the Initial Purchasers, and dated the time of purchase or the additional time of purchase, as the case may be, with reproduced copies for each of the other Initial Purchasers and in form reasonably satisfactory to Dewey Ballantine LLP, counsel for the Initial Purchasers, stating that:

(i) the Company has been duly incorporated and is validly existing as a corporation and in good standing under the laws of the State of Delaware, with full corporate power and authority to own, lease and operate its properties and conduct its

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business as described in the Offering Memorandum, to execute and deliver this Agreement, the Registration Rights Agreement and the Indenture and to issue, sell and deliver the Notes and, if issued on the date hereof, the Shares in accordance with the terms of the Indenture, as herein contemplated;

(ii) the Company is duly qualified to do business as a foreign corporation and is in good standing in each jurisdiction in which such qualification is necessary, except where the failure to so qualify would not reasonably be expected to have a Material Adverse Effect;

(iii) this Agreement has been duly authorized, executed and delivered by the Company;

(iv) the Registration Rights Agreement has been duly authorized, executed and delivered by the Company and is a legal, valid and binding agreement of the Company, enforceable against the Company in accordance with its terms;

(v) the Indenture has been duly authorized, executed and delivered by the Company and is a legal, valid and binding agreement of the Company, enforceable against the Company in accordance with its terms;

(vi) the Company has authorized and outstanding (as of the dates indicated) shares of capital stock as set forth in the Offering Memorandum under the caption "Capitalization"; the outstanding shares of capital stock of the Company (A) have been duly authorized and validly issued and are fully paid and non-assessable and (B) were issued in compliance with all preemptive rights, co-sale rights and rights of first refusal under (1) the Delaware General Corporation Law (the "DGCL"), (2) the Certificate of Incorporation, as amended, and Bylaws of the Company and (3) any contract, commitment or instrument filed as an exhibit to a document filed by the Company pursuant to the Exchange Act and incorporated by reference in the Offering Memorandum (collectively, the "Material Agreements"); with respect to the Company's issuance of the Shares upon conversion of the Notes, there are no applicable preemptive rights under the DGCL, the Certificate of Incorporation, as amended, or Bylaws of the Company or any of the Material Agreements;

(vii) the common stock of the Company conforms in all material respects to the description thereof contained in the Offering Memorandum (as incorporated by reference therein from the Company's Registration Statement on Form 8-A filed with the Commission on April 12, 1991 and from the Company's Certificate of Amendment of Restated Certificate of Incorporation filed with the Company's Quarterly Report on Form 10-Q for the period ended June 30, 2001, as amended);

(viii) no approval, authorization, consent or order of or filing with any national, state or local governmental or regulatory commission, board, body, authority or agency is required to be obtained or made by the Company in connection with the execution and delivery of this Agreement, the Registration Rights Agreement and the Indenture and the issuance and sale of the Notes and, if issued on the date hereof, the Shares, except for such as (A) may be required under state securities laws and except for the filing of a Form D with the Securities and Exchange Commission pursuant to Regulation D under the Act, (B) are required in connection with the filing of the shelf registration

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statement(s) as contemplated by the Registration Rights Agreement and (C) have been obtained or made prior to the date hereof;

(ix) the execution and delivery of this Agreement, the Registration Rights Agreement, the Indenture and the Notes by the Company, the issuance of the Notes and, if issued on the date hereof, the issuance of the Shares upon the conversion of the Notes do not constitute, and will not result in, a Default Event pursuant to (A) any provision of the Certificate of Incorporation, as amended, or Bylaws of the Company, (B) any Material Agreement, (C) any law, regulation or rule applicable to the Company (other than state or foreign securities laws, as to which such counsel expresses no opinion) or (D) any decree, judgment or order known by such counsel to be applicable to the Company or any of the Subsidiaries other than, in the case of clause (B) such Default Events as would not, individually or in the aggregate, reasonably be expected to have a Material Adverse Effect;

(x) to the best of such counsel's knowledge, there are no related party transactions, contracts, licenses, agreements, leases or documents of a character which are required to be filed as exhibits to the documents incorporated by reference in the Offering Memorandum or to be summarized or described in such documents which have not been so filed, summarized or described;

(xi) to the best of such counsel's knowledge, except as disclosed in the Offering Memorandum, there are no actions, suits, claims, investigations or proceedings pending or overtly threatened to which the Company or any of the Subsidiaries is subject or of which any of their respective properties is subject, whether at law, in equity or before or by any federal, state, local or foreign governmental or regulatory commission, board, body, authority or agency which, if determined adversely to the Company, would, individually or in the aggregate, reasonably be expected to have a Material Adverse Effect;

(xii) the Company is not and, after giving effect to the offer and sale of the Notes, will not be an "investment company" or an entity "controlled" by an "investment company," as such terms are defined in the Investment Company Act;

(xiii) the Notes have been duly authorized and executed by the Company and when duly authenticated in accordance with the terms of the Indenture and delivered to and paid for by the Initial Purchasers in accordance with the terms of this Agreement will constitute legal, valid and binding obligations of the Company;

(xiv) the Shares initially issuable upon conversion of the Notes have been duly authorized and reserved for issuance upon conversion of the Notes and are initially sufficient in number to meet the conversion requirements of the Notes, and such Shares, when so issued in accordance with the terms of the Indenture, will be duly and validly issued and fully paid and non-assessable;

(xv) assuming (A) the veracity of the representations and warranties of the Company set forth in Section 3 of this Agreement and of the Initial Purchasers set forth in Section 4 of this Agreement and (B) compliance by the Company with the covenants and agreements set forth in Section 5 of this Agreement and by the Initial Purchasers with the covenants and agreements set forth in Section 4 of this Agreement, it is not

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necessary in connection with (x) the offer, sale and delivery of the Notes to the Initial Purchasers pursuant to this Agreement or (y) the initial resales of the Notes by the Initial Purchasers in the manner contemplated in the Offering Memorandum to register the Notes under the Act or to qualify the Indenture in respect thereof under the Trust Indenture Act of 1939, as amended, it being understood that no opinion is expressed as to any subsequent resale of any Note or Share;

(xvi) the statements set forth in the Offering Memorandum under the caption "Description of convertible notes," insofar as such description purports to describe the provisions of documents referred to therein, fairly present in all material respects such documents;

(xvii) those statements in the Offering Memorandum under the captions "Risk factors—Provisions in our certificate of incorporation, other agreements and Delaware law may prevent stockholders from receiving a premium for their shares" and "Risk factors—If registration rights that we have previously granted are exercised, then the price of our securities may be negatively affected" that are descriptions of contracts, agreements or other legal documents or of legal proceedings, or refer to statements of law or legal conclusions, are accurate in all material respects and present fairly the information or applicable law referred to therein;

(xviii) those statements in the Offering Memorandum under the caption "Material United States federal income tax considerations," insofar as such statements constitute a discussion of the United States federal tax laws referred to therein, are accurate in all material respects and fairly present in all material respects the United States federal tax laws referred to therein; and

(xix) except as described in the Offering Memorandum (including those documents incorporated by reference therein), no person has the right, pursuant to the terms of any Material Agreement, to have any securities issued by the Company and owned by such person registered pursuant to the Act, as a result of the transactions contemplated by this Agreement or otherwise, except for such rights as have been complied with or waived.

In addition, such counsel shall state that, during the course of the preparation of the Offering Memorandum (it being understood that such counsel did not participate in the preparation of the documents incorporated by reference), such counsel has participated in conferences with officers and other representatives of the Company, representatives of the independent public accountants of the Company and representatives of the Initial Purchasers at which the contents of the Offering Memorandum were discussed. Although such counsel has not independently verified and is not passing upon and does not assume responsibility for the accuracy, completeness or fairness of the statements contained in the Offering Memorandum (except as and to the extent stated in subparagraphs (vii), (xvi), (xvii) and (xviii) above), on the basis of the foregoing nothing has come to the attention of such counsel that causes such counsel to believe that the Offering Memorandum or any amendment or supplement thereto at the date of such Offering Memorandum or such amendment or supplement, and at all times up to and including the time of purchase or additional time of purchase, as the case may be, contained or contains an untrue statement of a material fact or omitted or omits to state a material fact required to be stated therein or necessary to make the statements therein, in light of the circumstances under which they were made, not misleading (it being understood that such counsel need express no opinion with respect to the financial statements and schedules and other financial or statistical data included in the Offering Memorandum).

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(b) You shall have received at the time of purchase and at the additional time of purchase, as the case may be, the opinion of Woodcock Washburn LLP, patent counsel to the Company, dated the time of purchase or the additional time of purchase, as the case may be, with reproduced copies for each of the other Initial Purchasers and in form reasonably satisfactory to Dewey Ballantine LLP, counsel for the Initial Purchasers, stating that:

(i) based on information brought to such counsel's attention by the Company with respect to the Company's investigation of the published literature and patent references relating to the inventions claimed in its patent applications in such counsel's care (the "relevant applications"), such counsel has disclosed all pertinent art references to the United States Patent and Trademark Office in such applications. To the best of such counsel's knowledge, all information submitted to the United States Patent and Trademark Office in the relevant applications and in connection with the prosecution of the relevant applications was accurate. Neither such counsel nor, to the best of its knowledge, the Company has made any misrepresentation or concealed any material fact from the Patent and Trademark Office in any of the relevant applications, or in connection with the prosecution of such applications;

(ii) the statements in the Offering Memorandum under the heading "Risk factors—Intellectual property litigation could be expensive and prevent us from pursuing our programs" and in the Company's Annual Report on Form 10-K for the year ended December 31, 2001 under the caption "Patents and Proprietary Rights" constitute an accurate summary of the matters referred to therein and fairly present the information called for with respect to such matters; and

(iii) other than as disclosed in the Offering Memorandum, to the best of such counsel's knowledge, the Company's products and products under development do not, and would not upon commercialization, infringe or conflict with asserted rights of any third party with respect to any material patents, trademarks, licenses, copyrights and proprietary or other confidential information employed by the Company in connection with its business.

With respect to subparagraph (i) of paragraph (b) above, Woodcock Washburn LLP may state that they have not independently conducted any investigation of the published literature and patent references relating to the inventions claimed in the Company's patent applications.

(c) You shall have received at the time of purchase and at the additional time of purchase, as the case may be, the opinion of Dewey Ballantine LLP, counsel for the Initial Purchasers, dated the time of purchase or the additional time of purchase, as the case may be, with respect to the issuance and sale of the Notes by the Company, the Offering Memorandum (together with any supplement thereto) and other related matters as the Initial Purchasers may require.

(d) You shall have received from Ernst & Young LLP letters dated, respectively, the date of this Agreement and the time of purchase and additional time of purchase, as the case may be, and addressed to the Initial Purchasers (with reproduced copies for each of the Initial Purchasers) in the forms heretofore approved by UBS Warburg LLC.

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(e) No amendment or supplement to the Offering Memorandum, or document which upon filing with the Commission would be incorporated by reference therein, shall at any time have been made or filed to which you have objected or shall object in writing.

(f) At the time of purchase or the additional time of purchase, as the case may be, the Offering Memorandum and all amendments or supplements thereto, or modifications thereof, if any, shall not contain an untrue statement of a material fact or omit to state a material fact required to be stated therein or necessary to make the statements therein, in the light of the circumstances under which they are made, not misleading.

(g) Between the time of execution of this Agreement and the time of purchase or the additional time of purchase, as the case may be, (i) no material and adverse change or any development involving a prospective material and adverse change (other than as specifically described in the Offering Memorandum), in the business, properties, condition (financial or otherwise) or results of operations of the Company and the Subsidiaries, taken as a whole, shall occur or become known and (ii) no transaction which is material and adverse to the Company shall have been entered into by the Company or any of the Subsidiaries.

(h) The Company will, at the time of purchase or additional time of purchase, as the case may be, deliver to you a certificate signed by one of the Company's executive officers to the effect that the representations and warranties of the Company as set forth in this Agreement are true and correct as of each such date, that the Company has performed such of its obligations under this Agreement as are to be performed at or before the time of purchase and at or before the additional time of purchase, as the case may be, and the conditions set forth in paragraphs (f) and (g) of this Section 7 have been met.

(i) You shall have received the letters referred to in Section 3(s).

(j) The Company shall have furnished to you such other documents and certificates as to the accuracy and completeness of any statement in the Offering Memorandum as of the time of purchase and the additional time of purchase, as the case may be, as you may reasonably request.

(k) The Notes shall have been designated for trading on PORTAL, subject only to notice of issuance at or prior to the time of purchase.

(l) Between the time of execution of this Agreement and the time of purchase or additional time of purchase, as the case may be, there shall not have occurred any downgrading, nor shall any notice or announcement have been given or made of (i) any intended or potential downgrading or (ii) any review or possible change that does not indicate an improvement, in the rating accorded any securities of or guaranteed by the Company or any Subsidiary by any "nationally recognized statistical rating organization", as that term is defined in rule 436(g)(2) under the Act.

8. Effective Date of Agreement; Termination. This Agreement shall become effective when the parties hereto have executed and delivered this Agreement.

The obligations of the several Initial Purchasers hereunder shall be subject to termination in the absolute discretion of UBS Warburg LLC or any group of Initial Purchasers (which may include UBS Warburg LLC) which has agreed to purchase in the aggregate at least 50% of the Firm Notes, (i) if, since the time of execution of this Agreement or the respective dates as of which information is given in

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the Offering Memorandum, there has been any material adverse change, financial or otherwise (other than as specifically described in the Preliminary Offering Memorandum at the time of execution of this Agreement), in the operations, business, condition or prospects of the Company and the Subsidiaries taken as a whole, which would, in the judgment of UBS Warburg LLC or in the judgment of such group of Initial Purchasers, make it impracticable to market the Notes in the manner and on the terms set forth in the Final Offering Memorandum, (ii) there shall have occurred any downgrading, or any notice shall have been given of (x) any intended or potential downgrading or (y) any review or possible change that does not indicate an improvement, in the rating accorded any securities of or guaranteed by the Company or any Subsidiary by any "nationally recognized statistical rating organization", as that term is defined in Rule 436(g)(2) under the Act or (iii) if, at any time prior to the time of purchase or, with respect to the purchase of any Additional Notes, the additional time of purchase, as the case may be, trading in securities on the New York Stock Exchange, the American Stock Exchange or the Nasdaq National Market shall have been suspended or limitations or minimum prices shall have been established on the New York Stock Exchange, the American Stock Exchange or the Nasdaq National Market, or if a banking moratorium shall have been declared either by the United States or New York State authorities, or if the United States shall have declared war in accordance with its constitutional processes or there shall have occurred any material outbreak or escalation of hostilities or other national or international calamity or crisis of such magnitude in its effect on the financial markets of the United States as, in the judgment of UBS Warburg LLC or in the judgment of such group of Initial Purchasers, to make it impracticable to market the Notes in the manner and on the terms set forth in the Final Offering Memorandum.

If you or any group of Initial Purchasers elects to terminate this Agreement as provided in this Section 8, the Company and each other Initial Purchaser shall be notified promptly by letter or telegram from such terminating Initial Purchaser.

If the sale to the Initial Purchasers of the Notes, as contemplated by this Agreement, is not carried out by the Initial Purchasers for any reason permitted under this Agreement or if such sale is not carried out because the Company shall be unable to comply with any of the terms of this Agreement, the Company shall not be under any obligation or liability under this Agreement (except to the extent provided in Sections 5(k), 6 and 10 hereof), and the Initial Purchasers shall be under no obligation or liability to the Company under this Agreement (except to the extent provided in Section 10 hereof) or to one another hereunder.

9. Increase in Initial Purchasers' Commitments. Subject to Sections 7 and 8, if any Initial Purchaser shall default in its obligation to purchase and pay for the Firm Notes to be purchased by it hereunder (otherwise than for a reason sufficient to justify the termination of this Agreement under the provisions of Section 8 hereof) and if the aggregate principal amount of Firm Notes which all Initial Purchasers so defaulting shall have agreed but failed to purchase and pay for does not exceed 10% of the total aggregate principal amount of Firm Notes to be purchased at such time, the non-defaulting Initial Purchasers shall purchase and pay for (in addition to the aggregate number of Firm Notes they are obligated to purchase pursuant to Section 1 hereof) the aggregate principal amount of Firm Notes agreed to be purchased by all such defaulting Initial Purchasers, as hereinafter provided. Such Notes shall be purchased and paid for by such non-defaulting Initial Purchaser or Initial Purchasers in such amount or amounts as you may designate with the consent of each Initial Purchaser so designated or, in the event no such designation is made, such Notes shall be purchased and paid for by all non-defaulting Initial Purchasers pro rata in proportion to the aggregate principal amount of Firm Notes set opposite the names of such non-defaulting Initial Purchasers in Schedule A.

Without relieving any defaulting Initial Purchaser from its obligations hereunder, the Company agrees with the non-defaulting Initial Purchasers that it will not sell any Firm Notes hereunder

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unless all of the Firm Notes are purchased by the Initial Purchasers (or by substituted Initial Purchasers selected by you with the approval of the Company or selected by the Company with your approval).

If a new Initial Purchaser or Initial Purchasers are substituted by the Initial Purchasers or by the Company for a defaulting Initial Purchaser or Initial Purchasers in accordance with the foregoing provision, the Company or you shall have the right to postpone the time of purchase for a period not exceeding five business days in order that any necessary changes in the Offering Memorandum and other documents may be effected.

The term Initial Purchaser as used in this Agreement shall refer to and include any Initial Purchaser substituted under this Section 9 with like effect as if such substituted Initial Purchaser had originally been named in Schedule A.

If the aggregate principal amount of Notes which the defaulting Initial Purchaser or Initial Purchasers agreed to purchase exceeds 10% of the total aggregate principal amount of Notes which all Initial Purchasers agreed to purchase hereunder, and if neither the non-defaulting Initial Purchasers nor the Company shall make arrangements within the five business day period stated above for the purchase of all the Notes which the defaulting Initial Purchaser or Initial Purchasers agreed to purchase hereunder, this Agreement shall terminate without further act or deed and without any liability on the part of the Company to any non-defaulting Initial Purchaser and without any liability on the part of any non-defaulting Initial Purchaser to the Company. Nothing in this paragraph, and no action taken hereunder, shall relieve any defaulting Initial Purchaser from liability in respect of any default of such Initial Purchaser under this Agreement.

10. Indemnity and Contribution.

(a) The Company agrees to indemnify, defend and hold harmless each Initial Purchaser, its partners, directors and officers, and any person who controls any Initial Purchaser within the meaning of Section 15 of the Act or Section 20 of the Exchange Act, and the successors and assigns of all of the foregoing persons from and against any loss, damage, expense, liability or claim (including the reasonable cost of investigation) which, jointly or severally, any such Initial Purchaser or any such person may incur under the Act, the Exchange Act, the common law or otherwise, insofar as such loss, damage, expense, liability or claim arises out of or is based upon (i) any untrue statement or alleged untrue statement of a material fact contained in the Offering Memorandum (the term Offering Memorandum for the purpose of this Section 10 being deemed to include any Preliminary Memorandum, the Final Memorandum and the Offering Memorandum as amended or supplemented by the Company), or arises out of or is based upon any omission or alleged omission to state a material fact required to be stated in the Offering Memorandum or necessary to make the statements made therein not misleading, except insofar as any such loss, damage, expense, liability or claim arises out of or is based upon any untrue statement or alleged untrue statement of a material fact contained in and in conformity with information furnished in writing by or on behalf of any Initial Purchaser through you to the Company expressly for use with reference to such Initial Purchaser in such Offering Memorandum or arises out of or is based upon any omission or alleged omission to state a material fact in connection with such information required to be stated in such Offering Memorandum or necessary to make such information not misleading, or (ii) any untrue statement or alleged untrue statement made by the Company in Section 3 of this Agreement or the failure by the Company to perform when and as required any agreement or covenant contained herein or (iii) any untrue statement or alleged untrue statement of any material fact contained in any audio or visual materials provided by the Company or based upon written information furnished by or

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on behalf of the Company including, without limitation, slides, videos, films, tape recordings, used in connection with the marketing of the Notes or (iv) the matters to be covered in the Final Memorandum under the caption "Risk factors—If this offering violated securities laws, purchasers in this offering would have the right to seek refunds or damages" (such description to be substantially as set forth on Exhibit B hereto), provided, however, that the indemnity agreement contained in clause (i) of this subsection (a) with respect to any Preliminary Memorandum or amended Preliminary Memorandum shall not inure to the benefit of any Initial Purchaser from whom the person asserting any such loss, damage, expense, liability or claim purchased the Notes which is the subject thereof if the Final Memorandum corrected any such alleged untrue statement or omission and if such Initial Purchaser failed to send or give a copy of the Final Memorandum to such person at or prior to the written confirmation of the sale of such Notes to such person, unless the failure is the result of noncompliance by the Company with Section 5(d) hereof.

If any action, suit or proceeding (together, a "Proceeding") is brought against an Initial Purchaser or any such person in respect of which indemnity may be sought against the Company pursuant to the foregoing paragraph, such Initial Purchaser or such person shall promptly notify the Company in

writing of the institution of such Proceeding and the Company shall assume the defense of such Proceeding, including the employment of counsel reasonably satisfactory to such indemnified party and payment of all fees and expenses; provided, however, that the omission to so notify the Company shall not relieve the Company from any liability which the Company may have to any Initial Purchaser or any such person or otherwise, except to the extent the Company is materially prejudiced thereby. Such Initial Purchaser or such person shall have the right to employ its or their own counsel in any such case, but the fees and expenses of such counsel shall be at the expense of such Initial Purchaser or of such person unless the employment of such counsel shall have been authorized in writing by the Company in connection with the defense of such Proceeding or the Company shall not have, within a reasonable period of time in light of the circumstances, employed counsel to have charge of the defense of such Proceeding or such indemnified party or parties shall have reasonably concluded that there may be defenses available to it or them which are different from, additional to or in conflict with those available to the Company (in which case the Company shall not have the right to direct the defense of such Proceeding on behalf of the indemnified party or parties), in any of which events such fees and expenses shall be borne by the Company and paid as incurred (it being understood, however, that the Company shall not be liable for the expenses of more than one separate counsel (in addition to any local counsel) in any one Proceeding or series of related Proceedings in the same jurisdiction representing the indemnified parties who are parties to such Proceeding). The Company shall not be liable for any settlement of any Proceeding effected without the written consent of the Company, but if settled with the written consent of the Company, the Company agrees to indemnify and hold harmless any Initial Purchaser and any such person from and against any loss or liability by reason of such settlement. Notwithstanding the foregoing sentence, if at any time an indemnified party shall have requested an indemnifying party to reimburse the indemnified party for fees and expenses of counsel as contemplated by the second sentence of this paragraph, then the indemnifying party agrees that it shall be liable for any settlement of any Proceeding effected without the Company's written consent if (i) such settlement is entered into more than 60 business days after receipt by the indemnifying party of the aforesaid request, (ii) such indemnifying party shall not have reimbursed the indemnified party in accordance with such request prior to the date of such settlement and (iii) such indemnified party shall have given the indemnifying party at least 30 days' prior notice of its intention to settle. No indemnifying party shall, without the prior written consent of the indemnified party, effect any settlement of any pending or threatened Proceeding in respect of which any indemnified party is or could have been a party and indemnity could have been sought hereunder by such indemnified party, unless such settlement includes an unconditional release of such indemnified party from all liability on claims that are

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the subject matter of such Proceeding and does not include an admission of fault, culpability or a failure to act, by or on behalf of such indemnified party.

(b) Each Initial Purchaser severally agrees to indemnify, defend and hold harmless the Company, its directors and officers, and any person who controls the Company within the meaning of Section 15 of the Act or Section 20 of the Exchange Act and the successors and assigns of all of the foregoing persons from and against any loss, damage, expense, liability or claim (including the reasonable cost of investigation) which the Company or any such person may incur under the Act, the Exchange Act, the common law or otherwise, insofar as such loss, damage, expense, liability or claim arises out of or is based upon any untrue statement or alleged untrue statement of a material fact contained in and in conformity with information furnished in writing by or on behalf of such Initial Purchaser through you to the Company expressly for use with reference to such Initial Purchaser in the Offering Memorandum (or in the Offering Memorandum as amended by the Company), or arises out of or is based upon any omission or alleged omission to state a material fact in connection with such information required to be stated in such Offering Memorandum or necessary to make such information not misleading.

If any Proceeding is brought against the Company or any such person in respect of which indemnity may be sought against any Initial Purchaser pursuant to the foregoing paragraph, the Company or such person shall promptly notify such Initial Purchaser in writing of the institution of such Proceeding and such Initial Purchaser shall assume the defense of such Proceeding, including the employment of counsel reasonably satisfactory to such indemnified party and payment of all fees and expenses; provided, however, that the omission to so notify such Initial Purchaser shall not relieve such Initial Purchaser from any liability which such Initial Purchaser may have to the Company or any such person or otherwise, except to the extent such Initial Purchaser is materially prejudiced thereby. The Company or such person shall have the right to employ their or its own counsel in any such case, but the fees and expenses of such counsel shall be at the expense of the Company or such person unless the employment of such counsel shall have been authorized in writing by such Initial Purchaser in connection with the defense of such Proceeding or such Initial Purchaser shall not have, within a reasonable period of time in light of the circumstances, employed counsel to defend such Proceeding or such indemnified party or parties shall have reasonably concluded that there may be defenses available to it or them which are different from or additional to or in conflict with those available to such Initial Purchaser (in which case such Initial Purchaser shall not have the right to direct the defense of such Proceeding on behalf of the indemnified party or parties, but such Initial Purchaser may employ counsel and participate in the defense thereof but the fees and expenses of such counsel shall be at the expense of such Initial Purchaser), in any of which events such fees and expenses shall be borne by such Initial Purchaser and paid as incurred (it being understood, however, that such Initial Purchaser shall not be liable for the expenses of more than one separate counsel (in addition to any local counsel) in any one Proceeding or series of related Proceedings in the same jurisdiction representing the indemnified parties who are parties to such Proceeding). No Initial Purchaser shall be liable for any settlement of any such Proceeding effected without the written consent of such Initial Purchaser but if settled with the written consent of such Initial Purchaser, such Initial Purchaser agrees to indemnify and hold harmless the Company and any such person from and against any loss or liability by reason of such settlement. Notwithstanding the foregoing sentence, if at any time an indemnified party shall have requested an indemnifying party to reimburse the indemnified party for fees and expenses of counsel as contemplated by the second sentence of this paragraph, then the indemnifying party agrees that it shall be liable for any settlement of any Proceeding effected without its written consent if (i) such settlement is entered into more than 60 business days after receipt by such indemnifying party of the aforesaid request, (ii) such indemnifying party shall not have reimbursed the indemnified party in accordance with such request prior to the date of such settlement and (iii) such indemnified party shall have given the indemnifying party at least 30 days' prior notice of its intention to settle. No indemnifying party shall,

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without the prior written consent of the indemnified party, effect any settlement of any pending or threatened Proceeding in respect of which any indemnified party is or could have been a party and indemnity could have been sought hereunder by such indemnified party, unless such settlement includes an

unconditional release of such indemnified party from all liability on claims that are the subject matter of such Proceeding and does not include an admission of fault, culpability or a failure to act, by or on behalf of such indemnified party.

(c) If the indemnification provided for in this Section 10 is unavailable to an indemnified party under subsections (a) and (b) of this Section 10 in respect of any losses, damages, expenses, liabilities or claims referred to therein, then each applicable indemnifying party, in lieu of indemnifying such indemnified party, shall contribute to the amount paid or payable by such indemnified party as a result of such losses, damages, expenses, liabilities or claims (i) in such proportion as is appropriate to reflect the relative benefits received by the Company on the one hand and the Initial Purchasers on the other hand from the offering of the Notes or (ii) if the allocation provided by clause (i) above is not permitted by applicable law, in such proportion as is appropriate to reflect not only the relative benefits referred to in clause (i) above but also the relative fault of the Company on the one hand and of the Initial Purchasers on the other in connection with the statements or omissions which resulted in such losses, damages, expenses, liabilities or claims, as well as any other relevant equitable considerations. The relative benefits received by the Company on the one hand and the Initial Purchasers on the other shall be deemed to be in the same respective proportions as the total proceeds from the offering (net of discounts and commissions but before deducting expenses) received by the Company and the total discounts and commissions received by the Initial Purchasers. The relative fault of the Company on the one hand and of the Initial Purchasers on the other shall be determined by reference to, among other things, whether the untrue statement or alleged untrue statement of a material fact or omission or alleged omission relates to information supplied by the Company or by the Initial Purchasers and the parties' relative intent, knowledge, access to information and opportunity to correct or prevent such statement or omission. The amount paid or payable by a party as a result of the losses, damages, expenses, liabilities and claims referred to in this subsection shall be deemed to include any legal or other fees or expenses reasonably incurred by such party in connection with investigating, preparing to defend or defending any Proceeding.

(d) The Company and the Initial Purchasers agree that it would not be just and equitable if contribution pursuant to this Section 10 were determined by pro rata allocation (even if the Initial Purchasers were treated as one entity for such purpose) or by any other method of allocation that does not take account of the equitable considerations referred to in subsection (c) above. Notwithstanding the provisions of this Section 10, in no case shall any Initial Purchaser be required to contribute any amount in excess of the amount by which the total price at which the Notes resold by it in the initial placement of such Notes with investors exceeds the amount of any damage which such Initial Purchaser has otherwise been required to pay by reason of such untrue statement or alleged untrue statement or omission or alleged omission. No person guilty of fraudulent misrepresentation (within the meaning of Section 11(f) of the Act) shall be entitled to contribution from any person who was not guilty of such fraudulent misrepresentation. The Initial Purchasers' obligations to contribute pursuant to this Section 10 are several in proportion to the respective principal amount of Notes they have purchased hereunder, and not joint.

(e) The indemnity and contribution agreements contained in this Section 10 and the covenants, warranties and representations of the Company and the Initial Purchasers contained in this Agreement shall remain in full force and effect regardless of any investigation

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made by or on behalf of any Initial Purchaser, its partners, directors or officers or any person (including each partner, officer or director of such person) who controls any Initial Purchaser within the meaning of Section 15 of the Act or Section 20 of the Exchange Act, or by or on behalf of the Company, its directors or officers or any person who controls any of the foregoing within the meaning of Section 15 of the Act or Section 20 of the Exchange Act, and shall survive any termination of this Agreement or the issuance and delivery of the Notes. The Company and each Initial Purchaser agree promptly to notify each other of the commencement of any Proceeding against it and against any of the officers or directors of the Company in connection with the issuance and sale of the Notes, or in connection with the Offering Memorandum.

11. Notices. Except as otherwise herein provided, all statements, requests, notices and agreements shall be in writing and, if to the Initial Purchasers, shall be sufficient in all respects if delivered or sent to UBS Warburg LLC, 299 Park Avenue, New York, NY 10171-0026, Attention: Syndicate Department; and if to the Company, shall be sufficient in all respects if delivered or sent to the Company at the offices of the Company at 2292 Faraday Avenue, Carlsbad, CA 92008, Attention: B. Lynne Parshall, Esq., Executive Vice President and Chief Financial Officer.

12. Information Furnished by the Initial Purchasers. The statements set forth in the last paragraph on the cover page of the Offering Memorandum and the statements set forth in the ninth paragraph (regarding over-allotment, stabilizing and syndicate covering transactions) under the caption "Plan of distribution" in the Offering Memorandum constitute the only information furnished by or on behalf of the Initial Purchasers as such information is referred to in Sections 3 and 10 hereof.

13. Governing Law; Construction. This Agreement and any claim, counterclaim or dispute of any kind or nature whatsoever arising out of or in any way relating to this Agreement ("Claim"), directly or indirectly, shall be governed by, and construed in accordance with, the laws of the State of New York. The section headings in this Agreement have been inserted as a matter of convenience of reference and are not a part of this Agreement.

14. Submission to Jurisdiction. Except as set forth below, no Claim may be commenced, prosecuted or continued in any court other than the courts of the State of New York located in the City and County of New York or in the United States District Court for the Southern District of New York, which courts shall have jurisdiction over the adjudication of such matters, and you and the Company consent to the jurisdiction of such courts and personal service with respect thereto. The Company hereby consents to personal jurisdiction, service and venue in any court in which any Claim arising out of or in any way relating to this Agreement is brought by any third party against an Initial Purchaser or any indemnified party. Each Initial Purchaser and the Company (on its behalf and, to the extent permitted by applicable law, on behalf of its stockholders and affiliates) waives all right to trial by jury in any action, proceeding or counterclaim (whether based upon contract, tort or otherwise) in any way arising out of or relating to this Agreement. The Company agrees that a final judgment not subject to appeal in any such action, proceeding or counterclaim brought in any such court shall be conclusive and binding thereupon, and may be enforced in any other courts in the jurisdiction to which the Company is or may be subject, by suit upon such judgment.

15. Parties at Interest. The Agreement herein set forth has been and is made solely for the benefit of the Initial Purchasers, the Company and, to the extent provided in Section 10 hereof, the controlling persons, directors and officers referred to in such section, and their respective successors, assigns, heirs, personal representatives and executors and administrators. No other person, partnership, association or corporation (including a purchaser, as such purchaser, from any of the Initial Purchasers) shall acquire or have any right under or by virtue of this Agreement.



16. Counterparts. This Agreement may be signed by the parties in one or more counterparts which together shall constitute one and the same agreement among the parties.

17. Successors and Assigns. This Agreement shall be binding upon the Initial Purchasers and the Company and their successors and assigns and any successor or assign of any substantial portion of the Company's and any of the Initial Purchasers' respective businesses and/or assets.

18. Miscellaneous. UBS Warburg LLC, an indirect, wholly owned subsidiary of UBS AG, is not a bank and is separate from any affiliated bank, including any U.S. branch or agency of UBS Warburg LLC. Because UBS Warburg LLC is a separately incorporated entity, it is solely responsible for its own contractual obligations and commitments, including obligations with respect to sales and purchases of securities. Securities sold, offered or recommended by UBS Warburg LLC are not deposits, are not insured by the Federal Deposit Insurance Corporation, are not guaranteed by a branch or agency, and are not otherwise an obligation or responsibility of a branch or agency.

A lending affiliate of UBS Warburg LLC may have lending relationships with issuers of securities underwritten or privately placed by UBS Warburg LLC. To the extent required under the securities laws, prospectuses and other disclosure documents for securities underwritten or privately placed by UBS Warburg LLC will disclose the existence of any such lending relationships and whether the proceeds of the issue will be used to repay debts owed to affiliates of UBS Warburg LLC.

If the foregoing correctly sets forth the understanding between the Company and the Initial Purchasers, please so indicate in the space provided below for the purpose, whereupon this letter and your acceptance shall constitute a binding agreement between the Company and the Initial Purchasers.

Very truly yours,

ISIS PHARMACEUTICALS, INC.

By: /s/ B. Lynne Parshall

Name:

Title:

Accepted and agreed to as of the date first above written:

UBS WARBURG LLC  
ROBERTSON STEPHENS, INC.  
NEEDHAM & COMPANY, INC.  
ROTH CAPITAL PARTNERS, LLC

on behalf of itself and the other Initial Purchasers named in Schedule A hereto:

By: UBS WARBURG LLC

By: /s/ Steve Meehan

Name: Steve Meehan

Title: Managing Director

By: /s/ S. Kelly

Name: S. Kelly

Title: Director

<u>Initial Purchasers</u>	<u>Principal Amount of Firm Notes</u>
UBS WARBURG LLC	\$ 122,375,000
ROBERTSON STEPHENS, INC.	1,500,000
NEEDHAM & COMPANY, INC.	750,000
ROTH CAPITAL PARTNERS, LLC	375,000
Total	<u>\$ 125,000,000</u>

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SCHEDULE B

<u>Name</u>	<u>Jurisdiction of Incorporation</u>
Orasense Ltd.	Bermuda
Hepasense Ltd.	Bermuda

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EXHIBIT A

Isis Pharmaceuticals, Inc.

Common Stock

(\$ .001 Par Value)

, 2002

UBS Warburg LLC  
Robertson Stephens, Inc.

c/o UBS Warburg LLC  
299 Park Avenue  
New York, New York 10171

Ladies and Gentlemen:

This Lock-Up Letter Agreement is being delivered to you in connection with the proposed Purchase Agreement (the "Purchase Agreement") to be entered into by and among Isis Pharmaceuticals, Inc. (the "Company"), you and the other Initial Purchasers named therein, with respect to an offering without registration under the Securities Act of 1933, as amended (the "Act"), in reliance on Rule 144A, Regulation S and Regulation D under the Act, Convertible Subordinated Notes due 2009 (the "Notes") of the Company (the "Offering").

In order to induce you to enter into the Purchase Agreement, the undersigned agrees that for a period of 90 days after the date of the Final Memorandum relating to the Offering the undersigned will not, without the prior written consent of UBS Warburg LLC, (i) sell, offer to sell, contract to sell, hypothecate, pledge, grant any option to purchase or otherwise dispose of, or establish or increase a put equivalent position or liquidate or decrease a call equivalent position within the meaning of Section 16 of the Securities Exchange Act of 1934, as amended, and the rules and regulations of the Commission promulgated thereunder with respect to, any Notes or Common Stock or any securities convertible into or exercisable or exchangeable for Common Stock or any securities substantially similar to the Notes or the Common Stock, (ii) enter into any swap or other arrangement that transfers to another, in whole or in part, any of the economic consequences of ownership of Common Stock or any securities convertible into or exercisable or exchangeable for any Notes or Common Stock or any securities substantially similar to the Notes or the Common Stock, whether any such transaction is to be settled by delivery of Common Stock or such other securities, in cash or otherwise, or (iii) publicly announce an intention to effect any transaction specified in clause (i) or (ii). The foregoing sentence shall not apply to (a) the sale of any Common Stock to the Initial Purchasers pursuant to the Purchase Agreement, (b) bona fide gifts, provided the recipient or recipients thereof agree in writing to be bound by the terms of this Lock-Up Letter Agreement, (c) dispositions to any trust for the direct or indirect

benefit of the undersigned and/or the immediate family of the undersigned, provided that such trust agrees in writing to be bound by the terms of this Lock-Up Letter Agreement, or (d) the sale of up to **[The Number Equal to the greater of (A) the number of shares subject to stock options that will expire by the end of 2002, or (B) 20,000 shares for**

Exhibit B-1

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**Executive Officers and 8,000 shares for Directors]** shares of Common Stock made after the tenth (10<sup>th</sup>) business day following the time of purchase (as defined in the Purchase Agreement). For sales of Common Stock made under the exception set forth in clause (d) above, the Company will recommend that the undersigned use designated personnel of UBS Warburg LLC previously approved by the Company to effectuate such sales.

In addition, the undersigned hereby waives any rights the undersigned may have to require registration of Common Stock in connection with the filing of a registration statement relating to the Offering. The undersigned further agrees that, for a period of 90 days after the date of the Final Memorandum relating to the Offering, the undersigned will not, without the prior written consent of UBS Warburg LLC, make any demand for, or exercise any right with respect to, the registration of Common Stock of the Company or any securities convertible into or exercisable or exchangeable for Common Stock.

If for any reason the Purchase Agreement shall be terminated prior to the time of purchase (as defined in the Purchase Agreement), this Lock-Up Letter Agreement shall be terminated and the undersigned shall be released from its obligations hereunder.

Yours very truly,

\_\_\_\_\_  
Name:

Exhibit A-2

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EXHIBIT B

**If this offering violated securities laws, purchasers in this offering would have the right to seek refunds or damages.**

On April 24, 2002, an article appeared in a San Diego newspaper regarding this offering in which one of our officers was interviewed. The newspaper article could form the basis for a claim that we have engaged in an unregistered public offering of the convertible notes in violation of securities laws. We would dispute any such claim. However, if such a claim were made and it prevailed, the initial purchasers and persons who purchase the convertible notes from the initial purchasers in this offering would have the right, for a period of one year, to obtain recovery of the consideration paid in connection with their purchase of the convertible notes or, if they have already sold the convertible notes, to recover any losses resulting from their purchase of the convertible notes.

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## ISIS PHARMACEUTICALS, INC.

THIS SECURITY HAS NOT BEEN REGISTERED UNDER THE SECURITIES ACT OF 1933, AS AMENDED (THE "SECURITIES ACT"), OR THE SECURITIES LAWS OF ANY STATE OR OTHER JURISDICTION. NEITHER THIS SECURITY NOR ANY INTEREST OR PARTICIPATION HEREIN MAY BE REOFFERED, SOLD, ASSIGNED, TRANSFERRED, PLEDGED, ENCUMBERED OR OTHERWISE DISPOSED OF IN THE ABSENCE OF SUCH REGISTRATION OR UNLESS SUCH TRANSACTION IS EXEMPT FROM, OR NOT SUBJECT TO, SUCH REGISTRATION. THE HOLDER HEREOF MAY NOT ENGAGE IN HEDGING TRANSACTIONS WITH RESPECT TO THIS SECURITY UNLESS SUCH TRANSACTIONS ARE IN COMPLIANCE WITH THE SECURITIES ACT.

THE HOLDER OF THIS SECURITY BY ITS ACCEPTANCE HEREOF AGREES TO OFFER, SELL OR OTHERWISE TRANSFER SUCH SECURITY, PRIOR TO THE DATE (THE "RESALE RESTRICTION TERMINATION DATE") WHICH IS THE LATER OF (X) TWO YEARS AFTER THE LATER OF THE ORIGINAL ISSUE DATE HEREOF AND THE LAST DATE ON WHICH THE COMPANY OR ANY AFFILIATE OF THE COMPANY WAS THE OWNER OF THIS SECURITY (OR ANY PREDECESSOR OF SUCH SECURITY), AND (Y) SUCH LATER DATE, IF ANY, AS MAY BE REQUIRED BY APPLICABLE LAW ONLY (A) TO THE COMPANY OR ANY SUBSIDIARY OF THE COMPANY, (B) PURSUANT TO A REGISTRATION STATEMENT THAT HAS BEEN DECLARED EFFECTIVE UNDER THE SECURITIES ACT, (C) FOR SO LONG AS THE SECURITIES ARE ELIGIBLE FOR RESALE PURSUANT TO RULE 144A UNDER THE SECURITIES ACT, TO A PERSON IT REASONABLY BELIEVES IS A "QUALIFIED INSTITUTIONAL BUYER" AS DEFINED IN RULE 144A UNDER THE SECURITIES ACT THAT PURCHASES FOR ITS OWN ACCOUNT OR FOR THE ACCOUNT OF A QUALIFIED INSTITUTIONAL BUYER TO WHOM NOTICE IS GIVEN THAT THE TRANSFER IS BEING MADE IN RELIANCE ON RULE 144A UNDER THE SECURITIES ACT OR (D) PURSUANT TO OFFERS AND SALES THAT OCCUR OUTSIDE THE UNITED STATES IN ACCORDANCE WITH REGULATIONS UNDER THE SECURITIES ACT, SUBJECT TO THE COMPANY'S AND THE TRUSTEE'S RIGHT PRIOR TO ANY SUCH OFFER, SALE OR TRANSFER PURSUANT TO THIS CLAUSE (D) TO REQUIRE THE DELIVERY OF AN OPINION OF COUNSEL, CERTIFICATION AND/OR OTHER INFORMATION SATISFACTORY TO EACH OF THEM. THIS LEGEND WILL BE REMOVED UPON THE REQUEST OF THE HOLDER AFTER THE RESALE RESTRICTION TERMINATION DATE.

THIS SECURITY IS A GLOBAL SECURITY WITHIN THE MEANING OF THE INDENTURE HEREINAFTER REFERRED TO AND IS REGISTERED IN THE NAME OF A DEPOSITARY OR A NOMINEE OF A DEPOSITARY OR A SUCCESSOR DEPOSITARY. THIS SECURITY IS NOT EXCHANGEABLE FOR SECURITIES REGISTERED IN THE NAME OF A PERSON OTHER THAN THE DEPOSITARY OR ITS NOMINEE EXCEPT IN THE LIMITED CIRCUMSTANCES DESCRIBED IN THE INDENTURE, AND NO TRANSFER OF THIS SECURITY (OTHER THAN A TRANSFER OF THIS SECURITY AS A WHOLE BY THE DEPOSITARY TO A NOMINEE OF THE DEPOSITARY OR BY A NOMINEE OF THE DEPOSITARY TO THE DEPOSITARY OR ANOTHER NOMINEE OF THE DEPOSITARY) MAY BE REGISTERED EXCEPT IN THE LIMITED CIRCUMSTANCES DESCRIBED IN THE INDENTURE.

UNLESS THIS CERTIFICATE IS PRESENTED BY AN AUTHORIZED REPRESENTATIVE OF THE DEPOSITARY TRUST COMPANY, A NEW YORK CORPORATION ("DTC"), TO THE COMPANY OR ITS AGENT FOR REGISTRATION OF TRANSFER, EXCHANGE, OR PAYMENT, AND ANY CERTIFICATE ISSUED IS REGISTERED IN THE NAME OF CEDE & CO. OR IN SUCH OTHER NAME AS IS REQUESTED BY AN AUTHORIZED REPRESENTATIVE OF DTC (AND ANY PAYMENT IS MADE TO CEDE & CO. OR TO SUCH OTHER ENTITY AS IS REQUESTED BY AN AUTHORIZED REPRESENTATIVE OF DTC), ANY TRANSFER, PLEDGE OR OTHER USE HEREOF FOR VALUE OR OTHERWISE BY OR TO ANY PERSON IS WRONGFUL INASMUCH AS THE REGISTERED OWNER HEREOF, CEDE & CO., HAS AN INTEREST HEREIN.

TRANSFERS OF THIS GLOBAL SECURITY SHALL BE LIMITED TO TRANSFERS IN WHOLE, BUT NOT IN PART, TO NOMINEES OF CEDE & CO. OR TO A SUCCESSOR THEREOF OR SUCH SUCCESSOR'S NOMINEE AND TRANSFERS OF PORTIONS OF THIS GLOBAL SECURITY SHALL BE LIMITED TO TRANSFERS MADE IN ACCORDANCE WITH THE RESTRICTIONS SET FORTH IN SECTION 2.16 OF THE INDENTURE.

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No. A-1

\$

**5 ½% Convertible Subordinated Note due 2009  
CUSIP No. 464337AA2**

**ISIS PHARMACEUTICALS, INC.**, a Delaware corporation (herein called the "Company"), for value received, hereby promises to pay to Cede & Co. or registered assigns, the principal sum of \_\_\_\_\_ on May 1, 2009, and to pay interest thereon, as provided on the reverse hereof, until the principal and any unpaid and accrued interest is paid or duly provided for. The right to payment of the principal and all other amounts due with respect hereto is subordinated to the rights of Senior Indebtedness as set forth in the Indenture referred to on the reverse side hereof.

Interest Payment Dates: May 1 and November 1, with the first payment to be made on November 1, 2002.

Record Dates: April 15 and October 15.

The provisions on the back of this certificate are incorporated as if set forth on the face hereof.

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**IN WITNESS WHEREOF, ISIS PHARMACEUTICALS, INC.** has caused this instrument to be duly signed.

ISIS PHARMACEUTICALS, INC.

By: \_\_\_\_\_

Name:  
Title:

Dated: \_\_\_\_\_

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TRUSTEE'S CERTIFICATE OF AUTHENTICATION

This is one of the Securities referred to  
in the within-mentioned Indenture.

WELLS FARGO BANK MINNESOTA, NATIONAL ASSOCIATION, as Trustee

By: \_\_\_\_\_

Authorized Signatory

Dated: \_\_\_\_\_

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[REVERSE OF SECURITY]

**ISIS PHARMACEUTICALS, INC.**

**5 ½% Convertible Subordinated Note due 2009**

1. **Interest.** **ISIS PHARMACEUTICALS, INC.**, a Delaware corporation (the "**Company**"), promises to pay interest on the principal amount of this Security at the rate *per annum* shown above. The Company will pay interest semi-annually on May 1 and November 1 of each year, with the first payment to be made on November 1, 2002. Interest on the Securities will accrue on the principal amount from the most recent date to which interest has been paid or, if no interest has been paid, from May 1, 2002. Interest will be computed on the basis of a 360-day year of twelve 30-day months.

2. **Maturity.** The Notes will mature on May 1, 2009.

3. **Method of Payment.** The Company will pay interest on the Securities (except defaulted interest) to the persons who are registered Holders of Securities at the close of business on the record date set forth on the face of this Security next preceding the applicable interest payment date. Holders must surrender Securities to a Paying Agent to collect the principal, Redemption Price, Provisional Redemption Price, if applicable, Make-Whole Payment, if applicable, or Repurchase Price of the Securities. The Company will pay all amounts due with respect to the Securities in money of the United States that at the time of payment is legal tender for payment of public and private debts. However, the Company may, at its option, pay all amounts due with respect to the Securities held other than by the Depository by check payable in such money. It may mail an interest check to a Holder's registered address.

4. **Paying Agent, Registrar, Conversion Agent.** Initially, Wells Fargo Bank Minnesota, National Association (the "**Trustee**") will act as Paying Agent, Registrar and Conversion Agent. The Company may change any Paying Agent, Registrar or Conversion Agent without notice. The Company may act in any such capacity.

5. **Indenture.** The Company issued the Securities under an Indenture dated as of May 1, 2002 (the "**Indenture**") between the Company and the Trustee. The terms of the Securities include those stated in the Indenture and those made part of the Indenture by reference to the Trust Indenture Act of 1939 (15 U.S. Code §§ 77aaa-77bbb) (the "**Act**") as in effect on the date of the Indenture. The Securities are subject to all such terms, and Securityholders are referred to the Indenture and the Act for a statement of such terms. The Securities are general unsecured senior subordinated obligations of the Company limited to \$125,000,000 aggregate principal amount (\$143,750,000 if the Initial Purchasers (as defined in the Indenture) have elected to exercise their over-allotment option to purchase an additional \$18,750,000 of the Securities), except as otherwise provided in the Indenture (except for Securities issued in substitution for destroyed, mutilated, lost or stolen Securities). Terms used herein which are defined in the Indenture have the meanings assigned to them in the Indenture.

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6. **Provisional and Optional Redemption.** The Securities will be redeemable prior to maturity at the option of the Company, in whole or in part, at any time on or after May 3, 2005, in cash, at the following redemption prices (expressed as percentages of the principal amount thereof), if redeemed during the periods commencing on the dates set forth below, in each case together with accrued and unpaid interest, if any, to the redemption date:

<u>Date</u>	<u>Redemption Price</u>
May 3, 2005 to April 30, 2006	103.143 %
May 1, 2006 to April 30, 2007	102.357 %
May 1, 2007 to April 30, 2008	101.571 %
May 1, 2008 through May 1, 2009 inclusive	100.786 %

The Securities may be redeemed at the election of the Company, as a whole or in parts from time to time, at any time prior to May 3, 2005 (a "**Provisional Redemption**"), at a redemption price equal to \$1,000 per \$1,000 principal amount of the Securities redeemed (such amount, together with the Make-Whole Payment (as defined below) the "**Provisional Redemption Price**"), on the date of redemption (the "**Provisional Redemption Date**") specified in the notice of Provisional Redemption if (1) the closing price of the Common Stock on the NNM (or other United States national securities exchange where the Company's Common Stock is traded) has exceeded 150% of the then current conversion price for at least 20 trading days within a period of any 30 consecutive trading days ending on the trading day prior to the date of mailing of the notice of Provisional Redemption (the "**Notice Date**"), and (2) a shelf registration statement covering resales of the Securities and the Common Stock issuable upon conversion thereof is effective and available for use and is expected to remain effective and available for use for the 30 days following the Provisional Redemption Date, unless registration is no longer required.

Upon any such Provisional Redemption, the Company shall make an additional payment (the “**Make-Whole Payment**”) with respect to the Securities called for redemption to holders on the Provisional Redemption Date in an amount equal to the total value of the aggregate amount of interest that would have been payable on the Securities from the last day through which interest was paid on the Securities (or May 1, 2002 if no interest has been paid) through May 1, 2005 (or May 2, 2005 if the Provisional Redemption is May 2, 2005). The Company may make the Make-Whole Payment, at its option, either in cash or Common Stock or a combination thereof. Payments made in Common Stock will be valued at 95% of the average closing sales prices of the Common Stock on the NNM (or other United States national securities exchange where the Common Stock is traded) for the five trading days ending on the day prior to the

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Provisional Redemption Date. The Company shall make the Make-Whole Payment on all Securities called for Provisional Redemption, including those Securities converted into Common Stock between the Notice Date and the Provisional Redemption Date.

7. **Notice of Redemption.** Notice of redemption will be mailed at least 30 days but not more than 60 days before the redemption date to each Holder of Securities to be redeemed at its registered address. Securities in denominations larger than \$1,000 principal amount may be redeemed in part but only in positive integral multiples of \$1,000 principal amount. On and after the redemption date interest ceases to accrue on Securities or portions of them called for redemption.

8. **Repurchase at Option of Holder.** In the event of a Change in Control with respect to the Company, then each Holder of the Securities shall have the right, at the Holder’s option, subject to the rights of the holders of Senior Indebtedness under **Article XI** of the Indenture, to require the Company to repurchase such Holder’s Securities including any portion thereof which is \$1,000 in principal amount or any positive integral multiple thereof on a business day (the “**Repurchase Date**”) that is no later than 30 business days after the date of the Change in Control Notice, unless otherwise required by applicable law, at a price equal to 100% of the outstanding principal amount of such Security, plus accrued and unpaid interest to the Repurchase Date.

Within 30 business days after the occurrence of the Change in Control, the Company is obligated to give notice of the occurrence of such Change in Control to each Holder. Such notice shall include, among other things, the date by which Holder must notify the Company of such Holder’s intention to exercise the Repurchase Right and of the procedure which such Holder must follow to exercise such right. To exercise a Repurchase Right, a Holder shall deliver to the Company (if it is acting as its own Paying Agent), or to a Paying Agent designated by the Company for such purpose in the Change in Control Notice, (i) no later than the close of business on the third business day immediately preceding the Repurchase Date, the Option of Holder To Elect Purchase Notice on the back of the Securities with respect to which the Repurchase Right is being exercised, duly completed and signed, with appropriate signature guarantee, and (ii) at any time after such delivery of such Option of Holder To Elect Purchase Notice, such Securities with respect to which the Repurchase Right is being exercised, duly endorsed for transfer to the Company. Upon so delivering such Option of Holder To Elect Purchase Notice and such Securities, the Holder of such Securities shall be entitled to receive from the Company (if it is acting as its own Paying Agent), or such Paying Agent, a nontransferable receipt of deposit evidencing such deposit.

A “**Change in Control**” of the Company means:

the acquisition by any “person,” entity or “group” within the meaning of Section 13(d)(3) or 14(d)(2) of the Exchange Act of beneficial ownership (within the meaning of Rule 13d-3 promulgated under the Exchange Act) of 50% or more of the voting power of the total outstanding Common Stock or other capital stock into which the Common Stock is hereafter reclassified or changed;

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persons who constitute the Board of Directors (the “**Incumbent Board**”) as of the date of the indenture, cease for any reason to constitute at least a majority of the Board of Directors, provided that any person subsequently becoming a director whose election, or nomination for election by stockholders, was approved by a vote of at least a majority of the directors then comprising the Incumbent Board shall be considered as though such person were a member of the Incumbent Board; or

the sale, lease or transfer of all or substantially all of the assets and property of the Company to any “person,” entity or “group” within the meaning of Section 13(d) or 14(d) of the Exchange Act.

However, a Change in Control will not be deemed to have occurred if either:

- (i) the last sale price of the Common Stock for any five trading days during the ten trading days immediately preceding the Change in Control is at least equal to 105% of the conversion price in effect on such trading day; or
- (ii) in the case of a merger or consolidation, all or substantially all of the consideration (excluding cash payments for fractional shares and cash payments pursuant to dissenters’ appraisal rights) in the merger or consolidation constituting the Change in Control consists of common stock quoted traded on a United States national securities exchange or on the NNM (or which will be so traded or quoted when issued or exchanged in connection with such Change in Control) and as a result of such transaction or transactions the Securities become convertible solely into such common stock.

9. **Conversion.** A Holder may convert his or her Security into Common Stock of the Company at any time prior to the close of business on May 1, 2009, or, (x) if the Security is called for redemption by the Company, the Holder may convert it at any time before the close of business on the business day immediately preceding the date fixed for such redemption, or (y) if the Security is to be repurchased by the Company pursuant to **paragraph 8** hereof, the Holder may convert it at any time before the close of business on the business day immediately preceding the Repurchase Date. The initial conversion rate is 60.1504 shares of Common Stock per \$1,000 principal amount of Securities, or an effective initial conversion price of approximately \$16.625 per share, subject to adjustment in the event of certain circumstances as specified in the Indenture. The Company will deliver a check in lieu of any fractional share. On conversion no payment or adjustment for any unpaid and accrued interest, or liquidated damages with respect to, the Securities will be made. If a Holder surrenders a Security for conversion between the record date for the payment of interest and the next interest payment date, such Security, when surrendered for conversion, must be accompanied by payment of an amount equal to the interest thereon which the registered Holder on such record date is to receive, unless the Securities have been called for redemption as described in the Indenture.

To convert a Security, a Holder must (1) complete and sign the Conversion Notice, with appropriate signature guarantee, on the back of the Security, (2) surrender the Security to a Conversion Agent, (3) furnish appropriate endorsements and transfer documents if required by the Registrar or Conversion Agent, (4) pay the amount of interest, if any, the Holder may be paid as provided in the last sentence of the above paragraph and (5) pay any transfer or similar tax if required. A Holder may convert a portion of a Security if the portion is \$1,000 principal amount or a positive integral multiple of \$1,000 principal amount.

Any shares issued upon conversion of a Security shall bear the Private Placement Legend until after the second anniversary of the later of the issue date for the Securities and the last date on which the Company or any Affiliate of the Company was the owner of such shares or the Security (or any predecessor security) from which such shares were converted (or such shorter period of time as permitted by Rule 144(k) under the Securities Act or any successor provision thereunder) (or such longer period of time as may be required under the Securities Act or applicable state securities laws in the Opinion of Counsel for the Company, unless otherwise agreed by the Company and the Holder thereof).

10. **Subordination.** The Securities are subordinated in right of payment, in the manner and to the extent set forth in the Indenture, to the prior payment in full of all Senior Indebtedness. Each Holder by accepting a Security agrees to such subordination and authorizes the Trustee to give it effect.

11. **Denominations, Transfer, Exchange.** The Securities are in registered form without coupons in denominations of \$1,000 principal amount and positive integral multiples of \$1,000 principal amount. The transfer of Securities may be registered and Securities may be exchanged as provided in the Indenture. The Registrar may require a Holder, among other things, to furnish appropriate endorsements and transfer documents. No service charge shall be made for any such registration of transfer or exchange, but the Company may require payment of a sum sufficient to cover any tax or other governmental charge payable in connection therewith. The Registrar need not exchange or register the transfer of any Security selected for redemption in whole or in part, except the unredeemed portion of Securities to be redeemed in part. Also, it need not exchange or register the transfer of any Securities for a period of 15 days before the mailing of a notice of redemption of the Securities selected to be redeemed.

12. **Persons Deemed Owners.** The registered Holder of a Security may be treated as the owner of such Security for all purposes.

13. **Merger or Consolidation.** The Company shall not consolidate with, or merge into, or transfer or lease all or substantially all of its properties or assets to, any person unless the person is a corporation, limited liability company or other limited liability entity organized under the laws of the United States, any State thereof or the District of Columbia, provided that this condition will not apply if independent tax counsel experienced in such matters delivers an Opinion of Counsel stating that, under then existing laws, there would be no adverse tax consequences to the Holders in the event that this condition is not satisfied, and such person assumes by supplemental indenture all the obligations of the Company under the Securities and the Indenture and immediately after giving effect to the transaction no Default or Event of Default exists.

14. **Amendments, Supplements and Waivers.** Subject to certain exceptions, the Indenture or the Securities may be amended or supplemented with the consent of the Holders of at least a majority in aggregate principal amount of the Securities then outstanding, and any existing Default or Event of Default may be waived with the consent of the Holders of a majority in aggregate principal amount of the Securities then outstanding. Without notice to or the consent of any Securityholder, the Indenture or the Securities may be amended or supplemented to cure any ambiguity, omission, defect or inconsistency, to provide for uncertificated Securities in addition to certificated Securities, to comply with **Sections 5.01** and **10.12** of the Indenture or to make any change that does not adversely affect the rights of any Securityholder.

15. **Defaults and Remedies.** An Event of Default includes the occurrence of any of the following: default in payment of principal at maturity, upon redemption or exercise of a Repurchase Right or otherwise; default for 30 days in payment of interest or other amounts due; failure by the Company for 60 days after notice to it to comply with any of its other agreements in the Indenture or the Securities; and certain events of bankruptcy or insolvency. If any Event of Default occurs and is continuing, the Trustee or the Holders of at least 25% in aggregate principal amount of the Securities then outstanding may declare all the Securities to be due and payable immediately, except as provided in the Indenture. If an Event of Default specified in **Section 6.01(iv)** or **(v)** of the Indenture with respect to the Company occurs, the principal of and accrued interest on all the Securities shall *ipso facto* become and be immediately due and payable without any declaration or other act on the part of the Trustee or any Securityholder. Securityholders may not enforce the Indenture or the Securities except as provided in the Indenture. The Trustee may require indemnity satisfactory to it before it enforces the Indenture or the Securities. Subject to certain limitations, Holders of a majority in principal amount of the Securities then outstanding may direct the Trustee in its exercise of any trust or power. The Trustee may withhold from Securityholders notice of any continuing Default or Event of Default (except a Default or Event of Default in payment) if it determines that withholding notice is in the interests of the Securityholders. The Company must furnish an annual compliance certificate to the Trustee.

16. **Registration Rights.** The Holders are entitled to registration rights as set forth in the Registration Rights Agreement (as defined in the Indenture). The Holders shall be entitled to receive liquidated damages in certain circumstances, all as set forth in the Registration Rights Agreement.

17. **Trustee Dealings with the Company.** The Trustee under the Indenture, or any banking institution serving as successor Trustee thereunder, in its individual or any other capacity, may make loans to, accept deposits from, and perform services for the Company or its Affiliates, and may otherwise deal with the Company or its Affiliates, as if it were not Trustee.

18. **No Recourse Against Others.** No past, present or future director, officer, employee, consultant or stockholder, as such, of the Company shall have any liability for any obligations of the Company under the Securities or the Indenture or for any claim based on, in respect of or by reason of such obligations or their creation. Each Securityholder by accepting a Security waives and releases all such liability. The waiver and release are part of the consideration for the issue of the Securities.

19. **Authentication.** This Security shall not be valid until authenticated by the manual signature of the Trustee or an authenticating agent.

20. **Abbreviations.** Customary abbreviations may be used in the name of a Securityholder or an assignee, such as: TEN COM (= tenants in common), TEN ENT (= tenants by the entirety), JT TEN (= joint tenants with right of survivorship and not as tenants in common), CUST (= Custodian), and U/G/M/A (Uniform Gifts to Minors Act).

THE COMPANY WILL FURNISH TO ANY SECURITYHOLDER UPON WRITTEN REQUEST AND WITHOUT CHARGE A COPY OF THE INDENTURE. REQUESTS MAY BE MADE TO:

ISIS Pharmaceuticals, Inc.  
2292 Faraday Avenue  
Carlsbad, CA 92008  
Attention: Corporate Secretary

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[FORM OF ASSIGNMENT]

I or we assign to

PLEASE INSERT SOCIAL SECURITY OR OTHER IDENTIFYING NUMBER

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(please print or type name and address)

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the within Security and all rights thereunder, and hereby irrevocably constitutes and appoints

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attorney to transfer the Security on the books of the Company with full power of substitution in the premises.

Dated: \_\_\_\_\_

NOTICE: The signature on this assignment must correspond with the name as it appears upon the face of the within Security in every particular way without alteration or enlargement or any change whatsoever and be guaranteed by a guarantor institution participating in the Securities Transfer Agents Medallion Program or in such other guarantee program acceptable to the Trustee.

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Signature Guarantee:

In connection with any transfer of this Security occurring prior to the date which is the earlier of (i) the date of the declaration by the Commission of the effectiveness of a registration statement under the Securities Act of 1933, as amended (the "Securities Act") covering resales of this Security (which effectiveness shall not have been suspended or terminated at the date of the transfer) and (ii) the Resale Restriction Termination Date, the undersigned confirms that it has not utilized any general solicitation or general advertising in connection with transfer:

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[Check One]

- (1)  to the Company or any subsidiary thereof; or
- (2)  pursuant to and in compliance with Rule 144A under the Securities Act of 1933, as amended; or
- (3)  outside the United States to a person other than a "U.S. person" in compliance with Rule 904 of Regulation S under the Securities Act of 1933, as amended; or
- (4)  pursuant to the exemption from registration provided by Rule 144 under the Securities Act of 1933, as amended; or
- (5)  pursuant to an effective registration statement under the Securities Act of 1933, as amended.

and unless the box below is checked, the undersigned confirms that such Security is not being transferred to an "affiliate" of the Company as defined in Rule 144 under the Securities Act of 1933, as amended (an "Affiliate");

The transferee is an Affiliate of the Company. (If the Security is transferred to an Affiliate, the restrictive legend must remain on the Security for two years following the date of the transfer).



Unless one of the items is checked, the Trustee will refuse to register any of the Securities evidenced by this certificate in the name of any person other than the registered Holder thereof; *provided, however*, that if item (4) is checked, the Company or the Trustee may require, prior to registering any such transfer of the Securities, in their sole discretion, such written legal opinions, certifications and other information as the Trustee or the Company have reasonably requested to confirm that such transfer is being made pursuant to an exemption from, or in a transaction not subject to, the registration requirements of the Securities Act of 1933, as amended.

If none of the foregoing items are checked, the Trustee or Registrar shall not be obligated to register this Security in the name of any person other than the Holder hereof unless and until the conditions to any such transfer of registration set forth herein and in **Section 2.16** of the Indenture shall have been satisfied.

Dated: \_\_\_\_\_ Signed: \_\_\_\_\_  
(Sign exactly as name appears on the other side of this Security)

Signature Guarantee: \_\_\_\_\_

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TO BE COMPLETED BY PURCHASER IF (2) ABOVE IS CHECKED

The undersigned represents and warrants that it is purchasing this Security for its own account or an account with respect to which it exercises sole investment discretion and that it and any such account is a "qualified institutional buyer" within the meaning of Rule 144A under the Securities Act of 1933, as amended, and is aware that the sale to it is being made in reliance on Rule 144A and acknowledges that it has received such information regarding the Company as the undersigned has requested pursuant to Rule 144A or has determined transferor is relying upon the undersigned's foregoing representations in order to claim the exemption from registration provided by Rule 144A.

Dated: \_\_\_\_\_ NOTICE: \_\_\_\_\_  
To be executed by an executive officer

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CONVERSION NOTICE

To convert this Security into Common Stock of the, check the box:

To convert only part of this Security, state the principal amount to be converted (must be in multiples of \$1,000):

\$ \_\_\_\_\_

If you want the stock certificate made out in another person's name, fill in the form below:

(Insert other person's soc. sec. or tax I.D. no.)

(Print or type other person's name, address and zip code)

Date: \_\_\_\_\_ Signature(s): \_\_\_\_\_

(Sign exactly as your name(s) appear(s) on the other side of this Security)

Signature(s) guaranteed by:

(All signatures must be guaranteed by a guarantor institution participating in the Securities Transfer Agents Medallion Program or in such other guarantee program acceptable to the Trustee.)

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OPTION OF HOLDER TO ELECT PURCHASE NOTICE

Certificate No. of Security: \_\_\_\_\_

If you want to elect to have this Security purchased by the Company pursuant to **Section 3.08** of the Indenture, check the box:

If you want to elect to have only part of this Security purchased by the Company pursuant to **Section 3.08** of the Indenture, state the principal amount:

\$ \_\_\_\_\_  
(in an integral multiple of \$1,000)

Date: \_\_\_\_\_

Signature(s): \_\_\_\_\_

(Sign exactly as your name(s) appear(s) on the other side of this Security)

Signature(s) guaranteed by: \_\_\_\_\_

(All signatures must be guaranteed by a guarantor institution participating in the Securities Transfer Agents Medallion Program or in such other guarantee program acceptable to the Trustee.)

**SCHEDULE A**

**SCHEDULE OR EXCHANGES OF INTERESTS IN THE GLOBAL SECURITY.**

The following exchanges of a part of this Global Security for an interest in another Global Security or for Securities in certificated form have been made:

Date of Exchange	Amount of decrease in Principal amount of this Global Security	Amount of increase in Principal amount of this Global Security	Principal amount of this Global Security following such decrease (or increase)	Signature or authorized signatory of Trustee or Note Custodian

May , 2002

Isis Pharmaceuticals, Inc.  
2292 Faraday Avenue  
Carlsbad, CA 92008

Ladies and Gentlemen:

You have requested my opinion with respect to certain matters in connection with the filing by Isis Pharmaceuticals, Inc., a Delaware corporation (the "Company"), of a Registration Statement on Form S-3 (the "Registration Statement") with the Securities and Exchange Commission pursuant to which the Company is registering under the Securities Act of 1933, as amended, the resale by the holders thereof of a total of \$125,000,000 principal amount of 5<sup>1</sup>/<sub>2</sub>% Convertible Subordinated Notes due May 1, 2009 (the "Notes") and up to 7,518,800 shares of common stock issuable upon conversion thereof (the "Shares"). The Notes were issued pursuant to the Indenture dated May 1, 2002 between the Company and Wells Fargo Bank Minnesota, National Association (the "Indenture").

In connection with this opinion, I have examined copies of the Indenture, the Notes and such other documents and have made such other inquiries and investigations of law as I have deemed necessary or appropriate to enable me to render the opinion expressed below. I have assumed the genuineness and authenticity of all documents submitted to me as originals and the conformity to originals of all documents where due execution and delivery are a prerequisite to the effectiveness thereof.

My opinion is expressed only with respect to the federal laws of the United States of America, the laws of the State of California and the General Corporation Law of the State of Delaware. I express no opinion as to whether the laws of any particular jurisdiction other than those identified above are applicable to the subject matter hereof. I note that the parties to the Indenture have designated the laws of the State of New York as the laws governing that agreement and the Notes. Accordingly, my opinion below as to the validity and binding effect of the Notes is premised upon the result that would be obtained if a California court were to apply the internal laws of the State of California (notwithstanding the designation of the laws of the State of New York to govern the interpretation and enforcement of the Indenture and the Notes).

On the basis of the foregoing and in reliance thereon, I am of the opinion that (i) the Notes constitute valid and binding obligations of the Company, except as may be limited by applicable bankruptcy, insolvency, reorganization, moratorium, fraudulent transfer and other similar laws of general application relating to or affecting creditors' rights, by general principles of equity, and by an implied covenant of good faith, and (ii) following the issuance upon conversion of the Notes in accordance with their terms, the Shares will be validly issued, fully paid and nonassessable.

I consent to the reference to my name under the caption "Legal Matters" in the prospectus included in the Registration Statement and to the filing of this opinion as an exhibit to the Registration Statement.

Sincerely,

/s/ Grantland E. Bryce

Grantland E. Bryce  
Vice President, Legal and  
General Counsel

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QuickLinks

[EXHIBIT 5.1](#)

**COMPUTATION OF RATIO OF EARNINGS TO FIXED CHARGES**  
(in thousands, except ratio of earnings to fixed charges)

The following table sets forth our ratio of earnings to fixed charges for the years ended December 31, 1997, 1998, 1999, 2000, 2001, for the three months ended March 31, 2002, for the pro forma year ended December 31, 2001, and the pro forma three months ended March 31, 2002. As earnings were inadequate to cover the combined fixed charges, we have provided the average deficiency amounts. For purposes of this computation, earnings are defined as net loss excluding the preferred stock dividend requirement on our Series A and Series B preferred stock. Fixed charges are the sum of (i) interest costs including the amortization of deferred financing costs; and (ii) the portion of operating lease rental expense that is representative of the interest factor of 15%. On a pro forma basis, we have assumed as of January 1, 2001, the early extinguishment of our 14% senior subordinated debt, which occurred on May 1, 2002, and assumed the receipt of \$125 million in proceeds from the private placement of our 5<sup>1</sup>/<sub>2</sub>% convertible subordinated notes due 2009, which occurred on May 1, 2002. The pro forma results are representative of the reduction in interest expense for the payment of our 14% senior subordinated debt and the additional interest expense associated with the issuance of our 5<sup>1</sup>/<sub>2</sub>% convertible subordinated notes.

	Years Ended December 31,					Three Months Ended March 31, 2002	Pro Forma Year Ended December 31, 2001	Pro Forma Three Months Ended March 31, 2002
	1997	1998	1999	2000	2001			
Net loss before accretion of dividend on preferred stock	\$ (31,066)	\$ (42,983)	\$ (59,225)	\$ (53,485)	\$ (73,832)	\$ (17,972)	(73,832)	(17,972)
Interest expense on indebtedness	\$ 3,585	\$ 9,355	\$ 11,424	\$ 13,160	\$ 15,248	\$ 4,631	12,473	3,711
Interest expense on portion of rent								
Expense representative of interest	\$ 223	\$ 268	\$ 352	\$ 605	\$ 605	\$ 177	605	177
<b>Earnings</b>	<b>\$ (27,258)</b>	<b>\$ (33,360)</b>	<b>\$ (47,449)</b>	<b>\$ (39,720)</b>	<b>\$ (57,979)</b>	<b>\$ (13,164)</b>	<b>(60,754)</b>	<b>(14,084)</b>
Interest expense on indebtedness	\$ 3,585	\$ 9,355	\$ 11,424	\$ 13,160	\$ 15,248	\$ 4,631	12,473	3,711
Interest expense on portion of rent								
Expense representative of interest	\$ 223	\$ 268	\$ 352	\$ 605	\$ 605	\$ 177	605	177
<b>Total Fixed Charges</b>	<b>\$ 3,808</b>	<b>\$ 9,623</b>	<b>\$ 11,776</b>	<b>\$ 13,765</b>	<b>\$ 15,853</b>	<b>\$ 4,808</b>	<b>13,078</b>	<b>3,888</b>
Ratio of earnings to fixed charges	—	—	—	—	—	—	—	—
Coverage deficiency	\$ (31,066)	\$ (42,983)	\$ (59,225)	\$ (53,485)	\$ (73,832)	\$ (17,972)	(73,832)	(17,972)

QuickLinks

[EXHIBIT 12.1](#)

[COMPUTATION OF RATIO OF EARNINGS TO FIXED CHARGES \(in thousands, except ratio of earnings to fixed charges\)](#)

**CONSENT OF ERNST & YOUNG, INDEPENDENT AUDITORS**

We consent to the reference to our firm under the caption "Experts" in the Registration Statement (Form S-3), and related Prospectus of Isis Pharmaceuticals, Inc. for the registration of \$125,000,000 of its <sup>5</sup>/<sub>1</sub>/<sub>2</sub>% Convertible Subordinated Promissory Notes due 2009 and the 7,518,800 shares of its common stock issuable upon the conversion of such notes and to the incorporation by reference therein of our report dated February 1, 2002, with respect to the financial statements of Isis Pharmaceuticals, Inc. included in its Annual Report on Form 10-K for the year ended December 31, 2001, filed with the Securities and Exchange Commission.

ERNST & YOUNG LLP

/s/ Ernst & Young

San Diego, California  
May 22, 2002

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[EXHIBIT 23.1](#)

[CONSENT OF ERNST & YOUNG, INDEPENDENT AUDITORS](#)

# SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

## FORM T-1

STATEMENT OF ELIGIBILITY  
UNDER THE TRUST INDENTURE ACT OF 1939 OF A  
CORPORATION DESIGNATED TO ACT AS TRUSTEE

- o CHECK IF AN APPLICATION TO DETERMINE ELIGIBILITY OF A TRUSTEE PURSUANT TO SECTION 305(b) (2)

### WELLS FARGO BANK MINNESOTA, NATIONAL ASSOCIATION

(Exact name of trustee as specified in its charter)

**A U.S. National Banking Association** **41-1592157**  
(Jurisdiction of incorporation or organization if (I.R.S. Employer Identification No.)  
not a U.S. national bank)

**Sixth Street and Marquette Avenue** **55479**  
**Minneapolis, Minnesota** (Zip code)  
(Address of principal executive offices)

**Stanley S. Stroup, General Counsel**  
**WELLS FARGO BANK MINNESOTA, NATIONAL ASSOCIATION**  
**Sixth Street and Marquette Avenue**  
**Minneapolis, Minnesota 55479**  
**(612) 667-1234**  
(Agent for Service)

### Isis Pharmaceuticals, Inc.

(Exact name of obligor as specified in its charter)

**Delaware** **33-0336973**  
(State or other jurisdiction of (I.R.S. Employer Identification No.)  
incorporation or organization)

**2292 Farraday Avenue** **92008**  
**Carlsbad, California** (Zip code)  
(Address of principal executive offices)

**5<sup>1</sup>/<sub>2</sub>% Convertible Subordinated Notes**  
(Title of the indenture securities)

Item 1. *General Information.* Furnish the following information as to the trustee:

- (a) Name and address of each examining or supervising authority to which it is subject.

Comptroller of the Currency  
Treasury Department  
Washington, D.C.

Federal Deposit Insurance Corporation  
Washington, D.C.

The Board of Governors of the Federal Reserve System  
Washington, D.C.

- (b) Whether it is authorized to exercise corporate trust powers.

The trustee is authorized to exercise corporate trust powers.

Item 2. *Affiliations with Obligor.* If the obligor is an affiliate of the trustee, describe each such affiliation.

None with respect to the trustee.

No responses are included for Items 3-14 of this Form T-1 because the obligor is not in default as provided under Item 13.

Item 16. *List of Exhibits.* List below all exhibits filed as a part of this Statement of Eligibility. Wells Fargo Bank incorporates by reference into this Form T-1 the exhibits attached hereto.

- Exhibit 1. a. A copy of the Articles of Association of the trustee now in effect.\*\*\*
- Exhibit 2. a. A copy of the certificate of authority of the trustee to commence business issued June 28, 1872, by the Comptroller of the Currency to The Northwestern National Bank of Minneapolis.\*
- b. A copy of the certificate of the Comptroller of the Currency dated January 2, 1934, approving the consolidation of The Northwestern National Bank of Minneapolis and The Minnesota Loan and Trust Company of Minneapolis, with the surviving entity being titled Northwestern National Bank and Trust Company of Minneapolis.\*
- c. A copy of the certificate of the Acting Comptroller of the Currency dated January 12, 1943, as to change of corporate title of Northwestern National Bank and Trust Company of Minneapolis to Northwestern National Bank of Minneapolis.\*
- d. A copy of the letter dated May 12, 1983 from the Regional Counsel, Comptroller of the Currency, acknowledging receipt of notice of name change effective May 1, 1983 from Northwestern National Bank of Minneapolis to Norwest Bank Minneapolis, National Association.\*
- e. A copy of the letter dated January 4, 1988 from the Administrator of National Banks for the Comptroller of the Currency certifying approval of consolidation and merger effective January 1, 1988 of Norwest Bank Minneapolis, National Association with various other banks under the title of "Norwest Bank Minnesota, National Association."\*
- f. A copy of the letter dated July 10, 2000 from the Administrator of National Banks for the Comptroller of the Currency certifying approval of consolidation effective July 8, 2000 of Norwest Bank Minnesota, National Association with various other banks under the title of "Wells Fargo Bank Minnesota, National Association."\*\*\*\*
- Exhibit 3. A copy of the authorization of the trustee to exercise corporate trust powers issued January 2, 1934, by the Federal Reserve Board.\*
- Exhibit 4. Copy of By-laws of the trustee as now in effect.\*\*\*
- Exhibit 5. Not applicable.
- Exhibit 6. The consent of the trustee required by Section 321(b) of the Act.
- Exhibit 7. A copy of the latest report of condition of the trustee published pursuant to law or the requirements of its supervising or examining authority. \*\*
- Exhibit 8. Not applicable.
- Exhibit 9. Not applicable.

\* Incorporated by reference to exhibit number 25 filed with registration statement number 33-66026.

\*\* Incorporated by reference to exhibit number 25 filed with registration statement number 333-84722

\*\*\* Incorporated by reference to exhibit T3G filed with registration statement number 022-22473.

\*\*\*\* Incorporated by reference to exhibit number 25.1 filed with registration statement number 001-15891.

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#### SIGNATURE

Pursuant to the requirements of the Trust Indenture Act of 1939, as amended, the trustee, Wells Fargo Bank Minnesota, National Association, a national banking association organized and existing under the laws of the United States of America, has duly caused this statement of eligibility to be signed on its behalf by the undersigned, thereunto duly authorized, all in the City of Minneapolis and State of Minnesota on the 21th day of May 2002.

WELLS FARGO BANK MINNESOTA,  
NATIONAL ASSOCIATION

/s/ MICHAEL G. SLADE

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**EXHIBIT 6**

May 21, 2002

Securities and Exchange Commission  
Washington, D.C. 20549

Gentlemen:

In accordance with Section 321(b) of the Trust Indenture Act of 1939, as amended, the undersigned hereby consents that reports of examination of the undersigned made by Federal, State, Territorial, or District authorities authorized to make such examination may be furnished by such authorities to the Securities and Exchange Commission upon its request therefor.

Very truly yours,

WELLS FARGO BANK MINNESOTA,  
NATIONAL ASSOCIATION

/s/ MICHAEL G. SLADE

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Michael G. Slade  
Corporate Trust Officer

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