

Registration No. 333-71176

SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

AMENDMENT NO. 1
to
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)

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Approximate date of commencement of proposed sale to the public:
As soon as practicable 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

Proposed maximum Proposed maximum Title of each class of Amount to be offering price per aggregate offering Amount of securities to be registered registered(1) share(2) price(2) registration fee(3) Common Stock, \$.001 per share.....	
5,750,000	\$18.28
\$105,110,000	\$26,278

- (1) Includes 750,000 shares of our common stock which may be purchased by the Underwriters to cover over-allotments, if any.
- (2) Estimated solely for the purpose of calculating the registration fee pursuant to Rule 457(c) of the Securities Act of 1933 based upon the average of the high and low prices of our common stock as reported on the Nasdaq National Market on October 2, 2001.
- (3) Previously paid by the Registrant.

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 date as the Commission, acting pursuant to said Section 8 (a), may determine.

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 IN WHICH THE OFFER OR SALE IS NOT PERMITTED.

PRELIMINARY PROSPECTUS Subject to completion October 22, 2001

5,000,000 Shares

[LOGO]

Common Stock

We are selling all of the 5,000,000 shares of common stock offered by this prospectus.

Our common stock is quoted on the Nasdaq National Market under the symbol

the front of this prospectus or that any document incorporated by reference is accurate as of any date other than its filing date. You should not consider this prospectus to be an offer or solicitation relating to the securities in any jurisdiction in which such an offer or solicitation relating to the securities is not authorized. Furthermore, you should not consider this prospectus to be an offer or solicitation relating to the securities if the person making the offer or solicitation is not qualified to do so, or if it is unlawful for you to receive such an offer or solicitation.

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Isis Pharmaceuticals-TM-, GeneTrove-TM- and Ibis Therapeutics-TM- are trademarks of Isis. Vitravene-Registered Trademark- is a registered trademark of Novartis AG. This prospectus also contains trademarks and servicemarks of other companies.

Prospectus 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 SHARES 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.

BUSINESS OVERVIEW

We are a biopharmaceutical company pioneering RNA-based drug discovery technologies to identify and commercialize novel drugs to treat significant unmet medical needs. RNA, or ribonucleic acid, is a molecule that provides to a cell the information needed to produce proteins, some of which are involved in disease. Interference with RNA can keep proteins involved in disease from being produced. We have strong proprietary positions in RNA-based drug discovery technologies. With our primary technology, antisense, we create inhibitors designed to bind with high specificity to their intended RNA target. With our Ibis technology, we use our expertise in RNA to design small molecule therapeutics that interfere with RNA. We also use our antisense technology in collaborations with pharmaceutical company partners 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 therapeutic intervention.

We have used our antisense technology to commercialize our first product, Vitravene. Vitravene demonstrates our ability to meet FDA regulatory requirements and to commercially manufacture antisense drugs. We have 12 products in our development pipeline with eight in human clinical trials designed to assess efficacy. Our products in development address numerous therapeutic areas with major market potential, including cancer, psoriasis, rheumatoid arthritis, hepatitis C and diabetes. We are expanding the therapeutic opportunities for antisense drugs by developing a variety of formulations to enhance patient compliance and convenience. We are also pursuing second-generation drugs that may be able to be dosed as infrequently as once per month and that may be able to be dosed orally.

ISIS 3521, our most advanced product currently under development, is undergoing Phase III clinical trials in combination with traditional chemotherapy cancer drugs. We initiated this Phase III trial in late 2000 for patients with non-small cell lung cancer, the most common form of lung cancer, based on promising results in patients in the Phase II trial. Results from this 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 November 2000, the FDA granted ISIS 3521 fast track review status. Prior to the end of 2001, we also plan to initiate Phase III clinical trials for another product, ISIS 2302, in an inflammatory bowel disease known as Crohn's disease. We have five 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 have collaborations in place with five major pharmaceutical partners for these services, including Eli Lilly and Company, Celera Genomics Group, Abbott Laboratories Inc., Aventis (Rhone-Poulenc Rorer) and the R.W. Johnson Pharmaceutical Research Institute, a member of the Johnson & Johnson family of companies. We have supplemented our GeneTrove services business with the introduction in August 2001 of a subscription database product in August 2001. This database is expected to contain proprietary information about the function of thousands of genes, which we believe pharmaceutical companies will find valuable in

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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 which bind to RNA. 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 June 2000, Ibis initiated its first collaboration with a pharmaceutical industry partner, Agouron Pharmaceuticals, Inc., a Pfizer company, in a research partnership worth up to \$37 million. In May 2001, we received a \$2.5 million milestone payment under this collaboration.

We have a broad patent portfolio relating to our technologies. We own or have an exclusive license to more than 800 issued patents, which we believe represents the largest antisense and RNA-oriented patent estate in the pharmaceutical industry. Our intellectual property is a strategic asset of the company. We are exploiting our patent estate to generate near-term revenues for the company.

RECENT DEVELOPMENTS

ELI LILLY AND COMPANY. In August 2001, we entered into a broad strategic relationship with Lilly that has four key components:

- Lilly purchased \$75 million of our common stock at \$18 per share.
- We licensed to Lilly rights to ISIS 3521, our antisense drug in Phase III trials for the treatment of non-small cell lung cancer.
- We initiated with Lilly a four-year antisense drug discovery collaboration in the areas of metabolic and inflammatory diseases and a related GeneTrove collaboration to determine the function of up to 1,000 genes.

- Lilly committed to lend us, interest-free, up to \$100 million over a four-year period to fund our obligations under the drug discovery collaboration. This loan is repayable at our option in either cash or our common stock, valued at \$40 per share.

If this collaboration is successful, the cumulative contingent funds over the life of the development process have the potential to exceed these committed funds.

MERCK & CO., INC. In May 2001, we licensed to Merck our preclinical antisense drug candidate, ISIS 113715, for adult onset, or Type 2, diabetes. Under the agreement, Merck has agreed to develop and commercialize ISIS 113715 in exchange for an upfront fee and milestone payments and royalties upon its successful development and approval. In August 2001, we received a \$2 million milestone payment under this agreement.

CELERA GENOMICS GROUP. In July 2001, Celera and our GeneTrove division entered into a collaboration to identify the biological role of more than 200 genes. Celera has the right to select for study a portfolio of genes, from which Celera can further select a limited number of genes for their exclusive use. The data for the remainder of the genes will be included in our human gene function database. We retain the rights to develop and commercialize antisense drugs to genes in the collaboration. Celera has agreed to pay us fees for this 18-month collaboration.

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The offering

Common stock offered.....	5,000,000 shares
Common stock outstanding after the offering.....	52,087,796 shares
Use of proceeds.....	For research, drug discovery and development activities, including preclinical and clinical studies, production of compounds for studies, capital expenditures, and other general corporate purposes. See "Use of Proceeds."
Nasdaq National Market symbol.....	"ISIP"

Unless we specifically state otherwise, the information in this prospectus assumes that the underwriters do not exercise their option to purchase up to 750,000 shares of common stock to cover over-allotments.

The number of shares of our common stock to be outstanding after the offering in the table above is based on the number of shares outstanding as of September 30, 2001, and does not include, as of that date:

- 8,443,801 shares of our common stock issuable upon exercise of outstanding options issued under our equity incentive plans at a weighted average exercise price of \$9.47 per share and an additional 2,228,952 shares of common stock available for future grants under our equity incentive plans;
- 1,029,881 shares of our common stock issuable upon exercise of outstanding warrants at a weighted average exercise price of \$25.16 per share;
- 1,562,020 shares of our common stock issuable upon conversion of our outstanding Series A and Series B Convertible Preferred Stock and related accreted dividends, assuming a stock price of \$17.05 per share, the closing price of our common stock on September 30, 2001;
- 3,007,182 shares of our common stock issuable upon the conversion of our outstanding indebtedness assuming a stock price of \$17.05 per share, the closing price of our common stock on September 30, 2001; and
- shares of our common stock issuable to Hybridon, with a maximum of 2,071,429 shares and a minimum of 673,077 shares.

Other information

Isis Pharmaceuticals, Inc. was incorporated in California in January 1989, and in April 1991 we changed our 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. Information contained on our website, www.isip.com, does not constitute part of this prospectus.

Our research and development programs have continued to evolve subsequent to our description of those programs in documents incorporated by reference in this prospectus. Some programs may have been deferred or abandoned, and some programs may have been added. While these changes may be material as to any particular program, we do not believe that, except as may be described herein or in a document incorporated by reference, they are material to our business overall.

Summary consolidated financial data

The as adjusted balance sheet data gives effect to the sale of 5,000,000 shares of our common stock in this offering at an assumed price of \$19.72 per share, after deducting the underwriting discount and estimated offering expenses. The following data should be read together with the financial statements, the related notes and other financial information included in this prospectus and incorporated herein by reference.

	Nine Months ended					Years Ended December 31,	
	1999	1998	1997	1996	2001	2000	Statement of
							operations data (unaudited)
							2000
revenues.....	\$37,255	\$33,925	\$39,171	\$32,722	\$22,663		
expenses.....	\$31,529	\$29,319	57,014	66,413			
Net loss applicable to common stock.....	(54,699)	(59,645)	(42,983)	(31,066)	(26,521)		
Basic and diluted net loss per share.....	(1.60)	(1.17)	(1.04)	(1.43)	(1.08)	(1.48)	(2.08)
Shares used in computing basic and diluted net loss per share.....	37,023	28,703	26,873	26,456	25,585	41,517	
			36,172				

	As of September 30, 2001		As of September 30, 2000	
	Actual	Adjusted(1)	Balance sheet data	As of September 30, 2000
Cash, cash equivalents and short-term investments.....	\$213,202	\$305,576	Working capital.....	183,852
assets.....	294,412	386,786	Total	276,226
Long-term debt and capital lease obligations, less current portion.....	123,651	123,651	Accumulated deficit.....	(370,635)
Stockholders' equity.....				118,030
				210,404

(1) THE FINANCIAL DATA ABOVE EXCLUDES TRANSACTIONS SUBSEQUENT TO SEPTEMBER 30, 2001, INCLUDING \$5 MILLION RECEIVED FROM LILLY ON OCTOBER 18, 2001 RELATED TO THE \$100 MILLION LOAN LILLY COMMITTED TO LEND ISIS.

INVESTING IN OUR COMMON STOCK 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 COMMON STOCK. 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 COMMON STOCK COULD DECLINE, AND YOU MIGHT LOSE ALL OR PART OF YOUR INVESTMENT.

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, 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 doing so. 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.

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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 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. We cannot be sure that any of these collaborations will be continued 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, ISIS 3521, 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 Merck & Company, Inc. and Elan Corporation, plc. 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

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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 avail themselves of 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 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.

If we fail to introduce our human gene function database in a timely fashion or if potential 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 September 30, 2001, our accumulated losses were approximately \$371 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 and existing sources of revenue and credit, together with the proceeds from this offering, will be adequate to satisfy our capital needs for the foreseeable future. If we fail to meet our goals regarding commercialization of our drug products, gene function database product and research

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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 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 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.

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 are successful commercializing 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. The manufacturers may not be able to comply or maintain compliance with Good Manufacturing Practices regulations. Non-compliance could significantly delay our receipt or marketing approval or result in FDA enforcement action.

 Risk factors

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 such 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 adequately protect our competitive advantage. Furthermore, our issued patents or patents licensed to us could potentially be successfully challenged, invalidated or circumvented so that our patent rights would not create an effective competitive barrier.

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 US 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 infringement of U.S. Patent 6,001,653. If we do not prevail in the defense of this patent, 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

 Risk factors

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 US 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, our stock price 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 our stock price 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.

Our stock price may continue 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. During the twelve months preceding October 18, 2001, the market price of our common stock has ranged from \$7.875 to \$21.98 per share. The market price can be affected by many factors, including, for example, fluctuations in our operating results, announcements of collaborations, clinical trial results, 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 2/3% 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.

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Risk factors

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 president, or by any holder of 10% or more of our outstanding common stock. We also have implemented a stockholders' rights plan, which is 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 our stock price 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 5,732,273 shares of our common stock which are currently outstanding, an additional \$14.5 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 our stock price. In addition, Reliance has registration rights with respect to the approximately \$66 million of notes we issued to Reliance.

If you purchase our common stock in this offering, you will incur immediate and substantial dilution in the book value of your shares.

You will experience an immediate and substantial dilution of \$16.55 per share in the net tangible book value per share of our common stock, assuming a public offering price of \$19.72 per share. After giving effect to this offering, and to other issuances of our common stock as described in the "Dilution" section of this prospectus, our pro forma adjusted net tangible book value as of September 30, 2001, would have been \$3.17 per share. In addition, this dilution will be increased to the extent that holders of outstanding options and warrants to purchase our common stock at prices below our net tangible book value per share after this offering exercise those options or warrants.

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Disclosure 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 activities 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" beginning on page 5 of this prospectus. As a result, you are cautioned not to rely on these forward-looking statements.

Use of proceeds

The net proceeds to us from the sale of the 5,000,000 shares of common stock we are offering will be approximately \$92.4 million. If the underwriters exercise the over-allotment option in full, the net proceeds to us will be approximately \$106.3 million. For the purpose of estimating net proceeds, we are assuming that the public offering price will be \$19.72 per share. "Net proceeds" is what we expect to receive after we pay the underwriting discount and other estimated expenses for this offering.

We intend to use the net proceeds of this offering for research, drug discovery and development programs, and for other general corporate purposes. Expenses to be funded with the offering proceeds include costs of preclinical and clinical studies, the production of compounds for these studies and capital expenditures. We have not identified precisely the amounts we plan to spend on each research, drug discovery and development program or the timing of these expenditures. However, we currently plan that a portion of the proceeds will be used to support our planned research and development efforts. The remaining proceeds will be used for general corporate purposes. The amounts actually expended for each purpose may vary significantly depending upon numerous factors, including the amount and timing of the proceeds from this offering, progress of our research, drug discovery and development programs, the results of preclinical and clinical studies, the timing of regulatory approvals, technological advances, determinations as to commercial potential of our compounds and the status of competitive products. In addition, expenditures will also depend upon the establishment of collaborative research arrangements with other companies, the availability of other financing and other factors.

We may use a portion of the net proceeds to acquire or invest in businesses, products or technologies that are complementary to our own. However, we are not currently a party to any agreement regarding a material acquisition and no

portion of the net proceeds have been allocated for any specific acquisition.

Pending any of the above uses, the net proceeds will be invested in investment-grade, interest-bearing debt securities.

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Capitalization

The following table sets forth our capitalization at September 30, 2001:

- on an actual basis; and
- on an as adjusted basis to give effect to the sale of the 5,000,000 shares of common stock offered by us, assuming a public offering price of \$19.72 per share and after deducting underwriting discounts and commissions and estimated offering expenses to be paid by us:

As of September 30, 2001	-----	As
Actual	Adjusted(1)	-----
----- (in thousands, except share data) Cash, cash equivalents and short term investments.....		
	\$ 213,202	\$ 305,576
===== Long-term debt and capital lease obligations, less current		
portion.....		
\$ 123,651	\$ 123,651	Stockholders' equity: Series A
Convertible Exchangeable 5% Preferred stock, \$.001 par value; 120,150 shares authorized, issued and outstanding, actual and adjusted.....		
	12,015	12,015
Accretion of Series A Preferred stock dividends.....		
	1,542	1,542
Series B Convertible Exchangeable 5% Preferred stock, \$.001 par value; 16,620 shares authorized, 12,015 shares issued and outstanding, actual and adjusted.....		
	12,015	12,015
Accretion of Series B Preferred stock dividends.....		
	1,060	1,060
Common stock, \$.001 par value; 100,000,000 shares authorized, 47,087,796 shares issued and outstanding, actual; and 52,087,796 shares issued and outstanding, as adjusted.....		
	47 52	Additional paid-in
capital.....	461,267	553,636
Deferred		
compensation.....	(297)	(297)
(297) Accumulated other comprehensive		
income.....	1,016	1,016
Accumulated deficit.....	(370,635)	(370,635)
(370,635) -----	-----	Total stockholders' equity.....
	118,030	210,404
----- Total		
capitalization.....		\$
241,681	\$ 334,055	=====

(1) THE FINANCIAL DATA ABOVE EXCLUDES TRANSACTIONS SUBSEQUENT TO SEPTEMBER 30, 2001, INCLUDING \$5 MILLION RECEIVED FROM LILLY ON OCTOBER 18, 2001 RELATED TO THE \$100 MILLION LOAN LILLY COMMITTED TO LEND ISIS.

The table should be read in conjunction with our consolidated financial statements and the related notes appearing elsewhere in this prospectus.

Market price of common stock

Our common stock is traded publicly through the Nasdaq National Market under the symbol "ISIP." The following table presents quarterly information on the price range of our common stock. This information indicates the high and low sale prices reported by the Nasdaq National Market. These prices do not include retail markups, markdowns or commissions.

Common Stock Price High Low -----			
----- Fiscal Year Ended December 31, 1999			
First			
Quarter.....	\$15.25	\$ 8.94	Second
Quarter.....	12.19	9.25	Third
Quarter.....	13.81	9.16	Fourth
----- Fiscal Year Ended December 31, 2000			
First			
Quarter.....	\$39.00	\$ 5.75	Second
Quarter.....	16.25	8.06	Third
Quarter.....	15.75	10.50	Fourth
----- Fiscal Year Ended December 31, 2001			
First			
Quarter.....	\$13.00	\$ 7.97	Second
Quarter.....	13.17	7.88	Third
Quarter.....	18.05	9.75	Fourth Quarter (through October 18, 2001).....
		21.98	16.70

On October 18, 2001, the last reported sale price for our common stock was \$19.72 per share, and there were approximately 1,044 stockholders of record of our common stock.

Dividend policy

We have not paid any dividends and do not anticipate paying cash dividends in the foreseeable future. We currently intend to retain all available funds and any future earnings for use in the operation of our business. Under the terms of certain of our term loans, we are restricted from paying cash dividends until the loans are fully repaid.

Dilution

Our net tangible book value as of September 30, 2001 was \$72,897,000, or approximately \$1.55 per share of common stock. Net tangible book value per share represents the amount of our tangible assets less total liabilities, divided by 47,087,796 shares of common stock.

Net tangible book value dilution per share represents the difference between the amount per share paid by purchasers of shares of common stock in this offering and the pro forma adjusted net tangible book value per share of common stock immediately after completion of this offering. After giving effect to the sale of 5,000,000 shares of common stock in this offering at an assumed public offering price of \$19.72 per share and the receipt of the estimated net proceeds therefrom (after deducting estimated offering expenses), our pro forma adjusted net tangible book value as of September 30, 2001 would have been \$165,271,000, or \$3.17 per share, an immediate increase of \$1.62 per share over the net tangible book value to existing stockholders and an immediate dilution of \$16.55 per share to the adjusted net tangible book value to purchasers of common stock

in this offering, as illustrated in the following table:

Assumed public offering price per share.....		\$19.72
Net tangible book value per share at September 30, 2001...	\$1.55	
Increase per share attributable to new investors in this offering.....	1.62	

Pro forma adjusted net tangible book value per share after offering.....		\$ 3.17

Net tangible book value dilution per share to new investors in this offering.....		\$16.55
		=====

To the extent that outstanding options and warrants are exercised, or our outstanding convertible preferred stock or convertible debt is converted, there could be further dilution to new investors.

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Selected consolidated financial data

The following selected consolidated financial data for the five years ended December 31, 2000 are derived from the audited consolidated financial statements of ISIS Pharmaceuticals, Inc. The financial data for the nine-month periods ended September 30, 2001 and 2000 are derived from unaudited consolidated financial statements. The unaudited financial statements include all adjustments, consisting of normal recurring accruals, which the Company considers necessary for a fair presentation of the financial position and the results of operations for these periods. Operating results for the nine months ended September 30, 2001 are not necessarily indicative of the results that may be expected for the entire year ending December 31, 2001. The data should be read in conjunction with the consolidated financial statements, the related notes, and other financial information incorporated by reference herein.

Nine Months ended Years Ended
December 31, September 30, -----

2000 1999 1998 1997 1996 2001 2000
Statement of operations data:
(unaudited) -----

----- (in
thousands, except per share data)
Total

revenues.....	\$37,255	\$33,925	\$39,171	\$32,722		
\$22,663	\$ 31,529	\$29,319	Research and development expenses.....			
57,014	66,413	62,200	55,940	45,653		
58,954	41,986	Net loss applicable to common stock.....	(54,699)			
	(59,645)	(42,983)	(31,066)			
(26,521)	(59,175)	(38,936)	Basic and diluted net loss per share.....	(1.48)	(2.08)	(1.60)
(1.17)	(1.04)	(1.43)	(1.08)	Shares used in computing basic and diluted net loss per share.....	37,023	28,703
26,873	26,456	25,585	41,517	36,172		

As of As of December 31,
September 30, -----

----- 2000

1999 1998 1997 1996 2001 Balance
 sheet data: (unaudited) -----

----- (in thousands) Cash,
 cash equivalents and short-term
 investments..... \$127,262
 \$ 52,839 \$ 58,848 \$ 86,786 \$
 77,624 \$ 213,202 Working
 capital.....
 118,568 44,213 40,651 62,573
 56,300 183,852 Total
 assets.....
 183,256 103,107 96,074 117,881
 101,305 294,412 Long-term debt
 and capital lease obligations,
 less current
 portion.....
 102,254 87,254 77,724 56,452
 19,864 123,651 Accumulated
 deficit.....
 (311,460) (256,761) (197,116)
 (154,133) (123,067) (370,635)
 Stockholders' equity
 (deficit)..... 66,366 869
 (4,186) 34,852 58,385 118,030

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Underwriting

We and the underwriters for this offering named below have entered into an underwriting agreement concerning the shares being offered. Subject to conditions, each underwriter has severally agreed to purchase the number of shares indicated in the following table. UBS Warburg LLC, Robertson Stephens, Inc., Needham & Company, Inc. and Fortis Securities Inc. are the representatives of the underwriters.

Underwriters	Number of Shares	-----
-----	-----	-----
	UBS Warburg	
LLC.....	
	Robertson Stephens,	
Inc.....	Needham &
Company, Inc.....	Company, Inc.....
	Fortis Securities	
Inc.....	-----
Total.....
	5,000,000	=====

If the underwriters sell more shares than the total number set forth in the table above, the underwriters have a 30-day option to buy up to 750,000 shares from us at the public offering price less the underwriting discounts and commissions to cover these sales. If any shares are purchased under this option, the underwriters will severally purchase shares in approximately the same proportion as set forth in the table above.

The following table provides information regarding the amount of the discount to be paid to the underwriters by us:

No Exercise of Full Exercise of over-allotment option	-----
over-allotment option	-----
-----	-----
	Per
share.....
	\$ \$
Total.....
	\$ \$

We estimate that the total expenses of this offering payable by us, excluding underwriting discounts and commissions, will be about \$310,000.

Shares sold by the underwriters to the public will initially be offered at the public offering price set forth on the cover of this prospectus. Any shares sold by the underwriters to securities dealers may be sold at a discount of up to

\$ per share from the public offering price. Any of these securities dealers may resell any shares purchased from the underwriters to other brokers or dealers at a discount of up to \$ per share from the public offering price. If all the shares are not sold at the public offering price, the representatives may change the offering price and the other selling terms.

We and each of our directors and executive officers have agreed with the underwriters not to offer, sell, contract to sell, hedge or otherwise dispose of, directly or indirectly, any of our common stock or securities convertible into or exchangeable for shares of common stock during the period from the date of this prospectus continuing through the date 90 days after the date of this prospectus without the prior written consent of UBS Warburg LLC.

In connection with this offering, the underwriters may purchase and sell shares of our common stock in the open market. These transactions may include stabilizing transactions, short sales and purchases to cover positions created by short sales. Stabilizing transactions consist of bids or purchases made for the purpose of preventing or retarding a decline in the market price of our common stock while this offering is in progress. Short sales involve the sale by the underwriters of a greater number of shares

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than they are required to purchase in this offering. Short sales may be either "covered short sales" or "naked short sales." Covered short sales are sales made in an amount not greater than the underwriters' over-allotment option to purchase additional shares in this offering. The underwriters may close out any covered short position by either exercising their over-allotment option or purchasing shares in the open market. In determining the source of shares to close out the covered short position, the underwriters will consider, among other things, the price of shares available for purchase in the open market as compared to the price at which they may purchase shares through the over-allotment option. Naked short sales are sales in excess of the over-allotment option. The underwriters must close out any naked short position by purchasing shares in the open market. A naked short position is more likely to be created if the underwriters are concerned there may be downward pressure on the price of shares in the open market after pricing that could adversely affect investors who purchase in this offering.

The underwriters also may impose a penalty bid. This occurs when a particular underwriter repays to the underwriters a portion of the underwriting discount received by it because the representatives have repurchased shares sold by or for the account of that underwriter in stabilizing or short covering transactions.

These activities by the underwriters may stabilize, maintain or otherwise affect the market price of our common stock. As a result, the price of our common stock may be higher than the price that otherwise might exist in the open market. If these activities are commenced, they may be discontinued by the underwriters at any time. These transactions may be effected on the Nasdaq National Market or otherwise.

In addition, in connection this offering certain of the underwriters (and selling group members) may engage in passive market making transactions in the common stock on the Nasdaq National Market prior to the pricing and completion of the offering. Passive market making consists of displaying bids on the Nasdaq National Market no higher than the bid prices of independent market makers and making purchases at prices no higher than these independent bids and effected in response to order flow. Net purchases by a passive market maker on each day are limited to a specified percentage of the passive market maker's average daily trading volume in the common stock during a specified period and must be discontinued when such limit is reached. Passive market making may cause the price of the common stock to be higher than the price that otherwise would exist in the open market in the absence of such transactions. If passive market making is commenced, it may be discontinued at any time.

We have agreed to indemnify the several underwriters against some liabilities, including liabilities under the Securities Act of 1933, and to contribute to payments that the underwriters may be required to make in respect thereof.

Fortis Bank (Nederland) N.V., an affiliate of Fortis Securities Inc., a co-managing underwriter of this offering, received \$60,000 in advisory fees from the Company in the six month period preceding the October 9, 2001 filing of the Registration Statement for this offering. These fees are deemed underwriting compensation under the NASD's Conduct Rules. In the ordinary course of their respective businesses, the underwriters and certain of their affiliates may in the future engage in investment and commercial banking or other transactions with us, including the provision of certain advisory services and making loans to us.

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 Citicorp Center, 500 West Madison Street, Suite 1400, Chicago, Illinois 60661-2511. 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>. Reports, proxy and information statements and other information concerning Isis may be inspected at The Nasdaq Stock Market at 1735 K Street, N.W., Washington, D.C. 20006.

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 this prospectus 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 all the shares of common stock that are part of this offering are sold.

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

- our Annual Report on Form 10-K/A for the year ended December 31, 2000;
- our Quarterly Report on Form 10-Q for the period ended March 31, 2001;
- our Quarterly Report on Form 10-Q, as amended on August 15, 2001, and on October 11, 2001, for the period ended June 30, 2001;
- our Quarterly Report on Form 10-Q for the period ended September 30, 2001;
- our Current Report on Form 8-K, filed with the SEC on August 29, 2001;
- our Current Report on Form 8-K/A, filed with the SEC on October 5, 2001; 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.

All documents that we file with the SEC pursuant to Section 13(a), 13(c), 14 or 15(d) of the Exchange Act after the date of this prospectus and before the termination of the offering of the common stock offered in this prospectus shall be deemed incorporated by reference into this prospectus and to be a part of this prospectus from the respective dates of filing such documents.

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 Isis' 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, superseded or replaced shall not be deemed, except as so modified, superseded or replaced, to constitute a part of this prospectus.

Legal matters

The validity of the issuance of the common stock offered hereby will be passed upon for us by Cooley Godward LLP, San Diego, California. Dewey Ballantine LLP, New York, New York, is counsel for the underwriters in connection with the offering.

Experts

Ernst & Young LLP, independent auditors, have audited our consolidated financial statements included in our Annual Report on Form 10-K, as amended on April 2, 2001, for the year ended December 31, 2000, 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 on their authority as experts in accounting and auditing.

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Part II

INFORMATION NOT REQUIRED IN PROSPECTUS

Item 14. Other Expenses of Issuance and Distribution

The following table sets forth all expenses payable by us in connection with the sale of the 5,750,000 shares of common stock being registered. All the amounts shown are estimates except for the registration fee.

SEC registration fee.....	\$	26,278
NASD filing fee.....		10,724
Blue Sky fees and expenses.....		7,500
Printing and engraving expenses.....		100,000
Legal fees and expenses.....		85,000
Accounting fees and expenses.....		30,000
Miscellaneous.....		50,498

Total.....	\$	310,000
		=====

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

of the
Series A
Convertible
Preferred
Stock.(2)
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.(8)
4.7 Specimen
Common Stock
Certificate.
(1) 4.8
Specimen
Series A
Preferred
Stock
Certificate.
(9) 4.9
Specimen
Series B
Preferred
Stock
Certificate.
(9) 4.10
Form of
Right
Certificate.
(8) 4.11
Purchase
Agreement
between the
Registrant
and Reliance
Insurance
Company for
14% Senior
Subordinated
Discount
Notes due
November 1,
2007 and
Warrants for
Common Stock
dated
October 24,
1997 (with
certain
confidential
information
deleted).(3)
4.12 First
Supplement
to Purchase
Agreement
between the
Registrant
and Reliance
Insurance
Company for
14% Senior
Subordinated
Discount
Notes due
November 1,
2007 and

Warrants for
Common Stock
dated May 1,
1998 (with
certain
confidential
information
deleted).(4)

4.15 Stock
Purchase
Agreement
between the
Registrant
and
Boehringer
Ingelheim
International
GmbH, dated
as of July
18, 1995
(with
certain
confidential
information
deleted).

(10) 4.16
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.

(5) 4.17
Agreement
dated August
31, 1999
between
Boehringer
Ingelheim
International
GmbH and the
Registrant,
together
with the
related
Amendment to

Exhibit
Number
Description
of Document

--- 4.18
Subscription,
Joint
Development
and
Operating
Agreement
dated
January 14,
2000 among
the
Registrant,
Elan
Corporation,
plc, Elan
International
Services,
Ltd. and
HepaSense,
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.

(6) 4.19
Securities
Purchase
Agreement,
dated August
17, 2001,
between the
Registrant
and Eli
Lilly and
Company. (12)

4.20
Registration
Rights and
Standstill
Agreement,

dated August
17, 2001,
between the
Registrant
and Eli
Lilly and
Company.(12)
4.21 Loan
Agreement,
dated August
17, 2001,
between the
Registrant
and Eli
Lilly and
Company.(12)
5.1 *
Opinion of
Cooley
Godward LLP.
23.1 Consent
of Ernst &
Young LLP,
independent
auditors.
23.2 Consent
of Cooley
Godward LLP.
Reference is
made to
Exhibit 5.1.
24.1 * Power
of Attorney.

* Previously filed.

- (1) Filed as an exhibit to the Registrant's Registration Statement on Form S-1 (No. 333-39640) or amendments thereto and incorporated herein by reference.
- (2) 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.
- (3) Filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 1997, and incorporated herein by reference.
- (4) Filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 1998 and incorporated herein by reference.
- (5) Filed as an exhibit to the Registrant's report on Form 8-K dated April 20, 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 the Registrant's report on Form 10-Q/A for the quarter ended June 30, 2001 and incorporated herein by reference.
- (8) Filed as an exhibit to the Registrant's Report on Form 8-K dated December 8, 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, 2000 and incorporated herein by reference.
- (10) Filed as an exhibit to the Registrant's Report on Form 8-K dated July 18, 1995 and incorporated herein by reference.
- (11) Filed as an exhibit to the Registrant's Report on Form 8-K dated August 31, 1999 and incorporated herein by reference.
- (12) Filed as an exhibit to the Registrant's Report on Form 8-K dated August 29, 2001 and incorporated herein by reference.

Item 17. Undertakings

Insofar as indemnification for liabilities arising under the Securities Act of 1933 may be permitted to directors, officers, and controlling persons of the Registrant pursuant to the provisions described in Item 15 or otherwise, the Registrant has been advised that in the opinion of the Securities and Exchange Commission, such indemnification is against public policy as expressed in the Act and is, therefore, unenforceable. In the event that a claim for indemnification against such liabilities (other than the payment by the Registrant of expenses incurred or paid by a director, officer, or controlling person of the Registrant in the successful defense of any action suit, or proceeding) is asserted by such director, officer, or controlling person in connection with the securities being registered, the Registrant will, unless in the opinion of its counsel the matter has been settled by controlling precedent, submit to a court of appropriate jurisdiction the question whether such indemnification by it is against public policy as expressed in the Securities Act and will be governed by the final adjudication of such issue.

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; (iii) to include any material information with respect to the plan of distribution not previously disclosed in the registration statement or any material change to such information in the Registration Statement; provided however, that clauses (i) and (ii) do not apply if the information required to be included in a post-effective amendment by these clauses is contained in periodic reports filed by the registrant pursuant to Section 13 or Section 15(d) of the Securities Exchange Act of 1934 that are incorporated by reference in the Registration Statement; (2) that, for the purpose of determining any liability under the Securities Act, each such post-effective amendment shall be deemed to be a new registration statement relating to the securities offered therein, and the offering of such securities at that time shall be deemed to be the initial bona fide offering thereof; and (3) to remove from registration by means of a post-effective amendment any of the securities being registered which remain unsold at the termination of the offering.

The undersigned Registrant hereby undertakes that, for the purposes of determining any liability under the Securities Act of 1933, each filing of the Registrant's annual report pursuant to Section 13(a) of Section 15(d) of the Securities Exchange Act of 1934 that is incorporated by reference in the registration statement shall be deemed to be a new registration statement relating to the securities offered therein, and the offering of such securities at that time shall be deemed to be the initial bona fide offering thereof.

The undersigned Registrant undertakes that: (1) for purpose of determining any liability under the Securities Act of 1933, the information omitted from the form of prospectus filed as part of the registration statement in reliance upon Rule 430A and contained in the form of prospectus filed by the Registrant pursuant to Rule 424(b) (1) or (4) or 497(h) under the Securities Act shall be deemed to be part of the registration statement as of the time it was declared effective; (2) for the purpose of determining any liability under the Securities Act of 1933, each post-effective amendment that contains a form of prospectus shall be deemed to be a new registration statement relating to the securities offered therein, and the offering of such securities at that time shall be deemed to be the initial bona fide offering thereof; and (3) for purposes of determining any liability under the Securities Act of 1933, each filing of the Registrant's annual report pursuant to Section 13(a) or Section 15(d) of the Securities Exchange Act of 1934 (and, where applicable, each filing of an employee benefit plan's annual report pursuant to Section 15(d) of the Securities Exchange Act of 1934) that is incorporated by reference in the registration statement shall be deemed to be a new registration statement relating to the securities offered therein, and the offering of such securities at that time shall be deemed to be the initial bona fide offering thereof.

Signatures

Pursuant to the requirements of the Securities Act of 1933, the registrant certifies that it has reasonable grounds to believe that it meets all of the requirements for filing on Form S-3 and has duly caused this Amendment No. 1 to the Registration Statement to be signed on its behalf by the undersigned thereunto duly authorized, in the city of Carlsbad, County of San Diego, State

ISIS PHARMACEUTICALS, INC.

By: /s/ B. LYNNE PARSHALL

B. Lynne Parshall
Executive Vice President and Chief Financial
Officer, Director (Principal financial and
accounting officer)

Pursuant to the requirements of the Securities Act of 1933, this Amendment No. 1 to the Registration Statement has been signed below by the following persons in the capacities indicated and on the dates indicated.

Signature
Title Date

STANLEY T.
CROOKE*
Chairman
of the
Board and
Chief ----

Executive
Officer
(Principal
executive
October
22, 2001

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

/s/ B.
LYNNE
PARSHALL
Executive
Vice
President
and Chief

Financial
Officer
(Principal
financial
October
22, 2001

B. Lynne
Parshall
and
accounting
officer),
Director

CHRISTOPHER
F.O.
GABRIELI*

- Director
October
22, 2001
Christopher
F.O.
Gabrieli
WILLIAM R.
MILLER* --

Director
October
22, 2001
William R.
Miller
FREDERICK
T. MUTO* -

Director
October
22, 2001
Frederick
T. Muto
MARK B.
SKALETSKY*

- Director
October
22, 2001
Mark B.
Skaletsky
JOSEPH H.
WENDER* --

Director
October
22, 2001
Joseph H.
Wender

*By: /s/ B. LYNNE PARSHALL

 B. Lynne Parshall
 Attorney-in-fact

Exhibit index

Exhibit Number	Description of Document
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-----	-----
-----	-----
---	1.1 Form of Underwriting Agreement.

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.(7)
4.3 Bylaws.
(7) 4.4
Certificate
of
Designation
of the
Series A
Convertible
Preferred
Stock.(2)
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.(8)
4.7 Specimen
Common Stock
Certificate.
(1) 4.8
Specimen
Series A
Preferred
Stock
Certificate.
(9) 4.9
Specimen
Series B
Preferred
Stock
Certificate.
(9) 4.10
Form of
Right
Certificate.
(8) 4.11
Purchase
Agreement
between the
Registrant
and Reliance
Insurance
Company for
14% Senior
Subordinated
Discount
Notes due
November 1,
2007 and
Warrants for
Common Stock
dated

October 24,
1997 (with
certain
confidential
information
deleted).(3)

4.12 First
Supplement
to Purchase
Agreement
between the
Registrant
and Reliance
Insurance
Company for
14% Senior
Subordinated
Discount
Notes due
November 1,
2007 and
Warrants for
Common Stock
dated May 1,
1998 (with
certain
confidential
information
deleted).(4)

4.15 Stock
Purchase
Agreement
between the
Registrant
and
Boehringer
Ingelheim
International
GmbH, dated
as of July
18, 1995
(with
certain
confidential
information
deleted).

(10) 4.16
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.
(5) 4.17
Agreement
dated August
31, 1999
between
Boehringer
Ingelheim
International
GmbH and the
Registrant,
together
with the
related
Amendment to
the Stock
Purchase
Agreement.
(11) 4.18
Subscription,
Joint
Development
and
Operating
Agreement
dated
January 14,
2000 among
the
Registrant,
Elan
Corporation,
plc, Elan
International
Services,
Ltd. and
HepaSense,
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.
(6) 4.19
Securities
Purchase
Agreement,
dated August
17, 2001,
between the
Registrant
and Eli
Lilly and
Company. (12)
4.20
Registration
Rights and

Standstill
Agreement,
dated August
17, 2001,
between the
Registrant
and Eli
Lilly and
Company.(12)
4.21 Loan
Agreement,
dated August
17, 2001,
between the
Registrant
and Eli
Lilly and
Company.(12)
5.1 *

Opinion of
Cooley
Godward LLP.
23.1 Consent
of Ernst &
Young LLP,
independent
auditors.
23.2 Consent
of Cooley
Godward LLP.
Reference is
made to
Exhibit 5.1.
24.1 * Power
of Attorney.

* Previously filed.

- (1) Filed as an exhibit to the Registrant's Registration Statement on Form S-1 (No. 333-39640) or amendments thereto and incorporated herein by reference.
- (2) 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.
- (3) Filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 1997, and incorporated herein by reference.
- (4) Filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 1998 and incorporated herein by reference.
- (5) Filed as an exhibit to the Registrant's report on Form 8-K dated April 20, 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 the Registrant's report on Form 10-Q/A for the quarter ended June 30, 2001 and incorporated herein by reference.
- (8) Filed as an exhibit to the Registrant's Report on Form 8-K dated December 8, 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, 2000 and incorporated herein by reference.
- (10) Filed as an exhibit to the Registrant's Report on Form 8-K dated July 18, 1995 and incorporated herein by reference.
- (11) Filed as an exhibit to the Registrant's Report on Form 8-K dated August 31, 1999 and incorporated herein by reference.
- (12) Filed as an exhibit to the Registrant's Report on Form 8-K dated

August 29, 2001 and incorporated herein by reference.

Isis Pharmaceuticals, Inc.

5,000,000 Shares

Common Stock

(\$0.001 Par Value)

UNDERWRITING AGREEMENT

_____, 2001

UNDERWRITING AGREEMENT

_____, 2001

UBS Warburg LLC
Robertson Stephens, Inc.
Needham & Company, Inc.
Fortis Securities Inc.

c/o UBS Warburg LLC
299 Park Avenue
New York, New York 10171-0026

Ladies and Gentlemen:

Isis Pharmaceuticals, Inc., a Delaware corporation (the "Company"), proposes to issue and sell to the Underwriters named in Schedule A annexed hereto (the "Underwriters") an aggregate of 5,000,000 shares of Common Stock, \$0.001 par value per share (the "Common Stock"), of the Company (the "Firm Shares"). In addition, solely for the purpose of covering over-allotments, the Company proposes to grant to the Underwriters the option to purchase from the Company up to an additional 750,000 shares of Common Stock (the "Additional Shares"). The Firm Shares and the Additional Shares are hereinafter collectively sometimes referred to as the Shares. The Shares are described in the Prospectus which is referred to below.

The Company has filed, in accordance with the provisions of the Securities Act of 1933, as amended, and the rules and regulations thereunder (collectively, the "Act"), with the Securities and Exchange Commission (the "Commission") a registration statement on Form S-3 (File No. 333-71176) including a prospectus, relating to the Shares. The Company has furnished to you, for use by the Underwriters and by dealers, copies of one or more preliminary prospectuses (each thereof being herein called a "Preliminary Prospectus") relating to the Shares. Except where the context otherwise requires, the registration statement, as amended when it becomes effective, including all documents filed as a part thereof, and including any information contained in a prospectus subsequently filed with the Commission pursuant to Rule 424(b) under the Act and deemed to be part of the registration statement at the time of effectiveness pursuant to Rule 430(A) under the Act, and also including any registration statement filed pursuant to Rule 462(b) under the Act, is herein called the Registration Statement, and the prospectus, in the form filed by the Company with the Commission pursuant to Rule 424(b) under the Act on or before the second business day after

the date hereof (or such earlier time as may be required under the Act) or, if no such filing is required, the form of final prospectus included in the Registration Statement at the time it became effective, is herein called the Prospectus. Any reference herein to the Registration Statement, a Preliminary Prospectus or the Prospectus shall be deemed to refer to and include the documents incorporated by reference therein pursuant to Form S-3, and any reference herein to the terms "amend", "amendment" or "supplement" with respect to the Registration Statement, any Preliminary Prospectus or the Prospectus shall be deemed to refer to and include the filing of any document under the Securities Exchange Act of 1934, as amended, and the rules and regulations thereunder (collectively, the "Exchange Act") after the effective date of the Registration Statement, or the Prospectus, as the case may be, deemed to be

incorporated therein by reference.

The Company and the Underwriters 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 respective Underwriters and each of the Underwriters, severally and not jointly, agrees to purchase from the Company the respective number of Firm Shares set forth opposite the name of such Underwriter in Schedule A annexed hereto in each case at a purchase price of \$____ per Share. The Company is advised by you that the Underwriters intend (i) to make a public offering of their respective portions of the Firm Shares as soon after the effective date of the Registration Statement as in your judgment is advisable and (ii) initially to offer the Firm Shares upon the terms set forth in the Prospectus.

In addition, the Company hereby grants to the several Underwriters the option to purchase, and upon the basis of the representations and warranties and subject to the terms and conditions herein set forth, the Underwriters shall have the right to purchase, severally and not jointly, from the Company, ratably in accordance with the number of Firm Shares to be purchased by each of them, all or a portion of the Additional Shares as may be necessary to cover over-allotments made in connection with the offering of the Firm Shares, at the same purchase price per share to be paid by the Underwriters for the Firm Shares. This option may be exercised by you on behalf of the several Underwriters at any time and from time to time on or before the 30th day following the date hereof by written notice to the Company. Such notice shall set forth the aggregate number of Additional Shares as to which the option is being exercised and the date and time when the Additional Shares 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 the time of purchase (as defined

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below) nor earlier than the second business day(1) after the date on which the option shall have been exercised nor later than the tenth business day after the date on which the option shall have been exercised. The number of Additional Shares to be sold to each Underwriter shall be the number which bears the same proportion to the aggregate number of Additional Shares being purchased as the number of Firm Shares set forth opposite the name of such Underwriter on Schedule A hereto bears to the total number of Firm Shares (subject, in each case, to such adjustment as you may determine to eliminate fractional shares.

2. PAYMENT AND DELIVERY. Payment of the purchase price for the Firm Shares shall be made to the Company by Federal Funds wire transfer, against delivery of the certificates for the Firm Shares to you through the facilities of the Depository Trust Company (DTC) for the respective accounts of the Underwriters. Such payment and delivery shall be made at 10:00 A.M., New York City time, on _____, 2001 (unless another time shall be agreed to by you and the Company or unless postponed in accordance with the provisions of Section 8 hereof). The time at which such payment and delivery are actually made is hereinafter sometimes called the time of purchase. Electronic transfer of the Firm Shares shall be made to you at the time of purchase in such names and in such denominations as you shall specify.

Payment of the purchase price for the Additional Shares shall be made at the additional time of purchase in the same manner and at the same office as the payment for the Firm Shares. Electronic transfer of the Firm Shares shall be made to you at the time of purchase in such names and in such denominations as you shall specify.

3. REPRESENTATIONS AND WARRANTIES OF THE COMPANY. The Company represents and warrants to each of the Underwriters that:

(a) The Company has not received nor has notice of any notice or order of the Commission preventing or suspending the use of any Preliminary Prospectus, nor has the Company received any notice of the Commission's instituting proceedings for that purpose, and each Preliminary Prospectus, at the time of filing thereof, conformed in all material respects to the requirements of the Act; and when the Registration Statement becomes effective, the Registration Statement and the Prospectus will conform in all material respects with the provisions of the Act, and the Registration Statement 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

not misleading, and the Prospectus 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 Registration Statement or the Prospectus in reliance upon and in conformity with information concerning the Underwriters and furnished in writing by or on behalf of any Underwriter through you to the Company for use in the Registration Statement or the Prospectus; and neither the Company nor any of its affiliates has distributed any offering material in connection with the offer or sale of the Shares other than the Registration Statement, the Preliminary Prospectus, the Prospectus or any other materials, if any, permitted by the Act;

(b) as of the date of this Agreement, the Company's capitalization is in all material respects as set forth under the heading entitled "Actual" in the section of the Registration Statement and the Prospectus entitled "Capitalization" and, as of the time of purchase, the Company's capitalization shall be in all material respects as set forth under the heading entitled "As Adjusted" in the section of the Registration Statement and the Prospectus 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 Registration Statement and the Prospectus and subject to the issuance of shares of Common Stock pursuant to agreements described in the Registration Statement and the Prospectus); 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 Registration Statement and the Prospectus;

(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 Registration Statement and the Prospectus; except for the Subsidiaries or as described in the Registration Statement and the Prospectus, 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 Registration Statement and the Prospectus; 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, by-laws 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 is 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, including the issuance and sale of the Shares and the consummation of the other transactions contemplated hereby, does not constitute and will not result in a Default Event under (w) any provisions of the charter, by-laws or other organizational documents of the Company or any of the Subsidiaries, (x)

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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 capital stock of the Company, including the Shares, conforms in all material respects to the description thereof contained in the Registration Statement and the Prospectus;

(h) the Shares have been duly and validly authorized by the Company and, when issued and delivered by the Company against payment therefor as provided herein, will be validly issued, fully paid and non-assessable;

(i) 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 Shares or the consummation by the Company of the other transactions contemplated hereby other than registration of the offer and sale of the Shares under the Act, which has been or will be effected, and any necessary qualification under the securities or blue sky laws of the various jurisdictions in which the Shares are being offered by the Underwriters;

(j) except as set forth in the Registration Statement and the Prospectus (i) no person has the right, contractual or otherwise, to cause the Company to issue or sell to it 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 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 Shares, in the case of each of the foregoing clauses (i), (ii) and (iii), whether as a result of the filing or effectiveness of the Registration Statement or the sale of the Shares as contemplated thereby 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

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other equity interests of the Company, or to include any such shares or interests in the Registration Statement or the offering contemplated thereby whether as a result of the filing or effectiveness of the Registration Statement or the sale of the Shares as contemplated thereby or otherwise, except as disclosed in the Registration Statement and Prospectus and except for such rights as have been complied with or waived;

(k) Ernst & Young LLP, whose report on the consolidated financial statements of the Company and the Subsidiaries is filed with the Commission as part of the Registration Statement and the Prospectus, are independent public accountants as required by the Act;

(l) 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 Registration Statement and the Prospectus, 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;

(m) all legal or governmental proceedings, contracts, leases or documents of a character required to be described in the Registration Statement or the Prospectus or any document incorporated by reference therein or to be filed as an exhibit to the Registration Statement or any document incorporated by reference therein have been so described or filed as required;

(n) except as disclosed in the Registration Statement and the Prospectus, 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;

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(o) the financial statements, together with the related schedules and notes, included in the Registration Statement and the Prospectus 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 Registration Statement and the Prospectus are accurately presented in all material respects and

prepared on a basis consistent with such financial statements and books and records of the Company; and there are no financial statements (historical or pro forma) that are required to be included in the Registration Statement and the Prospectus that are not included as required;

(p) subsequent to the respective dates as of which information is given in the Registration Statement and the Prospectus, 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; neither the Company nor any of the Subsidiaries has any material contingent obligation which is not disclosed in the Registration Statement and the Prospectus;

(q) the Company has obtained for the benefit of the Underwriters the agreement (a "LOCK-UP AGREEMENT"), in the form set forth as EXHIBIT C hereto, of each of its executive officers and directors; the Company will not release or purport to release any of its officers or directors from any Lock-Up Agreement without the prior written consent of UBS Warburg;

(r) the Company is not and, after giving effect to the offering and sale of the Shares, 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");

(s) any statistical and market related data included in the Prospectus are based on or derived from sources that the Company believes to be reliable and

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accurate, and the Company has obtained the written consent to the use of such data from such sources to the extent required;

(t) 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 Shares;

(u) 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;

(v) neither the Company nor any of the Subsidiaries has sustained since the date of the latest financial statements included in the Prospectus 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 Registration Statement and the Prospectus or other than any losses or interferences which would not, individually or in the aggregate, reasonably be expected to have a Material Adverse Effect;

(w) the Company and each of the Subsidiaries have good title to all personal property owned by them as described in the Registration Statement and the Prospectus, which to the Company's knowledge is free and clear of all liens, encumbrances and defects except such as (i) are described in the Registration Statement and the Prospectus, (ii) were incurred in the ordinary course of business and not required to be described in the Registration Statement and the Prospectus or (iii) would not, individually or in the aggregate, reasonably be expected to have a Material Adverse Effect; except as

described in the Registration Statement and the Prospectus, 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;

(x) 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

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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;

(y) 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;

(z) 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;

(aa) all documents incorporated by reference by the Registration Statement, the Preliminary Prospectus or the Prospectus complied in all material respects, at the time the Registration Statement was filed with the Commission, with the requirements of the Exchange Act;

(bb) other than as set forth in the Registration Statement and the Prospectus, 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 Registration Statement and the Prospectus, without any known conflict with or infringement of the interests of others. Except as described in the Registration Statement and the Prospectus, 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 which are required to be described in the Registration Statement and the Prospectus, and, except as described in the Registration Statement and the Prospectus, neither the Company nor either of the Subsidiaries is a party to or bound by any options, licenses or

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agreements with respect to the Intellectual Property of any other person or entity which are required to be described in the Registration Statement and the Prospectus; 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 Registration Statement and the Prospectus, 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 Registration Statement and the Prospectus 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; and

(cc) 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 its products or product candidates have participated that are described in the Prospectus or the results of which are referred to in the Prospectus were and, if still pending, are being conducted in accordance with standard medical and scientific research procedures; except to the extent disclosed in the Registration Statement and the Prospectus, 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 Registration Statement and the Prospectus, 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 Prospectus or the results of which are referred to in the Prospectus.

4. CERTAIN COVENANTS OF THE COMPANY. The Company hereby

agrees:

(a) to furnish such information as may be required and otherwise to cooperate in qualifying 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 Shares; 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

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offering and sale of the Shares); and to promptly advise you of the receipt by the Company of any notification with respect to the suspension of the qualification of the Shares for sale in any jurisdiction or the initiation or threat of any proceeding for such purpose;

(b) to make available to the Underwriters in New York City, as soon as practicable after the Registration Statement becomes effective, and thereafter from time to time to furnish to the Underwriters, as many copies of the Prospectus (or of the Prospectus as amended or supplemented if the Company shall have made any amendments or supplements thereto after the effective date of the Registration Statement) as the Underwriters may request for the purposes contemplated by the Act; in case any Underwriter is required to deliver a prospectus after the nine-month period referred to in Section 10(a)(3) of the Act in connection with the sale of the Shares, the Company will prepare promptly upon request such amendment or amendments to the Registration Statement and such prospectuses as may be necessary to permit compliance with the requirements of Section 10(a)(3) of the Act;

(c) to advise you promptly and (if requested by you) to confirm such advice in writing, (i) when the Registration Statement has become effective and when any post-effective amendment thereto becomes effective and (ii) if Rule 430A under the Act is used, when the Prospectus is filed with the Commission pursuant to Rule 424(b) under the Act (which the Company agrees to file in a timely manner under such Rules);

(d) to advise you promptly, confirming such advice in writing (if requested by you), of any request by the Commission for amendments or supplements to the Registration Statement or the

Prospectus or for additional information with respect thereto, or of notice of institution of proceedings for, or the entry of a stop order suspending the effectiveness of the Registration Statement and, if the Commission should enter a stop order suspending the effectiveness of the Registration Statement, to make every reasonable effort to obtain the lifting or removal of such order as soon as possible; to advise you promptly of any proposal to amend or supplement the Registration Statement or Prospectus and to file no such amendment or supplement to which you shall object in writing;

(e) if necessary or appropriate, to file a registration statement pursuant to Rule 462(b) under the Act;

(f) to furnish, upon request, to you and, upon request, to each of the other Underwriters for a period of five years from the date of this Agreement (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,

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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;

(g) to advise the Underwriters promptly of the happening of any event known to the Company within the time during which a Prospectus relating to the Shares is required to be delivered under the Act which would require the making of any change in the Prospectus then being used so that the Prospectus would not 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 are made, not misleading, and, during such time, to prepare and furnish, at the Company's expense, to the Underwriters promptly such amendments or supplements to such Prospectus as may be necessary to reflect any such change and to furnish you a copy of such proposed amendment or supplement before filing any such amendment or supplement with the Commission;

(h) to make generally available to its security holders, and to deliver to you, an earnings statement of the Company (which will satisfy the provisions of Section 11(a) of the Act) covering a period of twelve months beginning after the effective date of the Registration Statement (as defined in Rule 158(c) of the Act) and ending not later than 15 months thereafter;

(i) to furnish to you five conformed copies of the Registration Statement, as initially filed with the Commission, and of all amendments thereto (including all exhibits thereto) and sufficient additional conformed copies (other than exhibits) for distribution of a copy to each of the other Underwriters;

(j) 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 6(f) hereof;

(k) to apply the net proceeds from the sale of the Shares in the manner set forth under the caption "Use of proceeds" in the Prospectus;

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(l) to pay all costs, expenses, fees and taxes in connection with (i) the preparation and filing of the Registration Statement, each Preliminary Prospectus, the Prospectus, and any amendments or supplements thereto, and the printing and furnishing of copies of each thereof to the Underwriters and to dealers (including

costs of mailing and shipment), (ii) the registration, issue, sale and delivery of the Shares, (iii) the printing of this Agreement, any Agreement Among Underwriters, any dealer agreements, any Powers of Attorney and any closing documents (including compilations thereof) and the reproduction and/or printing and furnishing of copies of each thereof to the Underwriters and (except closing documents) to dealers (including costs of mailing and shipment), (iv) the qualification of 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 Underwriters) and the printing and furnishing of copies of any blue sky surveys or legal investment surveys to the Underwriters and to dealers, (v) any listing of the Shares on any securities exchange or qualification of the Shares for quotation on the Nasdaq National Market and any registration thereof under the Exchange Act, (vi) review of the public offering of the Shares by NASD Regulation, Inc. (including associated filing fees and the reasonable legal fees and disbursements of counsel for the Underwriters), (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 Shares to prospective investors and the Representatives' 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.

(m) for so long as the delivery of the Prospectus is required in connection with the offer or sale of the Shares, to furnish to you, before filing with the Commission, a copy of any document proposed to be filed pursuant to Section 13, 14 or 15(d) of the Exchange Act;

(n) 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 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 Common Stock, or file or cause to be declared effective a registration statement under the Act relating to the offer and sale of any shares of Common Stock or securities convertible into or exercisable or exchangeable for Common Stock or other rights to purchase Common Stock or any

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other securities of the Company that are substantially similar to 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 except for (i) the registration of the Shares and the sales to the Underwriters pursuant to this Agreement, (ii) issuances of Common Stock upon the exercise of options or warrants or upon the conversion of convertible securities disclosed as outstanding in the Registration Statement and the Prospectus, (iii) the issuance of stock options not exercisable during the Lock-up Period pursuant to stock option plans described in the Registration Statement and the Prospectus and (iv) the issuance of securities which may be required pursuant to the Company's or the Subsidiaries' currently outstanding agreements which are described in the Registration Statement and the Prospectus, including without limitation the issuance of Common Stock to Hybridon, Inc. and the registration thereof under the Act.

5. REIMBURSEMENT OF UNDERWRITERS' EXPENSES. If the Shares are not delivered for any reason other than the termination of this Agreement pursuant to the last paragraph of Section 8 hereof or the default by one or more of the Underwriters in its or their respective obligations hereunder, the Company agrees, in addition to paying the amounts described in Section 4(1) hereof, to reimburse the Underwriters for all of their out-of-pocket expenses, including the reasonable fees and disbursements of their counsel.

6. CONDITIONS OF UNDERWRITERS' OBLIGATIONS. The several obligations of the Underwriters 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 Underwriters 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 Underwriters, 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 Underwriters and in form reasonably satisfactory to Dewey Ballantine LLP, counsel for the Underwriters, 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 business as described in the Registration Statement and the Prospectus, to execute and deliver this Agreement and to issue, sell and deliver the Shares as herein contemplated;

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(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 Firm Shares have been duly authorized and, when issued (in the case of the Firm Shares) and delivered to and paid for by the Underwriters in accordance with and for the consideration set forth herein, will be duly and validly issued and will be fully paid and non-assessable;

(v) the Company has authorized and outstanding (as of the dates indicated) shares of capital stock as set forth in the Registration Statement and the Prospectus 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) are free of preemptive rights, resale rights, rights of first refusal and similar rights under the Delaware General Corporation Law (the "DGCL") or the charter or bylaws or other organizational documents of the Company or any contract, commitment or instrument filed as an exhibit to the Registration Statement; the Firm Shares when issued will be free of preemptive or similar rights under the DGCL or any contract, commitment or instrument filed as an exhibit to the Registration Statement; and the certificates for the Shares are in due and proper form and conform to the requirements of the DGCL and the Nasdaq National Market;

(vi) the common stock of the Company, including the Shares, conforms in all material respects to the description thereof contained in the Registration Statement and Prospectus (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);

(vii) the Registration Statement and the Prospectus (except as to the financial statements and schedules and other financial and statistical data contained therein, as to which such counsel need express no opinion) comply as to form in all material respects with the requirements of the Act;

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(viii) the Registration Statement has become effective under the Act, and to such counsel's knowledge no

stop order with respect to the effectiveness thereof has been issued and no stop order proceedings with respect thereto have been instituted or are overtly threatened under the Act; and any required filing of the Prospectus and any supplement thereto pursuant to Rule 424 under the Act has been made in the manner and within the time period required by such Rule 424;

(ix) 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 in connection with the execution and delivery of this Agreement and the issuance and sale of the Shares and consummation of the other transactions contemplated hereby other than those that have been obtained under the Act, the Exchange Act and the rules of the Nasdaq National Market, other than any necessary qualification under the state securities or blue sky laws of the various jurisdictions in which the Shares are being offered by the Underwriters or any necessary approval of the Corporate Financing Department of NASD Regulation, Inc., as to which such qualification and approval such counsel need express no opinion;

(x) the execution, delivery and performance of this Agreement by the Company, including the consummation of the transactions contemplated hereby and by the Registration Statement, do not constitute, and will not result in, a Default Event pursuant to (A) any provision of the charter or bylaws or other organizational documents of the Company, (B) any provision of any license, permit, franchise, authorization, indenture, mortgage, deed of trust, note, bank loan, credit agreement, other evidence of indebtedness, lease, contract, agreement or instrument filed as an exhibit to the Registration Statement, (C) any federal, state, local or foreign law, regulation or rule applicable to the Company 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;

(xi) to such counsel's knowledge, there are no contracts, licenses, agreements, leases or documents of a character which are required to be filed as exhibits to the Registration Statement or to be summarized or described in the Prospectus which have not been so filed, summarized or described;

(xii) to such counsel's knowledge, 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

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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 are required to be described in the Prospectus but are not so described;

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

(xiv) those statements in the Registration Statement and the Prospectus under the captions "Risk Factors--If registration rights that we have previously granted are exercised, then our stock price may be negatively affected." and "Risk Factors--Provisions in our certificate of incorporation, other agreements and Delaware law may prevent stockholders from receiving a premium for their shares." and in the Company's Annual Report on Form 10-K for the year ended December 31, 2000 under the caption "Recent Sales of Unregistered Securities" 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 required to be shown; and

(xv) except as described in the Registration Statement and the Prospectus (including those rights held by Hybridon, Inc. pursuant to the agreements described in the Registration Statement and the Prospectus), no person has the right, pursuant to the terms of any contract, agreement or other instrument filed as an exhibit to the Registration Statement to have any securities issued by the Company and owned by them registered pursuant to the Act, included in the Registration Statement or sold in the offering contemplated thereby, whether as a result of the filing or effectiveness of the Registration Statement or 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 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 Underwriters at which the contents of the Registration Statement and Prospectus 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 Registration Statement or Prospectus (except as and to the extent stated in subparagraphs (vi) (vii) and (xiv) above), on the basis of the foregoing nothing has come to the attention of such counsel that causes them to believe that the Registration Statement or any amendment thereto at the time such Registration Statement or amendment became effective contained an untrue statement of a material fact or omitted to state a material fact required to be stated therein or necessary to make the statements therein not misleading, or that the Prospectus or any

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supplement thereto at the date of such Prospectus or such supplement, and at all times up to and including the time of purchase or additional time of purchase, as the case may be, contained an untrue statement of a material fact or omitted 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 Registration Statement or Prospectus).

(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 Underwriters and in form reasonably satisfactory to Dewey Ballantine LLP, counsel for the Underwriters, stating that:

(i) based on information brought to our 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 our care (the "relevant applications"), we have disclosed all pertinent art references to the United States Patent and Trademark Office in such applications. To the best of our 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 we nor, to the best of our 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. Woodcock Washburn LLP has not independently conducted any investigation of the published literature and patent references relating to the inventions claimed in the Company patent applications;

(ii) the statements in the Prospectus 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, 2000 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 Prospectus, to the best of our knowledge, the Company's products and products under development do not, and would not upon commercialization, infringe or conflict with asserted rights

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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 Underwriters, 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 Shares by the Company, the Registration Statement, the Prospectus (together with any supplement thereto) and other related matters as the Underwriters 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 Underwriters (with reproduced copies for each of the Underwriters) in the forms heretofore approved by UBS Warburg.

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

(f) The Registration Statement shall have become effective, or if Rule 430A under the Act is used, the Prospectus shall have been filed with the Commission pursuant to Rule 424(b) under the Act, at or before 5:00 P.M., New York City time, on the date of this Agreement, unless a later time (but not later than 5:00 P.M., New York City time, on the second full business day after the date of this Agreement) shall be agreed to by the Company and you in writing or by telephone, confirmed in writing; PROVIDED, HOWEVER, that the Company and you and any group of Underwriters, including you, who have agreed hereunder to purchase in the aggregate at least 50% of the Firm Shares may from time to time agree on a later date.

(g) Prior to the time of purchase or the additional time of purchase, as the case may be, (i) no stop order with respect to the effectiveness of the Registration Statement shall have been issued under the Act or proceedings initiated under Section 8(d) or 8(e) of the Act; (ii) the Registration Statement and all amendments thereto, or modifications thereof, if any, shall not contain an untrue statement of a material fact or

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omit to state a material fact required to be stated therein or necessary to make the statements therein not misleading; and (iii) the Prospectus 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.

(h) 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 Registration Statement and Prospectus), 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.

(i) 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 (g) and (h) of this Section 6 have been met.

(j) You shall have received the letters referred to in Section 3(q).

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

(l) The Shares shall have been approved for listing for quotation on the Nasdaq National Market, subject only to notice of issuance at or prior to the time of purchase or the additional time of purchase, as the case may be.

(m) 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

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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.

7. EFFECTIVE DATE OF AGREEMENT; TERMINATION. This Agreement shall become effective (i) if Rule 430A under the Act is not used, when you shall have received notification of the effectiveness of the Registration Statement, or (ii) if Rule 430A under the Act is used, when the parties hereto have executed and delivered this Agreement.

The obligations of the several Underwriters hereunder shall be subject to termination in the absolute discretion of you or any group of Underwriters (which may include you) which has agreed to purchase in the aggregate at least 50% of the Firm Shares, (i) if, since the time of execution of this Agreement or the respective dates as of which information is given in the Registration Statement and Prospectus, there has been any material adverse change, financial or otherwise (other than as specifically described in the Registration Statement and Prospectus), in the operations, business, condition or prospects of the Company and the Subsidiaries taken as a whole, which would, in your judgment or in the judgment of such group of Underwriters, make it impracticable to market the Shares, (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 Shares, 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 your judgment or in the judgment of such group of Underwriters, to make it impracticable to market the Shares.

If you or any group of Underwriters elects to terminate this Agreement as provided in this Section 7, the Company and each other Underwriter shall be notified promptly by letter or telegram from such terminating Underwriter.

If the sale to the Underwriters of the Shares, as contemplated by this Agreement, is not carried out by the Underwriters 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

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liability under this Agreement (except to the extent provided in Sections 4(1), 5 and 9 hereof), and the Underwriters shall be under no obligation or liability to the Company under this Agreement (except to the extent provided in Section 9 hereof) or to one another hereunder.

8. INCREASE IN UNDERWRITERS' COMMITMENTS. Subject to Sections 6 and 7, if any Underwriter shall default in its obligation to purchase and pay for the Firm Shares to be purchased by it hereunder (otherwise than for a reason sufficient to justify the termination of this Agreement under the provisions of Section 7 hereof) and if the number of Firm Shares which all Underwriters so defaulting shall have agreed but failed to purchase and pay for does not exceed 10% of the total number of Firm Shares, the non-defaulting Underwriters shall purchase and pay for (in addition to the aggregate number of Firm Shares they are obligated to purchase pursuant to Section 1 hereof) the number of Firm Shares agreed to be purchased by all such defaulting Underwriters, as hereinafter provided. Such Shares shall be purchased and paid for by such non-defaulting Underwriter or Underwriters in such amount or amounts as you may designate with the consent of each Underwriter so designated or, in the event no such designation is made, such Shares shall be purchased and paid for by all non-defaulting Underwriters pro rata in proportion to the aggregate number of Firm Shares set opposite the names of such non-defaulting Underwriters in Schedule A.

Without relieving any defaulting Underwriter from its obligations hereunder, the Company agrees with the non-defaulting Underwriters that it will not sell any Firm Shares hereunder unless all of the Firm Shares are purchased by the Underwriters (or by substituted Underwriters selected by you with the approval of the Company or selected by the Company with your approval).

If a new Underwriter or Underwriters are substituted by the Underwriters or by the Company for a defaulting Underwriter or Underwriters 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 Registration Statement and Prospectus and other documents may be effected.

The term Underwriter as used in this Agreement shall refer to and include any Underwriter substituted under this Section 8 with like effect as if such substituted Underwriter had originally been named in Schedule A.

If the aggregate number of Shares which the defaulting Underwriter or Underwriters agreed to purchase exceeds 10% of the total number of Shares which all Underwriters agreed to purchase hereunder, and if neither the non-defaulting Underwriters nor the Company shall make arrangements within the five business day period stated above for the purchase of all the Shares which the defaulting Underwriter or Underwriters 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 Underwriter and without any

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liability on the part of any non-defaulting Underwriter to the Company. Nothing in this paragraph, and no action taken hereunder, shall relieve any defaulting Underwriter from liability in respect of any default of such Underwriter under this Agreement.

9. INDEMNITY AND CONTRIBUTION.

(a) The Company agrees to indemnify, defend and hold harmless each Underwriter, its partners, directors and officers, and any person who controls any Underwriter 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 Underwriter 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 Registration Statement (or in the Registration Statement as amended by any post-effective amendment thereof by the Company) or in a Prospectus (the term Prospectus for the purpose of this Section 9 being deemed to include any Preliminary Prospectus, the Prospectus and the Prospectus 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 either such Registration Statement or Prospectus 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 Underwriter through you to the Company expressly for use with reference to such Underwriter in such Registration Statement or such Prospectus 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 Registration Statement or such Prospectus 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 on behalf of the Company including, without limitation, slides, videos, films, tape recordings, used in connection with the marketing of the Shares, PROVIDED, HOWEVER, that the indemnity agreement contained in clause (i) of this subsection (a) with respect to any Preliminary Prospectus or amended Preliminary Prospectus shall not inure to the benefit of any Underwriter from whom the person asserting any such loss, damage, expense, liability or claim purchased the Shares which is the subject thereof if the Prospectus corrected any such alleged untrue statement or omission and if such Underwriter failed to send or give a copy of the Prospectus to such person at or prior to the written confirmation of the sale of such Shares

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to such person, unless the failure is the result of noncompliance by the Company with Section 4(b) hereof.

If any action, suit or proceeding (together, a "Proceeding") is brought against an Underwriter or any such person in respect of which indemnity may be sought against the Company pursuant to the foregoing paragraph, such Underwriter 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 Underwriter or any such person or otherwise, except to the extent the Company is materially prejudiced thereby. Such Underwriter 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 Underwriter 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 Underwriter 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,

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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 Underwriter 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 Underwriter through you to the Company expressly for use with reference to such Underwriter in the Registration Statement (or in the Registration Statement as amended by any post-effective amendment thereof by the Company) or in a Prospectus, 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 Registration Statement or such Prospectus 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 Underwriter pursuant to the foregoing paragraph, the Company or such person shall promptly notify such Underwriter in writing of the institution of such Proceeding and such Underwriter 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 Underwriter shall not relieve such Underwriter from any liability which such Underwriter may have to the Company or any such person or otherwise, except to the extent such Underwriter 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 Underwriter in connection with the defense of such Proceeding or such Underwriter 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 Underwriter (in which case such Underwriter shall not have the right to direct the defense of such Proceeding on behalf of the indemnified party or parties, but such Underwriter may employ counsel and participate in the defense thereof but the fees and expenses of such counsel shall be at the expense of such Underwriter), in any of which events such fees and expenses shall be borne by such Underwriter and paid as incurred (it being

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understood, however, that such Underwriter 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 Underwriter shall be liable for any settlement of any such Proceeding effected without the written consent of such Underwriter but if settled with the written consent of such Underwriter, such Underwriter 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.

(c) If the indemnification provided for in this Section 9 is unavailable to an indemnified party under subsections (a) and (b) of this Section 9 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 Underwriters on the other hand from the offering of the Shares 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 Underwriters 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 Underwriters on the other shall be deemed to be in the same respective proportions as the total proceeds from the offering (net of underwriting discounts and commissions but before deducting expenses) received by the Company and the total underwriting discounts and commissions received by the Underwriters, bear to the aggregate public offering price of the Shares. The relative fault of the Company on the one hand and of the Underwriters on the

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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 Underwriters 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 Underwriters agree that it would not be just and equitable if contribution pursuant to this Section 9 were determined by pro rata allocation (even if the Underwriters 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 9, in no case shall any Underwriter be required to contribute any amount in excess of the amount by which the total price at which the Shares underwritten by such Underwriter and distributed to the public were offered to the public exceeds the amount of any damage which such Underwriter 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 Underwriters' obligations to contribute pursuant to this Section 9 are several in proportion to their respective underwriting commitments and not joint.

(e) The indemnity and contribution agreements contained in this Section 9 and the covenants, warranties and representations of the Company contained in this Agreement shall remain in full force and effect regardless of any investigation made by or on behalf of any Underwriter, its partners, directors or officers or any person (including each partner, officer or director of such person) who controls any Underwriter 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 Shares. The Company and each Underwriter 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 Shares, or in connection with the Registration Statement or Prospectus.

10. NOTICES. Except as otherwise herein provided, all statements, requests, notices and agreements shall be in writing and, if to the Underwriters, shall be sufficient in all respects if delivered or sent to UBS Warburg LLC, 299 Park Avenue, New York, N.Y. 10171-

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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.

11. INFORMATION FURNISHED BY THE UNDERWRITERS. The statements set forth in the last paragraph on the cover page of the Prospectus and the statements set forth in the fifth, seventh, eighth, ninth and tenth paragraphs under the caption "Underwriting" in the Prospectus constitute the only information furnished by or on behalf of the Underwriters as such information is referred to in Sections 3 and 9 hereof.

12. 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.

13. 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 Underwriter or any indemnified party. Each Underwriter 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.

14. PARTIES AT INTEREST. The Agreement herein set forth has been and is made solely for the benefit of the Underwriters, the Company and, to the extent provided in Section 9 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 Underwriters) shall acquire or have any right under or by virtue of this Agreement.

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15. 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.

16. SUCCESSORS AND ASSIGNS. This Agreement shall be binding upon the Underwriters 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 Underwriters' respective businesses and/or assets.

17. 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.

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

Very truly yours,

ISIS PHARMACEUTICALS, INC.

By:

Name:
Title:

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

UBS WARBURG LLC
ROBERTSON STEPHENS, INC.
NEEDHAM & COMPANY, INC.
FORTIS SECURITIES INC.

On their behalf and on behalf of each of the several underwriters named in Schedule A hereto.

By: UBS WARBURG LLC

By:

Name:
Title:

By:

Name:
Title:

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SCHEDULE A

UNDERWRITER NUMBER OF FIRM SHARES -----	
-- ----- UBS Warburg	
LLC.....	Robertson Stephens,
	Inc.....
	Needham & Company,
	Inc.....
	Fortis Securities
Inc.....	-----
	Total
5,000,000 -----	

SCHEDULE B

NAME
JURISDICTION
OF
INCORPORATION

ORASENSE
LTD. BERMUDA
HEPASENSE
LTD. BERMUDA

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EXHIBIT C

ISIS PHARMACEUTICALS, INC.

Common Stock

(\$.001 Par Value)

_____, 2001

UBS Warburg LLC
Robertson Stephens, Inc.
Needham & Company, Inc.
Fortis Securities 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 Underwriting Agreement (the "Underwriting Agreement") to be entered into by and among Isis Pharmaceuticals, Inc. (the "Company"), you and the other Underwriters named therein, as representatives of the several Underwriters, with respect to a public offering (the "Offering") of 5,000,000 shares of Common Stock of the Company, \$.001 par value per share (the "Common Stock").

In order to induce you to enter into the Underwriting Agreement, the undersigned agrees that for a period of 90 days after the date of the final prospectus 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 Common Stock or any securities convertible into or exercisable or exchangeable for 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

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Stock or any securities convertible into or exercisable or exchangeable for 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 Underwriters pursuant to the Underwriting 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, or (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.

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 prospectus 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 (i) the registration statement filed with the Securities and Exchange Commission with respect to the Offering is withdrawn or (ii) for any reason the Underwriting Agreement shall be terminated prior to the time of purchase (as defined in the Underwriting Agreement), this Lock-Up Letter Agreement shall be terminated and the undersigned shall be released from its obligations hereunder.

Yours very truly,

Name:

CONSENT OF ERNST & YOUNG LLP, INDEPENDENT AUDITORS

We consent to the reference to our firm under the caption "Experts" in the Amendment No. 1 to the Registration Statement (Form S-3 No. 333-71176) and related Prospectus of Isis Pharmaceuticals, Inc. and to the incorporation by reference therein of our report dated February 2, 2001, with respect to the consolidated financial statements of Isis Pharmaceuticals, Inc. included in its Annual Report (Form 10-K, as amended on April 2, 2001) for the year ended December 31, 2000, to be filed with the Securities and Exchange Commission.

/s/ ERNST & YOUNG LLP

ERNST & YOUNG LLP

San Diego, California
October 19, 2001