QuickLinks -- Click here to rapidly navigate through this document

As Filed with the Securities and Exchange Commission on October 30, 2001

Registration No. 333-71116

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	**33-0336973**
(State or Other Jurisdiction of Incorporation or Organization)	(I.R.S. Employer Identification Number)

2292 FARADAY AVENUE
CARLSBAD, CALIFORNIA 92008
(760) 931-9200

(Address, Including Zip Code, and Telephone Number, Including Area Code, of Registrant's Principal Executive Offices)

B. LYNNE PARSHALL, ESQ.
EXECUTIVE VICE PRESIDENT AND CHIEF FINANCIAL OFFICER
ISIS PHARMACEUTICALS, INC.
2292 FARADAY AVENUE
CARLSBAD, CALIFORNIA 92008
(760) 931-9200

(Name, Address, Including Zip Code, and Telephone Number, Including Area Code, of Agent For Service)

Copies to:
Julie M. Robinson, Esq
Cooley Godward llp
4401 Eastgate Mall
San Diego, CA 92121
(858) 550-6000

Approximate date of commencement of proposed sale to the public:
From time to time after the effective date of this registration statement.

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

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

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.

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.

PROSPECTUS

357,143 Shares

ISIS PHARMACEUTICALS, INC.

Common Stock

We are registering our common stock for resale by the selling stockholder identified in this prospectus. We are not selling any shares of our common stock under this prospectus and will not receive any of the proceeds from the sale of shares by the selling stockholder.

For a description of the plan of distribution of the resale shares, see page 10 of this prospectus.

Our common stock is currently traded on the Nasdaq National Market under the symbol "ISIP." On October 29, 2001, the last reported sales price for our common stock was $21.92 per share.

Investment in our common stock involves a high degree of risk.
See "Risk Factors" beginning on page 4 of this prospectus.

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

The date of this prospectus is October 31, 2001.

SUMMARY

The SEC allows us to incorporate by reference information that we file with them, which means that we can disclose important information to you by referring you to those documents. The information incorporated by reference is considered to be part of this prospectus, and information that we file later with the SEC will automatically update and supersede this information. You should read the following summary together with the more detailed information regarding our company, our common stock and our financial statements and notes to those statements appearing elsewhere in this prospectus or incorporated here by reference. References in this prospectus to "our company," "we," "our," and "us" refer to Isis Pharmaceuticals, Inc.

Our Business

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. Isis' world wide web address is *http://www.isisph.com.* Information contained on our website should not be considered to be part of this prospectus.

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

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.

The Offering

Common stock offered in this prospectus	357,143
Common stock outstanding after the offering	52,837,796 (1)
Use of Proceeds	We will not receive any of the proceeds from the sale of the shares of common stock offered by the selling stockholder
Nasdaq National Market Symbol	ISIP

(1) Based on shares outstanding as of September 30, 2001, as adjusted to reflect the subsequent issuance on October 25, 2001 of 5,000,000 shares of our common stock in our registered public offering and also an additional 750,000 shares we issued on October 30, 2001 pursuant to an overallotment option granted to the underwriters in connection with that offering. Also does not include:

- 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.

RISK FACTORS

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.

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

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 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

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.

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 U.S. Patent and Trademark Office or the International Trade Commission. Intellectual property litigation can be extremely expensive, and this expense, as well as the consequences should we not prevail, could seriously harm our business.

On July 9, 2001, we initiated litigation against Sequitur, Inc. alleging 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 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 30, 2001, the market price of our common stock has ranged from $7.88 to $22.30 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.

Our certificate of incorporation also requires that any action required or permitted to be taken by our stockholders must be taken at a duly called annual or special meeting of stockholders and may not be taken by written consent. In addition, special meetings of our stockholders may be called only by the board of directors, the chairman of the board or the chief executive officer. We also have implemented a stockholders' rights plan, 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, inclusive of the shares offered in this prospectus, 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.

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 4 of this prospectus. As a result, you are cautioned not to rely on these forward-looking statements.

USE OF PROCEEDS

We will not receive any of the proceeds from the sale of the shares of common stock offered by the selling stockholder.

SELLING STOCKHOLDER

We are registering for resale shares of our common stock held by Hybridon, Inc., the selling stockholder. The selling stockholder acquired the resale shares as partial consideration for intellectual property that we licensed from the selling stockholder.

The following table is based in part upon information provided by the selling stockholder and sets forth (i) the name of the selling stockholder; (ii) the number of shares of our common stock that the selling stockholder owned prior to the offering for resale of any of the shares of our common stock being registered hereby; (iii) the maximum number of shares of our common stock that may be offered for resale for the account of the selling stockholder pursuant to this prospectus; and (iv) the percentage of shares of our common stock to be held by the selling stockholder after the offering of the resale shares (assuming all of the resale shares are sold by the selling stockholder). However, our registration of the common stock does not necessarily mean that the selling stockholder will sell all or any of its shares. In addition, the selling stockholder may have sold, transferred or otherwise disposed of, or may sell, transfer or otherwise dispose of, at any time or from time to time since the date on which the selling stockholder provided the information regarding the shares of common stock owned by it, all or a portion of the shares of common stock owned by it in transactions exempt from the registration requirements of the Securities Act of 1933.

The percentage in the table below is based on 52,837,796 shares outstanding on September 30, 2001, as adjusted to reflect the subsequent issuance on October 25, 2001 of 5,000,000 shares of our common stock in our registered public offering and also an additional 750,000 shares we issued on October 30, 2001 pursuant to an overallotment option granted to the underwriters in connection with that offering.

SELLING STOCKHOLDER	SHARES OF COMMON STOCK OWNED	SHARES OF COMMON STOCK OFFERED	PERCENTAGE OF COMMON STOCK OUTSTANDING AFTER THE OFFERING
Hybridon, Inc.	357,143	357,143	0%

In May 2001, we and Hybridon entered into an agreement under which we acquired an exclusive license to all of Hybridon's antisense chemistry and delivery patents and technology, subject to retained rights by Hybridon. Hybridon received a license to our suite of RNaseH patents. In exchange for the license to Hybridon's antisense patents, we paid Hybridon $15 million in cash and will pay Hybridon $19.5 million in our common stock, inclusive of the shares offered in this prospectus, over the two years following the date of the agreement. In return for access to Isis' patents, Hybridon will pay Isis $6.0 million in Hybridon common stock over the three years following the date of the agreement.

PLAN OF DISTRIBUTION

The selling stockholder may sell the resale shares from time to time in one or more transactions at:

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

- negotiated prices.

The selling stockholder will act independently of us in making decisions regarding the timing, manner and size of each sale. The selling stockholder may effect these transactions by selling the resale shares to or through broker-dealers. Broker-dealers engaged by the selling stockholder may arrange for other broker-dealers to participate in the resales. The selling stockholder currently intends to use Bear Sterns, Inc. as a broker-dealer for all of the 357,143 shares being offered by the selling stockholder. The resale shares may be sold in one or more of the following transactions:

- a block trade in which a broker-dealer attempts to sell the shares as agent but may resell a portion of the block as principal to facilitate the transaction;
- a purchase by a broker-dealer as principal and resale by the broker-dealer for its account under this prospectus;
- an exchange distribution in accordance with the rules of the exchange;
- ordinary brokerage transactions and transactions in which a broker solicits purchasers;
- on any national securities exchange or quotation service at which the common stock may be listed or quoted at the time of sale including the NASDAQ National Market;
- in the over-the-counter market;
- through options;

- by pledge to secure debts and other obligations;
- privately negotiated transactions; and
- a combination of any of the above transactions.

If required, we will distribute a supplement to this prospectus to describe material changes in the terms of the offering.

Broker-dealers or agents may receive compensation from the selling stockholder in the form of commissions, discounts or concessions. Broker-dealers or agents may also receive compensation from the purchasers of the resale shares for whom they act as agents or to whom they sell as principals, or both. A broker-dealer's compensation will be negotiated in connection with the sale and may exceed the broker-dealer's customary commissions. Broker-dealers, agents or the selling stockholder may be deemed to be "underwriters" within the meaning of the Securities Act in connection with sales of the resale shares. Any commission, discount or concession received by these broker-dealers or agents and any profit on the resale of the shares purchased by them may be deemed to be underwriting discounts or commissions under the Securities Act.

Because the selling stockholder may be deemed to be an "underwriter" within the meaning of the Securities Act, they will be subject to the prospectus delivery requirements of the Securities Act. In addition, any securities covered by this prospectus which qualify for sale pursuant to Rule 144 under the Securities Act may be sold under Rule 144 rather than under this prospectus.

The resale shares will be sold only through registered or licensed brokers or dealers if required under applicable state securities laws. In addition, in certain states the resale shares may not be sold unless they have been registered or qualified for sale in the applicable state or an exemption from the registration or qualification requirement is available and is complied with.

Under applicable rules and regulations under the Exchange Act, any person engaged in the distribution of the resale shares may not simultaneously engage in market making activities with respect to our common stock for a period of two business days prior to the commencement of the distribution. In addition, the selling stockholder will be subject to applicable provisions of the Exchange Act and the

rules and regulations thereunder, including Regulation M, which may limit the timing of purchases and sales of shares of our common stock by the selling stockholder or any other person. We will make copies of this prospectus available to the selling stockholder and have informed them of the need to deliver a copy of this prospectus to each purchaser at or prior to the time of the sale.

We will pay all costs, expenses and fees associated with the registration of the resale shares, estimated to be $23,000. The selling stockholder will pay all commissions and discounts, if any, associated with the sale of the resale shares. The selling stockholder may agree to indemnify any broker-dealer or agent that participates in sales of the resale shares against specified liabilities, including liabilities arising under the Securities Act. The selling stockholder has agreed to indemnify certain persons, including broker-dealers and agents, against specified liabilities in connection with the offering of the resale shares, including liabilities arising under the Securities Act.

DIVIDEND POLICY

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

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, as amended on April 2, 2001, 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;

- our Current Report on Form 8-K, filed with the SEC on October 29, 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

Grantland E. Bryce, our Vice President and General Counsel will pass upon the validity of the issuance of the common stock offered by this prospectus.

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 upon their authority as experts in accounting and auditing.

WHERE YOU CAN FIND MORE INFORMATION

This prospectus is part of a registration statement on Form S-3 that we filed with the Securities and Exchange Commission. Certain information in the registration statement has been omitted from this prospectus in accordance with the rules of the SEC. We are a public company and file proxy statements and annual, quarterly and special reports and other information with the SEC. You can inspect and copy the registration statement as well as the reports, proxy statements and other information we have filed with the SEC at the public reference room maintained by the SEC at 450 Fifth Street, N.W., Washington, D.C. 20549, and at the SEC Regional Office 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.

You should rely only on the information contained in this prospectus. We have not authorized anyone to provide you with information different from that contained in this prospectus or any prospectus supplement. This prospectus is not an offer of these securities in any jurisdiction where an offer and sale is not permitted. The information contained in this prospectus is accurate only as of the date of this prospectus, regardless of the time of delivery of this prospectus or any sale of our common stock.

TABLE OF CONTENTS

357,143 Shares

Common Stock

ISIS PHARMACEUTICALS, INC.

Prospectus

October 31, 2001

PART II

INFORMATION NOT REQUIRED IN PROSPECTUS

Item 14. Other Expenses of Issuance and Distribution.

The following table sets forth all expenses payable by the Registrant in connection with the sale of the common stock being registered. The selling stockholder will not bear any portion of such expenses. All the amounts shown are estimates except for the registration fee.

SEC Registration Fee	$	1,446
Printing and engraving expenses	$	5,000
Legal fees and expenses	$	10,000
Accounting fees and expenses	$	5,000
Miscellaneous	$	1,554
Total	$	23,000

Item 15. Indemnification of Officers and Directors.

Under Section 145 of the Delaware General Corporation Law, Isis 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.

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

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

---

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

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

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

Item 16. ***Exhibits.***

INDEX TO EXHIBITS

Exhibit Number	Description of Document
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 Grantland E. Bryce.
23.1	Consent of Ernst & Young LLP, independent auditors.
23.2	Consent of Grantland E. Bryce. 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, as amended (the "Act"), 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 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. Notwithstanding the foregoing, any increase or decrease in volume of securities offered (if the total dollar value of securities offered would not exceed that which was registered) and any deviation from the low or high end of the estimated maximum offering range may be reflected in the form of prospectus filed with the Commission pursuant to Rule 424(b) if, in the aggregate, the changes in volume and price represent no more than a 20% change in the maximum aggregate offering price set forth in the "Calculation of Registration Fee" table in the effective registration statement; and

(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 those clauses is contained in periodic reports filed with or furnished to the Commission 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 of 1933, 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;

(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; and

(4) that, 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 San Diego, State of California, on the 29th day of October, 2001.

ISIS PHARMACEUTICALS, INC.

By: /s/ B. LYNNE PARSHALL

B. Lynne Parshall
Executive Vice President,
Chief Financial Officer and 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 and on the dates indicated.

Signature	Title	Date
STANLEY R. CROOKE, M.D., PH.D. * Stanley R. Crooke, M.D., Ph.D.	Chairman of the Board and Chief Executive Officer *(Principal Executive Officer)*	October 29, 2001
/s/ B. LYNNE PARSHALL B. Lynne Parshall	Executive Vice President, Chief Financial Officer, and Director *(Principal Financial and Accounting Officer)*	October 29, 2001
CHRISTOPHER F.O. GABREILI* Christopher F.O. Gabreili	Director	October 29, 2001
WILLIAM R. MILLER* William R. Miller	Director	October 29, 2001
FREDERICK T. MUTO* Frederick T. Muto	Director	October 29, 2001
MARK B. SKALETSKY* Mark B. Skaletsky	Director	October 29, 2001
JOSEPH H. WENDER* Joseph H. Wender	Director	October 29, 2001

*By: /s/ B. LYNNE PARSHALL

B. Lynne Parshall
Attorney-in-fact

INDEX TO EXHIBITS

Exhibit Number	Description of Document
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 Grantland E. Bryce.

23.1	Consent of Ernst & Young LLP, independent auditors.
23.2	Consent of Grantland E. Bryce. 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.

QuickLinks -- Click here to rapidly navigate through this document

EXHIBIT 23.1

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. 333-71116) and related Prospectus of Isis Pharmaceuticals, Inc. for the registration of 357,143 shares of its common stock 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, filed with the Securities and Exchange Commission.

/s/ ERNST & YOUNG LLP

San Diego, California
October 29, 2001

QuickLinks

EXHIBIT 23.1

CONSENT OF ERNST & YOUNG LLP, INDEPENDENT AUDITORS