AS FILED WITH THE SECURITIES AND EXCHANGE COMMISSION ON JUNE 4, 1999

REGISTRATION NO. 333-71911

SECURITIES AND EXCHANGE COMMISSION
WASHINGTON, D.C. 20549

AMENDMENT NO. 4

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
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:

D. BRADLEY PECK, ESQ.
SCOTT R. CUTLER, ESQ.
COOLEY GODWARD LLP
4365 EXECUTIVE DRIVE, SUITE 1100
SAN DIEGO, CA 92121
(619) 550-6000

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. [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.

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THE INFORMATION CONTAINED IN THIS PROSPECTUS IS NOT COMPLETE AND MAY BE CHANGED. THESE SECURITIES MAY NOT BE SOLD TO YOU UNTIL THE REGISTRATION STATEMENT FILED WITH THE SECURITIES AND EXCHANGE COMMISSION IS EFFECTIVE. THIS PROSPECTUS IS NOT AN OFFER TO SELL THESE SECURITIES AND IT IS NOT SOLICITING AN OFFER TO BUY THESE SECURITIES IN ANY STATE WHERE THE OFFER OR SALE IS NOT PERMITTED.

SUBJECT TO COMPLETION, DATED JUNE 4, 1999

PROSPECTUS

4,000,000 Shares

ISIS PHARMACEUTICALS, INC.

Common Stock

This prospectus will allow us to issue common stock over time. This means:

- we will provide a prospectus supplement each time we issue common stock;

- the prospectus supplement will inform you about the specific terms of that offering and also may add, update or change information contained in this document; and

- you should read this document and any prospectus supplement carefully before you invest.

Isis' common stock is traded on the Nasdaq National Market under the symbol "ISIP". On June 1, 1999, the last reported sale price for our common stock on the Nasdaq National Market was $9.75 per share.

INVESTING IN OUR COMMON STOCK INVOLVES CERTAIN RISKS. SEE "RISK FACTORS" BEGINNING ON PAGE 5.

NEITHER THE SECURITIES AND EXCHANGE COMMISSION NOR ANY STATE SECURITIES COMMISSION HAS APPROVED OR DISAPPROVED OF THE SECURITIES OR PASSED UPON THE ACCURACY OR ADEQUACY OF THIS PROSPECTUS. ANY REPRESENTATION TO THE CONTRARY IS A CRIMINAL OFFENSE.

The date of this prospectus is , 1999

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PROSPECTUS SUMMARY

The following summary is qualified in its entirety by reference to the more detailed information and consolidated financial statements appearing elsewhere or incorporated by reference in this prospectus.

THE COMPANY

Isis was incorporated in California in January 1989 and in April 1991 changed its state of incorporation to Delaware. Our executive offices are located at 2292 Faraday Avenue, Carlsbad, California 92008, and our telephone number is (760) 931-9200. Isis' world wide web address is http://www.isip.com. Information contained in our world wide web site should not be considered to be part of this prospectus.

In February 1999, Dr. Daniel Kisner, President, Chief Operating Officer and a director of Isis, resigned all positions to assume the position of Chief Executive Officer of Caliper Technologies, a privately held company. Dr. Debby Jo Blank joined Isis as Executive Vice President overseeing corporate development, business development, strategic planning and marketing, human resources and operations, and investor relations. B. Lynne Parshall, Executive Vice President and Chief Financial Officer assumed responsibility for Isis' manufacturing and regulatory affairs activities in addition to her previous responsibilities.

THE OFFERING

Common stock offered in this prospectus.....	4,000,000 shares
Common stock outstanding after the offering.....	32,242,989 shares(1)
Use of proceeds.....	For research, drug discovery and development activities, including preclinical and clinical studies, production of compounds for such studies and capital expenditures, and other general corporate purposes. See "Use of Proceeds."
Nasdaq National Market symbol...	ISIP

(1) Based on shares outstanding as of June 1, 1999. Does not include 7,923,718 shares of common stock issuable upon exercise of outstanding options or 1,015,000 shares of common stock issuable upon exercise of outstanding warrants as of June 1, 1999.

RISK FACTORS

Please consider the following risk factors carefully in addition to the other information contained in this prospectus and in any other documents incorporated by reference into this prospectus from our other SEC filings.

OUR BUSINESS WILL SUFFER IF WE FAIL TO OBTAIN REGULATORY APPROVAL FOR OUR PRODUCTS.

We must conduct time-consuming, extensive and costly clinical trials, in compliance with U.S. Food and Drug Administration regulations, to show the safety and efficacy of each of our drug candidates, as well as its optimum dosage, before the FDA can approve a drug candidate for sale. We cannot guarantee that we will be able to obtain necessary regulatory approvals on a timely basis, if at all, for any of our products under development. Delays in receiving these approvals, failure by us or our partners to receive these approvals at all or failure to comply with existing or future regulatory requirements could have a material adverse effect on our business, financial condition and results of operations.

While limited trials of our products have to date produced favorable results, significant additional trials may be required, and we may not be able to demonstrate that our drug candidates are safe or effective. We have only introduced one commercial product, Vitravene. We cannot guarantee that any of our other product candidates will obtain required government approvals or that we can successfully commercialize any products. We expect to have ongoing discussions with the FDA and foreign regulatory agencies with respect to all of our drugs in clinical development.

OUR BUSINESS WILL SUFFER IF OUR PRODUCTS ARE NOT USED BY DOCTORS TO TREAT PATIENTS.

We cannot guarantee that any of our products in development, if approved for marketing, will be used by doctors to treat patients. We currently have one product, Vitravene, a treatment for CMV retinitis in AIDS patients, which addresses a small commercial market with significant competition. We delivered our first commercial shipment of Vitravene to our partner CIBA Vision in 1998, earning product revenue of $560,000.

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 clinical efficacy and safety of our product candidates and their potential advantages over competitive products, and
- reimbursement policies of government and third-party payors.

In addition, we cannot guarantee that physicians, patients, patient advocates, payors or the medical community in general will accept and use any products that we may develop.

OUR BUSINESS WILL SUFFER IF ANY OF OUR COLLABORATIVE PARTNERS FAIL TO DEVELOP, FUND OR SELL ANY OF OUR PRODUCTS UNDER DEVELOPMENT.

If any collaborative partner fails to develop or sell any product in which we have rights, our business may be negatively affected. While we believe that our collaborative

partners will have sufficient motivation to continue their funding, development and commercialization activities, we cannot be sure that any of these collaborations will be continued or result in commercialized products. The failure of a corporate partner to continue funding any particular program could delay or stop the development or commercialization of any products resulting from such program.

Collaborative partners may be 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.

We also may wish to rely on additional collaborative arrangements to develop and commercialize our products in the future. However, we may not be able to negotiate acceptable collaborative arrangements in the future, and, even if successfully negotiated, the collaborative arrangements themselves may not be successful.

OUR BUSINESS COULD SUFFER IF THE RESULTS OF FURTHER CLINICAL TESTING INDICATE THAT ANY OF OUR PRODUCTS UNDER DEVELOPMENT ARE NOT SUITABLE FOR COMMERCIAL USE.

Drug discovery and development involves inherent risks, including the risk that molecular targets prove unsuccessful and the risk that compounds that demonstrate attractive activity in preclinical studies do not demonstrate similar activity in human beings or have undesirable side effects. Most of our resources are dedicated to applying molecular biology and medicinal chemistry to the discovery and development of drug candidates based upon antisense technology, a novel drug discovery tool in designing drugs that work at the genetic level to block the production of disease-causing proteins.

WE HAVE INCURRED LOSSES AND OUR BUSINESS WILL SUFFER IF WE FAIL TO ACHIEVE PROFITABILITY IN THE FUTURE.

Because of the nature of the business of drug discovery and development, our expenses have exceeded our revenues since Isis was founded in January 1989. As of December 31, 1998, our accumulated losses were approximately $197 million. Most of the losses have resulted from costs incurred in connection with our research and development programs and from general and administrative costs associated with our growth and operations. These costs have exceeded our revenues, most of which have come from collaborative arrangements, interest income and research grants. Our current product revenues are derived solely from sales of Vitravene. This product has limited sales potential relative to most pharmaceutical products. We expect to incur additional operating losses over the next several years and we expect losses to increase as our preclinical testing and clinical trial efforts continue to expand. We cannot guarantee that we will successfully develop, receive regulatory approval for, commercialize, manufacture, market or sell any additional products, or achieve or sustain future profitability.

OUR BUSINESS WILL SUFFER IF WE FAIL TO OBTAIN TIMELY FUNDING.

Based on our current operating plan, we believe that our available cash and existing sources of revenue and credit, together with the proceeds of this offering and interest earned thereon, will be adequate to satisfy our capital needs until at least the end of 2000.

We expect that we will need substantial additional funding in the future. Our future capital requirements will depend on many factors, such as the following:

- 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;
- the market acceptance of Vitravene;
- the costs involved in filing, prosecuting and enforcing patent claims;
- competing technological and market developments, including the introduction of new therapies that address our markets; and
- changes in existing collaborative relationships and our ability to establish and maintain additional collaborative arrangements.

If we are unable to raise the total amount of proceeds covered by this prospectus, we will need to raise additional funds to finance our research and development and other operating activities. If we find that we do not have enough money, additional funds may be raised, including through public or private financing. Additional financing may not be available, or, if available, may not be on acceptable terms. If additional funds are raised by issuing equity securities, the shares of existing stockholders will be subject to further dilution and share prices 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.

OUR BUSINESS WILL SUFFER IF WE CANNOT MANUFACTURE OUR PRODUCTS OR HAVE A THIRD PARTY MANUFACTURE OUR PRODUCTS AT LOW COSTS SO AS TO ENABLE US TO CHARGE COMPETITIVE PRICES TO BUYERS.

To establish additional commercial manufacturing capability on a large scale, we must improve our manufacturing processes and reduce our product costs. The manufacture of sufficient quantities of new drugs is typically a time-consuming and complex process. Pharmaceutical products based on chemically modified oligonucleotides have never been manufactured on a large commercial scale. There are 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. We may not be able to manufacture at a cost or in quantities necessary to make commercially successful products.

In 1998, we entered into an antisense oligonucleotide manufacturing collaboration with Zeneca Life Science Molecules of Manchester, England pursuant to which Zeneca LSM will supply a portion of our requirements of drugs for clinical trials. As of the date of this prospectus, we have not received any supply of drugs under this arrangement, and we cannot guarantee that Zeneca LSM will prove to be an acceptable alternative supplier.

OUR BUSINESS WILL SUFFER IF WE FAIL TO COMPETE EFFECTIVELY WITH OUR COMPETITORS.

Our competitors are engaged in all areas of drug discovery in the United States and other countries, are numerous, and include, among others, major pharmaceutical and chemical companies, specialized biopharmaceutical firms, universities and other research institutions. Our competitors may succeed in developing other new therapeutic drug candidates that are more effective than any drug candidates that we have been developing. These competitive developments could make our technology and products obsolete or non-competitive before we have had enough time to recover our research, development or commercialization expenses.

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 manufacturing efficiency and marketing capabilities, areas in which we have limited or no experience.

OUR BUSINESS WILL SUFFER IF WE ARE UNABLE TO PROTECT OUR PATENTS OR OUR PROPRIETARY RIGHTS.

Our success depends to a significant degree upon our ability to develop proprietary products. However, we cannot assure you that patents will be granted on any of our patent applications in the United States or in other countries. We also cannot assure you that the scope of any of our issued patents will be sufficiently broad to offer meaningful protection. In addition, our issued patents or patents licensed to us could be successfully challenged, invalidated or circumvented so that our patent rights would not create an effective competitive barrier.

INTELLECTUAL PROPERTY LITIGATION COULD HARM OUR BUSINESS.

We have not experienced any patent or other intellectual property litigation. However, we cannot guarantee that we will not have to defend our intellectual property rights in the future. In the event of an intellectual property dispute, we may be forced to litigate or otherwise defend our intellectual property assets. Such 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 such expense, as well as the consequences should we not prevail, could seriously harm our business.

If a third party claimed an intellectual property right to technology we use, we might be forced to discontinue an important product or product line, alter our products and processes, pay license fees or cease certain activities. Although we might under these circumstances attempt to obtain a license to such intellectual property, we may not be able to do so on favorable terms, if at all.

THE LOSS OF KEY PERSONNEL, OR THE INABILITY TO ATTRACT AND RETAIN HIGHLY SKILLED PERSONNEL, COULD ADVERSELY AFFECT OUR BUSINESS.

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. Recently, Dr. Daniel Kisner, our President and Chief Operating Officer and director resigned all positions to assume the position of Chief Executive Officer of Caliper Technologies, a privately held company. Dr. Kisner's resignation is not expected to have a material adverse effect on our business. It is also critical to our success to recruit and retain qualified scientific personnel to perform research and development work. Although we believe we will be successful in attracting and keeping skilled and experienced scientific personnel, we may not be able to do so on acceptable terms, because of stiff competition for experienced scientists among many pharmaceutical and health care companies, universities and non-profit research institutions.

OUR STOCK PRICE MAY CONTINUE TO BE HIGHLY VOLATILE.

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 last twelve months, the market price of our common stock has ranged from $7 to $16. The market price can be affected by many factors, including, for example, fluctuation in our operating results, announcements of 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 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 the 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, 15% or more of our voting stockholders, 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 president, or by any holder of 10% or more of our outstanding common stock. The classified board, stockholder vote requirements and other charter provisions protect us in two ways. First, these provisions may discourage certain types of transactions in which the stockholders might otherwise receive a premium for their shares over then current market prices, and may limit the ability of the stockholders to approve transactions that they think may be in their best interests. Second, the 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 Isis without action by the stockholders.

WHERE YOU CAN GET MORE INFORMATION

We are a reporting company and file annual, quarterly and current reports, proxy statements and other information with the SEC. You may read and copy these reports, proxy statements and other information at the SEC's public reference rooms in Washington, D.C., New York, NY and Chicago, IL. You can request copies of these documents by writing to the SEC and paying a fee for the copying cost. Please call the SEC at 1-800-SEC-0330 for more information about the operation of the public reference rooms. Our SEC filings are also available at the SEC's Web site at "http://www.sec.gov". In addition, you can read and copy our SEC filings at the office of the National Association of Securities Dealers, Inc. at 1735 K Street, Washington, D.C. 20006.

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 an important part of this prospectus, and information that we file later with the SEC will automatically update and supersede this information. We incorporate by reference the documents listed below and any future filings we will make with the SEC under Section 13(a), 13(c), 14 or 15(d) of the Securities Exchange Act of 1934:

- Annual Report on Form 10-K for the year ended December 31, 1998;

- Quarterly Report on Form 10-Q for the quarter ended March 31, 1999;

- Proxy Statement for the 1999 Annual Meeting of Stockholders;

- Current Report on Form 8-K dated as of April 20, 1999; and

- Isis' registration statement on Form 8-A filed on April 2, 1991, which includes a description of our common stock.

You may request a copy of these filings at no cost, by writing or telephoning us at the following address or telephone number:

Isis Pharmaceuticals, Inc.
Attn: Vice President of Finance
2292 Faraday Avenue
Carlsbad, CA 92008
Telephone Number (760) 931-9200

This prospectus is part of a larger registration statement we filed with the SEC. You should rely only on the information incorporated by reference or provided in this prospectus. We have not authorized anyone else to provide you with different information. We are not making an offer of these securities in any state where the offer is not permitted. You should not assume that the information in this prospectus is accurate as of any date other than the date on the front of the document.

USE OF PROCEEDS

We cannot guarantee that we will receive any proceeds in connection with this offering.

Companies in the biopharmaceutical industry generally expend significant capital resources in product research and development. We anticipate that we will be required to raise substantial additional capital over a period of several years in order to finance our research and development programs. Additional capital may be raised through additional public or private financings, as well as collaborative relationships, borrowings and other available sources.

We intend to use the net proceeds of this offering, if any, for our 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 such 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 such expenditures. Isis, however, currently plans that the proceeds, if any, will be used for product development, including clinical trials, preclinical studies, manufacturing scale-up and facilities and equipment acquisition. The remaining proceeds, if any, will be used to expand selected research activities and for general and administrative 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.

Other methods of financing our operations, including the acquisition of tenant improvements and capital equipment, such as mortgage or lease financing, may be used by us if available on attractive terms. In the past, Isis has made a practice of using lease financing for equipment purchases and intends to continue to do so in the future to the extent the terms of such financing remain commercially attractive. To the extent such financing is used, proceeds of this offering will be reallocated to working capital.

Based upon our current operating plan, we believe that our available cash and existing sources of revenue and credit, together with the proceeds of this offering and interest earned thereon, will be adequate to satisfy our capital needs until at least the end of 2000.

Proceeds of this offering, if any, may also be used to acquire companies or products that complement the business of Isis. We are not planning or negotiating any such transactions as of the date of this prospectus.

DILUTION

The net tangible deficit of Isis at March 31, 1999 was $26,402,000 or approximately $0.97 per share of common stock. Net tangible deficit per share represents the amount of our tangible assets less total liabilities, divided by 27,329,000 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 the offering made hereby and the pro forma net tangible book value per share of common stock immediately after completion of the offering. After giving effect to the sale of 4,000,000 shares of common stock in this offering at an assumed offering price of $10.05 per share and the application of the estimated net proceeds therefrom (after deducting estimated offering expenses) the pro forma net tangible book value of Isis as of March 31, 1999 would have been $13,698,000 or $0.44 per share, an immediate increase in net tangible book value of $1.41 per share to existing stockholders and an immediate dilution in net tangible book value of $9.61 per share to purchasers of common stock in the offering, as illustrated in the following table:

Assumed public offering price per share.....		$10.05
Net tangible book value per share at March 31, 1999.....	$(.97)	
Increase per share attributable to new investors.....	$1.41	
Pro forma net tangible book value per share after offering.....		$ .44
Net tangible book value dilution per share to new investors.....		$ 9.61

To the extent that outstanding options and warrants are exercised, there will be further dilution to new investors.

PLAN OF DISTRIBUTION

We may offer the common stock:

- directly to purchasers;
- to or through underwriters;
- through dealers, agents or institutional investors; or
- through a combination of such methods.

Regardless of the method used to sell the common stock, we will provide a prospectus supplement that will disclose:

- the identity of any underwriters, dealers, agents or investors who purchase the common stock;
- the material terms of the distribution, including the number of shares sold and the consideration paid;
- the amount of any compensation, discounts or commissions to be received by the underwriters, dealers or agents;
- the terms of any identification provisions, including indemnification from liabilities under the federal securities laws; and
- the nature of any transaction by an underwriter, dealer or agent during the offering that is intended to stabilize or maintain the market price of the common stock.

LEGAL MATTERS

The validity of the issuance of the common stock offered in this prospectus will be passed upon for Isis by Grantland E. Bryce, Vice President and General Counsel of Isis. Mr. Bryce does not beneficially own any shares of common stock as of the date of this prospectus.

EXPERTS

The financial statements of Isis Pharmaceuticals, Inc., appearing in Isis Pharmaceuticals, Inc.'s Annual Report on Form 10-K for the year ended December 31, 1998, have been audited by Ernst & Young LLP, independent auditors, as set forth in their report. We incorporate by reference their report as a part of this prospectus. Such financial statements are incorporated into this prospectus in reliance upon the reports of Ernst & Young LLP given upon the authority of Ernst & Young LLP as experts in accounting and auditing.

PART II

INFORMATION NOT REQUIRED IN PROSPECTUS

ITEM 14. OTHER EXPENSES OF ISSUANCE AND DISTRIBUTION

The following table sets forth all expenses payable by Isis in connection with the sale of the 4,000,000 shares of common stock being registered. All the amounts shown are estimates except for the registration fee.

SEC registration fee	$ 14,734
Legal fees and expenses	$ 40,000
Accounting fees and expenses	$ 10,000
Nasdaq fees for newly issued shares	$ 17,500
Miscellaneous	$ 17,766
Total	$100,000

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.

The Registrant 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

EXHIBIT NUMBER	DESCRIPTION OF DOCUMENT
4.1	Amended and Restated Certificate of Incorporation.(1)
4.2	By-laws.(1)
4.3	Certificate of Designation of the Series A Convertible Preferred Stock*
5.1	Opinion of Grantland E. Bryce.*
23.1	Consent of Ernst & Young LLP.*
23.2	Consent of Grantland E. Bryce. Reference is made to Exhibit 5.1.
24.1	Power of Attorney. Reference is made to page II-5.
27.1	Financial Data Schedule.*
99.1	Form of Confidentiality Agreement.*

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(1) Filed as an exhibit to the Registration Statement on Form S-1 (No. 33-39649) or amendments thereto and incorporated herein by reference.

* Previously Filed

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 pursuant to this registration statement, a post-effective amendment to this registration statement 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;

(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; 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; and (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.

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. 4 to Registration Statement to be signed on its behalf by the undersigned thereunto duly authorized, in the city of Carlsbad, County of San Diego, State of California, on the 4th day of June, 1999.

ISIS PHARMACEUTICALS, INC.

By: /s/ STANLEY T. CROOKE

Stanley T. Crooke, M.D., Ph.D.
Chairman of the Board
and Chief Executive Officer
(Principal executive officer)

POWER OF ATTORNEY

KNOW ALL PERSONS BY THESE PRESENTS, that each person whose signature appears below constitutes and appoints STANLEY T. CROOKE and B. LYNNE PARSHALL, and each of them, as his or her true and lawful attorney-in-fact and agents, with full power of substitution and resubstitution, for the undersigned and in his or her name, place and stead, in any and all capacities, to sign any or all amendments (including post-effective amendments) to the Registration Statement and to file the same, with all exhibits thereto, and all documents in connection therewith, with the Securities and Exchange commission, granting unto said attorneys-in-fact and agents, and each of them, full power of authority to do and perform each and every act and thing requisite and necessary to be done in connection therewith, as fully to all intents and purposes as he or she might or could do in person, hereby ratifying and confirming all that said attorneys-in-fact and agents, each acting alone, or his or her substitute or substitutes, may lawfully do or cause to be done by virtue hereof.

Pursuant to the requirements of the Securities Act of 1933, this Amendment No. 4 to Registration Statement has been signed below by the following persons in the capacities indicated and on the dates indicated.

SIGNATURES	TITLE	DATE
/s/ STANLEY T. CROOKE Stanley T. Crooke, M.D., Ph.D.	Chairman of the Board and Chief Executive Officer (Principal executive officer)	June 4, 1999
* B. Lynne Parshall	Executive Vice President and Chief Financial Officer (Principal financial and accounting officer)	June 4, 1999

SIGNATURES	TITLE	DATE
*	Director	June 4, 1999
Alan C. Mendelson		
*	Director	June 4, 1999
Christopher F.O. Gabrieli		
*	Director	June 4, 1999
William R. Miller		
*	Director	June 4, 1999
Mark B. Skaletsky		
*	Director	June 4, 1999
Larry Soll, Ph.D.		
*	Director	June 4, 1999
Joseph H. Wender		
	Director	June 4, 1999
Burkhard Blank		

By: /s/ STANLEY T. CROOKE

Stanley T. Crooke, M.D., Ph.D.
Attorney In Fact

EXHIBIT INDEX

EXHIBIT NO.	DESCRIPTION	SEQUENTIAL PAGE NO.
4.1	Amended and Restated Certificate of Incorporation(1).....	
4.2	By-laws(1).....	
4.3	Certificate of Designation of the Series A Convertible Preferred Stock*.....	
5.1	Opinion of Grantland E. Bryce*.....	
23.1	Consent of Ernst & Young LLP*.....	
23.2	Consent of Grantland E. Bryce. Reference is made to Exhibit 5.1.....	
24.1	Power of Attorney. Reference is made to page II-5.....	
27.1	Financial Data Schedule*.....	
99.1	Form of Confidentiality Agreement.*	

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(1) Filed as an exhibit to the Registration Statement on Form S-1 (No. 33-39649) or amendments thereto and incorporated herein by reference.

* Previously Filed.