FILING PURSUANT TO RULE 424(b)(2)
REGISTRATION STATEMENT NO. 333-71911

PROSPECTUS SUPPLEMENT
(TO PROSPECTUS DATED JUNE 21, 1999)

937,339 SHARES

ISIS PHARMACEUTICALS, INC.
COMMON STOCK

You should read this prospectus supplement and the accompanying prospectus carefully before you invest. Both documents contain information you should consider carefully before making your investment decision.

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

PLAN OF DISTRIBUTION

Pursuant to this prospectus supplement, we are offering 937,339 shares of our common stock to Ridgeway Investment Limited at a negotiated price of $10.59 per share. We will not pay any other compensation in conjunction with the sale of our common stock. See "Plan of Distribution" beginning on page 12.

USE OF PROCEEDS

We will use the proceeds of this offering as described in the prospectus. See "Use of Proceeds" beginning on page 11.

WHERE YOU CAN GET MORE INFORMATION

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 supplement and the accompanying prospectus. We incorporate the documents listed below, in addition to those indicated on page 10 of the prospectus:

- Annual Report on Form 10-K for the year ended December 31, 1999, dated as of March 28, 2000; and

- Current Report on Form 8-K dated as of January 28, 2000.

MARKET FOR OUR COMMON STOCK

On June 13, 2000, the last reported sale price of our common stock on the Nasdaq National Market was $13.00 per share. Our common stock is listed on the Nasdaq National Market under the symbol "ISIP." The common stock sold under this prospectus supplement will be listed on the Nasdaq National Market after we notify the Nasdaq National Market that the shares have been issued.

As of June 12, 2000, we had 37,248,006 shares of common stock outstanding.

GENERAL

You should rely only on the information provided or incorporated by reference in this prospectus supplement and the prospectus. We have not authorized anyone else to provide you with different information. You should not assume that the information in this prospectus supplement is accurate as of any date other than the date on the front of these documents.

NEITHER THE SECURITIES 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 supplement is June 14, 2000.

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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 7, 1999, the last reported sale price for our common stock on the Nasdaq National Market was $9.91 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 June 21, 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.

Isis Pharmaceuticals is a trademark of Isis. Vitravene(TM) is a trademark of CIBA Vision Corporation. All other brand names or trademarks appearing in this prospectus are the property of their respective holders.

THE OFFERING

Common stock offered in this prospectus.....	4,000,000 shares
Common stock outstanding after the offering.....	32,245,139 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 7, 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 7, 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, as amended on June 8, 1999;

- 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, as amended on June 8, 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.