FILING PURSUANT TO RULE 424(b)(2)
REGISTRATION STATEMENT NO. 333-90811

AMENDMENT NO. 1 TO

PROSPECTUS SUPPLEMENT
(TO PROSPECTUS DATED DECEMBER 6, 1999)

1,627,430 SHARES

ISIS PHARMACEUTICALS, INC.
COMMON STOCK

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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 sold 1,000,000 shares of our common stock to Acqua Wellington North American Equities Fund, Ltd. at a negotiated price of $27.25 per share which offering is underwritten by Ridgeway Investment Limited. In addition, pursuant to this prospectus supplement, we sold 627,430 shares of our common stock to Ridgeway Investment Limited. These shares were purchased at a price of $12.75 per share as determined under the terms of the Common Stock Purchase Agreement filed as an exhibit to the prospectus dated December 6, 1999. The $12.75 purchase price reflects the average of recent trading prices of the common stock on the Nasdaq National Market. We did 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.

## MARKET FOR OUR COMMON STOCK

On March 8, 2000, the last reported sale price of our common stock on the Nasdaq National Market was $25.50 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 March 8, 2000, we had 34,518,000 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 amendment to the prospectus supplement is March 10, 2000.

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PROSPECTUS

4,000,000 Shares

ISIS PHARMACEUTICALS, INC.

Common Stock

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Isis entered into a common stock purchase agreement with Ridgeway Investment Limited. Under the purchase agreement, Isis may issue and sell to Ridgeway, from time to time, shares of its common stock for cash consideration up to an aggregate of $120 million at a per share purchase price equal to the average price of the common stock over a period of time less a discount from 4.5% to 5.875%. Pursuant to the terms of the purchase agreement, none of the shares will be sold until at least January 1, 2000.

Isis' common stock is traded on the Nasdaq National Market under the symbol "ISIP". On November 19, 1999, the last reported sale price for our common stock on the Nasdaq National Market was $14.1875 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 December 6, 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.

## THE OFFERING

| | |
|---|---|
| Common stock offered in this prospectus..... | 4,000,000 shares |
| Common stock outstanding after the offering..... | 34,708,001 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 November 10, 1999. Does not include 7,850,253 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 November 10, 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 the optimum dosage for each, 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 September 30, 1999, our accumulated losses were approximately $239 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 will need to 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 Avecia Life Science Molecules of Manchester, England, pursuant to which Avecia 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 Avecia 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 potentially 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.

To date, 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 those 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. 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 retaining 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 twelve months preceding the date of this prospectus, the market price of our common stock has ranged from $9 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. These provisions 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, 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 and June 14, 1999;

- Quarterly Reports on Form 10-Q for the quarters ended March 31, 1999, June 30, 1999 and September 30, 1999;

- Proxy Statement for the 1999 Annual Meeting of Stockholders;

- Current Reports on Form 8-K dated as of April 20, 1999, as amended on June 8, 1999 and June 14, 1999, and dated as of September 2, 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 to support the continued development of ISIS 2302, an antisense anti-inflammatory drug that recently completed pivotal trials in Crohn's disease, and additional planned research and development efforts, including Phase III clinical trials of ISIS 3521 in non-small cell lung cancer, and other drugs in Isis' clinical programs. The remaining proceeds, if any, will be used for general corporate purposes. The amounts actually expended for each purpose may vary significantly depending upon numerous factors, including the amount and timing of the proceeds from this offering, progress of our research, drug discovery and development programs, the results of preclinical and clinical studies, the timing of regulatory approvals, technological advances, determinations as to commercial potential of our compounds and the status of competitive products. In addition, expenditures will also depend upon the establishment of collaborative research arrangements with other companies, the availability of other financing and other factors.

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 this type of financing remain commercially attractive. To the extent this type of 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, if any, 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 September 30, 1999 was $20,770,000 or approximately $.71 per share of common stock. Net tangible deficit per share represents the amount of our tangible assets less total liabilities, divided by 29,198,000 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 $13.00 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 September 30, 1999 would have been $31,130,000 or $.94 per share, an immediate increase in net tangible book value of $1.65 per share to existing stockholders and an immediate dilution in net tangible book value of $12.06 per share to purchasers of common stock in the offering, as illustrated in the following table:

| | | |
|---|---|---|
| Assumed public offering price per share..... | | $13.00 |
| Net tangible book value per share at September 30, 1999..... | $ (.71) | |
| Increase per share attributable to new investors..... | $ 1.65 | |
| Pro forma net tangible book value per share after offering..... | | $ .94 |
| Net tangible book value dilution per share to new investors..... | | $12.06 |

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

## PLAN OF DISTRIBUTION

We plan to enter into a common stock purchase agreement with Ridgeway. From a period of 14 months following the later of the effective date of the registration statement of which this prospectus forms a part or January 1, 2000, Isis may, from time to time and at its sole discretion, present Ridgeway with draw down requests to sell up to $5,000,000, or such other amount mutually agreed upon by the parties, worth of shares of Isis' common stock. Isis will issue and sell the shares to Ridgeway at a per share purchase price equal to the average price of Isis' common stock over a period of time less a discount from 4.5% to 5.875% subject to a minimum price as set forth in the purchase agreement. Isis may present Ridgeway with up to 12 draw down notices during the term of the purchase agreement.

Upon the receipt of a draw down request, Ridgeway may exercise a call option to purchase up to an additional $5,000,000, or such other amount mutually agreed upon by the parties, worth of shares of Isis' common stock for a purchase price equal to the average price of the common stock over a period specified in the purchase agreement less a discount from 4.5% to 5.75% subject to a minimum price as set forth in the purchase agreement.

Isis will pay Ridgeway a fee equal to .25% of each draw down amount and each call option amount.

Pursuant to the terms of the purchase agreement, none of the shares will be sold until at least January 1, 2000.

Ridgeway and its pledgees, donees, transferees and other subsequent owners, may offer their shares at various times in one or more of the following transactions:

- in the over-the-counter market; or

- in privately negotiated transactions

at prevailing market prices at the time of sale, at prices related to those prevailing market prices, at negotiated prices or at fixed prices.

Ridgeway may also sell its shares under Rule 144 instead of under this prospectus, if Rule 144 is available for those sales.

The transactions in the shares may be effected by one or more of the following methods:

- ordinary brokerage transactions and transactions in which the broker solicits purchasers;

- purchases by a broker or dealer as principal, and the resale by that broker or dealer for its account under this prospectus, including resale to another broker or dealer;

- block trades in which the broker or dealer will attempt to sell the shares as agent but may position and resell a portion of the block as principal in order to facilitate the transaction; or

- negotiated transactions between selling stockholders and purchasers without a broker or dealer.

Ridgeway is an "underwriter" within the meaning of the Securities Act in connection with its sale of the shares purchased under the purchase agreement with Isis. Broker-dealers or other persons acting on behalf of parties that participate in the distribution of the shares may also be deemed to be underwriters. Any commissions or profits they receive on the resale of the shares may be deemed to be underwriting discounts and commissions under the Securities Act.

During the time Ridgeway is engaged in distributing shares covered by this prospectus, Ridgeway will comply with the requirements of the Securities Act and Rule 10b-5 and Regulation M under the Exchange Act. Under those rules and regulations, they:

- may not engage in any stabilization activity in connection with our securities;

- must furnish each broker which offers shares of common stock covered by this prospectus with the number of copies of this prospectus which are required by each broker; and

- may not bid for or purchase any of our securities or attempt to induce any person to purchase any of our securities other than as permitted under the Exchange Act.

In the purchase agreement with Ridgeway, we will agree to indemnify and hold harmless Ridgeway and each person who controls Ridgeway against certain liabilities, including liabilities under the Securities Act, which may be based upon, among other things, any untrue statement or alleged untrue statement of a material fact or any omission or alleged omission of a material fact contained in any prospectus or prospectus supplement, unless made or omitted in reliance upon written information provided to us by Ridgeway.

We have agreed to bear the expenses incident to the registration of the shares, other than selling discounts and commissions. These expenses are estimated to be $85,000.

## 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

Ernst & Young LLP, independent auditors, have audited our financial statements included in our Annual Report on Form 10-K, as amended, for the year ended December 31, 1998, 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.