

FILING PURSUANT TO RULE 424(b)(2)  
REGISTRATION STATEMENT NO. 333-38844

PROSPECTUS SUPPLEMENT  
(TO PROSPECTUS DATED SEPTEMBER 8, 2000)

316,206 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 are offering 316,206 shares of our common stock to Acqua Wellington North American Equities Fund Limited at a negotiated price of \$12.65 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.

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## MARKET FOR OUR COMMON STOCK

On November 7, 2000, the last reported sale price of our common stock on the Nasdaq National Market was \$11.75 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 November 7, 2000, we had 39,013,173 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 November 8, 2000.

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