

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

PROSPECTUS SUPPLEMENT
(TO PROSPECTUS DATED SEPTEMBER 8, 2000)

160,151 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 160,151 shares of our common stock to Ridgeway Investment Limited. These shares will be purchased at a price of \$10.4068 per share, as determined under the terms of the Common Stock Purchase Agreement filed as an exhibit to the prospectus dated September 8, 2000. The \$10.4068 per share purchase price reflects the average of recent trading prices of our common stock on the Nasdaq National Market. 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.

S-1

MARKET FOR OUR COMMON STOCK

On December 8, 2000, the last reported sale price of our common stock on the Nasdaq National Market was \$10.0625 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 December 8, 2000, we had 39,927,296 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 December 12, 2000.

TABLE OF CONTENTS

	PAGE

PROSPECTUS SUPPLEMENT	
Plan of Distribution.....	S-1
Use of Proceeds.....	S-1
Market for Our Common Stock.....	S-2
General.....	S-2
PROSPECTUS	
Prospectus Summary.....	3
The Company.....	3
The Offering.....	4
Risk Factors.....	5
Where You Can Get More Information.....	10
Use of Proceeds.....	11
Dilution.....	12
Plan of Distribution.....	12
Legal Matters.....	15
Experts.....	15