

**Supplement to Prospectus
Dated August 21, 2006
Isis Pharmaceuticals, Inc.**

The Prospectus, dated August 21, 2006 is hereby supplemented as follows to restate, in its entirety, the "Selling Stockholders" section on pages 12-14 of the Prospectus.

The date of this Prospectus Supplement is February 8, 2008

SELLING STOCKHOLDERS

The shares of common stock covered hereby consist of 4,250,000 shares of our common stock issuable upon exercise of warrants to purchase common stock. We issued the warrants to the selling stockholders in connection with our collaboration with Symphony GenIsis, Inc.

In connection with the registration rights we granted to the selling stockholders, we filed with the Securities and Exchange Commission a registration statement on Form S-3, of which this prospectus forms a part, with respect to the resale or other disposition of the shares of common stock offered by this prospectus or interests therein from time to time on The Nasdaq National Market, in privately negotiated transactions or otherwise. We have also agreed to prepare and file amendments and supplements to the registration statement to the extent necessary to keep the registration statement effective for the period of time required under our agreements with the selling stockholders. The warrants held by the selling stockholders are exercisable at any time in whole or in part beginning October 4, 2006 and ending April 7, 2011.

The actual number of shares of common stock covered by this prospectus, and included in the registration statement of which this prospectus forms a part, includes additional shares of common stock that may be issued with respect to the shares of common stock or the warrants described herein as a result of stock splits, stock dividends, reclassifications, recapitalizations, combinations or similar events.

Beneficial ownership is determined in accordance with the rules of the Securities and Exchange Commission, or SEC and is based upon information provided by each respective selling stockholder, Schedules 13D and 13G and other public documents filed with the SEC. Since the warrants held by the selling stockholders are exercisable beginning October 4, 2006 and the shares of common stock issuable upon exercise of the warrants are being offered in this prospectus, those shares of common held by the selling stockholders are included in the table below. The percentages of shares owned after the offering are based on 92,662,274 shares of our common stock outstanding as of February 6, 2008.

Unless otherwise indicated below, to our knowledge, all persons named in this table have sole voting and investment power with respect to their shares of common stock, except to the extent authority is shared by spouses under applicable law. The inclusion of any shares in this table does not constitute an admission of beneficial ownership for the person named below.

We do not know when or in what amounts a selling stockholder may offer shares for sale or other disposition. The selling stockholders might not sell or dispose of any or all of the shares offered by this prospectus. Because the selling stockholders may offer all or some of the shares pursuant to this offering, and because there are currently no agreements, arrangements or understandings with respect to the sale of any of the shares, we cannot estimate the number of the shares that will be held by the selling stockholders after completion of the offering. However, for purposes of this table, we have assumed that, after completion of the offering, none of the shares covered by this prospectus will be held by the selling stockholders.

The following table sets forth, to our knowledge, information about the selling stockholders as of February 6, 2008.

	Shares of Common Stock Beneficially Owned Prior to Offering			Shares of Common Stock Offered	Percentage Of Common Stock Outstanding After The Offering
	Shares of Common Stock Held	Shares of Common Stock Issuable Upon Exercise of Warrants	Total Number of Shares Beneficially Owned		
Selling stockholders (1)(2)					
UBS O'Conner LLC for the benefit of O'Connor PIPES Corporate Strategies Master Limited 299 Park Avenue New York, NY 10171	—	53,267	53,267	53,267	—
OTA Swaps LLC (3) One Manhattanville Road Purchase, NY 10577	—	852,268	1,912,534	852,268	1.1%

* Less than one percent

(1) The term “selling stockholders” includes donees, pledgees, transferees or other successors-in-interest selling shares received after the date of this prospectus from a selling stockholder as a gift, pledge, partnership distribution or other non-sale related transfer.

(2) For those selling stockholders which may be considered affiliates of broker dealers, each selling stockholder has represented and warranted that it has purchased in the ordinary course of business and that, at the time of the purchase, it had no agreements or understandings to distribute the securities.

(3) Total number of shares beneficially owned includes the 852,268 shares issuable upon exercise of the Warrants and 1,060,266 shares of common stock issuable upon other warrants held by the selling stockholder.

Relationship with Selling Stockholders

To our knowledge, no selling stockholder has held any position or office or otherwise had a material relationship with us within the past three years.
