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SECURITIES AND EXCHANGE COMMISSION  
Washington, D.C. 20549

FORM S-8  
REGISTRATION STATEMENT  
UNDER  
THE SECURITIES ACT OF 1933

ISIS PHARMACEUTICALS, INC.  
(Exact Name Of Registrant As Specified In Its Charter)

DELAWARE  
(State Or Other Jurisdiction Of  
Incorporation Or Organization)

33-0336973  
(I.R.S. Employer Identification No.)

2292 FARADAY AVENUE  
CARLSBAD, CALIFORNIA 92008  
(Address Of Principal Executive Offices)

1989 STOCK OPTION PLAN  
(Full Title Of The Plan)

B. LYNNE PARSHALL, ESQ.  
EXECUTIVE VICE PRESIDENT, CHIEF FINANCIAL OFFICER AND SECRETARY  
ISIS PHARMACEUTICALS, INC.  
2292 FARADAY AVENUE  
CARLSBAD, CALIFORNIA 92008  
(760) 931-9200  
  
(Name, Address, Including Zip Code, And Telephone Number, Including  
Area Code, Of Agent For Service)

Copies to:

D. BRADLEY PECK, ESQ.  
COOLEY GODWARD LLP  
4365 EXECUTIVE DRIVE, SUITE 1100  
SAN DIEGO, CALIFORNIA 92121  
(619) 550-6000

## CALCULATION OF REGISTRATION FEE

TITLE OF SECURITIES TO BE REGISTERED	AMOUNT TO BE REGISTERED	PROPOSED MAXIMUM OFFERING PRICE PER SHARE (1)	PROPOSED MAXIMUM AGGREGATE OFFERING PRICE (1)	AMOUNT OF REGISTRATION FEE
Stock Options and Common Stock (par value \$.001)	2,000,000	\$13.5625-\$15.4375	\$27,148,859	\$8,008.91

(1) Estimated solely for the purpose of calculating the amount of the registration fee pursuant to Rule 457(c) and (h)(1). The price per share and the aggregate offering price are calculated on the basis of (a) the weighted average of \$14.4375 - \$15.4375, the exercise price for 15,470 shares subject to outstanding options granted under the Registrant's 1989 Stock Option Plan and (b) \$13.5625, the average of the high and low sales prices of Registrant's Common Stock on May 27, 1998 as reported on the Nasdaq National Market.

INCORPORATION BY REFERENCE OF CONTENTS OF  
REGISTRATION STATEMENT ON FORM S-8 NO. 33-42356, NO. 33-51236,  
NO. 33-54840, NO. 33-58450, NO. 33-75150, NO. 33-90780 AND NO. 333-05825

The contents of Registration Statements on Form S-8 Nos. 33-42356, 33-51236, 33-54840, 33-58450, 33-75150, 33-90780 and 333-05825 filed with the Securities and Exchange Commission on August 23, 1991, August 25, 1992, November 20, 1992, February 16, 1993, February 4, 1994, March 30, 1995 and June 12, 1996, respectively, are incorporated by reference herein.

EXHIBITS

EXHIBIT  
NUMBER

- 5.1 Opinion of Cooley Godward LLP
- 23.1 Consent of Ernst & Young LLP
- 23.2 Consent of Cooley Godward LLP is contained in Exhibit 5.1 to this Registration Statement.
- 24.1 Power of Attorney is contained on the signature pages.
- 99.1\* 1989 Stock Option Plan, as amended.

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\* Filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 1997, and incorporated herein by reference.

## SIGNATURES

Pursuant to the requirements of the Securities Act of 1933, as amended, the Registrant certifies that it has reasonable grounds to believe that it meets all of the requirements for filing on Form S-8 and has duly caused this Registration Statement to be signed on its behalf by the undersigned, thereunto duly authorized, in the City of Carlsbad, State of California, on May 22, 1998.

ISIS PHARMACEUTICALS, INC.

By /s/ B. LYNNE PARSHALL

-----  
 B. Lynne Parshall  
 Executive Vice President, Chief  
 Financial Officer and Secretary  
 (Principal Financial and Accounting  
 Officer)

## POWER OF ATTORNEY

KNOW ALL PERSONS BY THESE PRESENTS, that each person whose signature appears below constitutes and appoints Stanley T. Crooke, Daniel L. Kisner and B. Lynne Parshall and each or any one of them, his or her true and lawful attorney-in-fact and agent, with full power of substitution and resubstitution, for him or her and in his or her name, place and stead, in any and all capacities, to sign any and all amendments (including post-effective amendments) to this Registration Statement, and to file the same, with all exhibits thereto, and other documents in connection therewith, with the Securities and Exchange Commission, granting unto said attorneys-in-fact and agents, and each of them, full power and authority to do and perform each and every act and thing requisite and necessary to be done in connection therewith, as fully to all intents and purposes as he or she might or could do in person, hereby ratifying and confirming all that said attorneys-in-fact and agents, or any of them, or their or his or her substitutes or substitute, may lawfully do or cause to be done by virtue hereof.

Pursuant to the requirements of the Securities Act of 1933, this Registration Statement has been signed by the following persons in the capacities and on the dates indicated.

SIGNATURE - - - - -	TITLE -----	DATE ----
/s/ STANLEY T. CROOKE ----- Stanley T. Crooke	Chairman of the Board and Chief Executive Officer (Principal Executive Officer)	May 22, 1998
/s/ B. LYNNE PARSHALL ----- B. Lynne Parshall	Executive Vice President, Chief Financial Officer and Secretary (Principal Financial and Accounting Officer)	May 22, 1998
/s/ DANIEL L. KISNER ----- Daniel L. Kisner	President, Chief Operating Officer and Director	May 22, 1998

/s/ CHRISTOPHER F.O. GABRIELI ----- Christopher F.O. Gabrieli	Director	May 22, 1998
/s/ BURKHART BLANK ----- Burkhart Blank	Director	May 22, 1998
/s/ ALAN C. MENDELSON ----- Alan C. Mendelson	Director	May 22, 1998
/s/ WILLIAM R. MILLER ----- William R. Miller	Director	May 22, 1998
/s/ MARK B. SKALETSKY ----- Mark B. Skaletsky	Director	May 22, 1998
/s/ LARRY SOLL ----- Larry Soll	Director	May 22, 1998
----- Joseph H. Wender	Director	May 22, 1998

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\* Filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 1997, and incorporated herein by reference.

May 27, 1998

ISIS PHARMACEUTICALS, INC.  
2292 Faraday Avenue  
Carlsbad, CA 92008

Ladies and Gentlemen:

You have requested our opinion with respect to certain matters in connection with the filing by Isis Pharmaceuticals, Inc. (the "Company") of a Registration Statement on Form S-8 (the "Registration Statement") with the Securities and Exchange Commission covering the offering of up to 2,000,000 shares of the Company's Common Stock, \$.001 par value pursuant to its 1989 Stock Option Plan (the "Option Plan") (the "Shares").

In connection with this opinion, we have examined the Registration Statement and related Prospectus, your Certificate of Incorporation and By-laws, as amended, and such other documents, records, certificates, memoranda and other instruments as we deem necessary as a basis for this opinion. We have assumed the genuineness and authenticity of all documents submitted to us as originals, the conformity to originals of all documents submitted to us as copies thereof, and the due execution and delivery of all documents where due execution and delivery are a prerequisite to the effectiveness thereof.

On the basis of the foregoing, and in reliance thereon, we are of the opinion that the Shares, when sold and issued in accordance with the Option Plan, the Registration Statement and related Prospectus, will be validly issued, fully paid, and nonassessable.

We consent to the filing of this opinion as an exhibit to the Registration Statement.

Very truly yours,

Cooley Godward LLP

By: /s/ L. KAY CHANDLER

-----  
L. Kay Chandler

## CONSENT OF ERNST &amp; YOUNG LLP, INDEPENDENT AUDITORS

We consent to the incorporation by reference in the Registration Statement (Form S-8) pertaining to the 1989 Stock Option Plan of Isis Pharmaceuticals, Inc. for the registration of 2,000,000 shares of common stock of our report dated January 23, 1998, except for the first and last paragraphs of Note 4, as to which the date is February 27, 1998, with respect to the financial statements of Isis Pharmaceuticals, Inc. included in its Annual Report (Form 10-K) for the year ended December 31, 1997, filed with the Securities and Exchange Commission.

ERNST &amp; YOUNG LLP

San Diego, California  
May 26, 1998