
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 of Incorporation)

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

2292 Faraday Avenue
Carlsbad, CA 92008
(Address of principal executive offices)

2000 BROAD BASED EQUITY INCENTIVE PLAN
(Full title of the plans)

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:
Julie M. Robinson, Esq.
COOLEY GODWARD LLP
4365 Executive Drive
San Diego, CA 92121
(858) 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
Common Stock, par value \$.001 per share	2,000,000 shares	\$6.81-13.56	\$13,620,000	\$3,405.00

(1) Estimated solely for the purpose of calculating the amount of the registration fee pursuant to Rule 457(h)(1) of the Securities Act of 1933, as amended (the "Securities Act"). The price per share and the aggregate offering price are calculated on the basis of (a) the weighted average of \$6.81 to \$13.56, the exercise price for 341,930 shares subject to outstanding options granted under the 2000 Broad Based Equity Incentive Plan (the "Equity Plan") and (b) \$9.30, the average of the high and low sales prices of Registrant's Common Stock on April 16, 2001, as reported on the NASDAQ National Market for the remainder of the shares subject to the Equity Plan registered hereunder.

The following documents filed by **ISIS PHARMACEUTICALS, INC.** ("ISIS" or the "Company") with the Securities and Exchange Commission are incorporated by reference into this Registration Statement:

(a) The Company's latest annual report on Form 10-K filed pursuant to Section 13(a) of the Securities Exchange Act of 1934, as amended (the "Exchange Act").

(b) All other reports filed pursuant to Sections 13(a) or 15(d) of the Exchange Act since the end of the fiscal year covered by the annual reports referred to in (a) above.

(c) The description of the Company's Common Stock which is contained in a registration statement filed under the Exchange Act, including any amendment or report filed for the purpose of updating such description.

All reports and other documents subsequently filed by the Company pursuant to Sections 13(a), 13(c), 14 and 15(d) of the Exchange Act prior to the filing of a post-effective amendment which indicates that all securities offered have been sold or which deregisters all securities then remaining unsold, shall be deemed to be incorporated by reference herein and to be a part of this registration statement from the date of the filing of such reports and documents.

DESCRIPTION OF SECURITIES

Not applicable.

INTERESTS OF NAMED EXPERTS AND COUNSEL

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 is the beneficial owner of options to purchase 88,200 shares of Isis common stock. As of June 19, 2001, Mr. Bryce will be vested as to options to purchase 41,605 shares of Isis common stock.

2

INDEMNIFICATION OF DIRECTORS AND OFFICERS

Under Section 145 of the Delaware General Corporation Law, the Company has broad powers to indemnify its directors and officers against liabilities they may incur in such capacities, including liabilities under the Securities Act of 1933.

The Company' certificate of incorporation and by-laws include provisions to (i) eliminate the personal liability of its directors for monetary damages resulting from breaches of their fiduciary duty to the extent permitted by Section 102(b)(7) of the General Corporation Law of Delaware and (ii) require the Company to indemnify its directors and officers to the fullest extent permitted by Section 145 of the Delaware Law, including circumstances in which indemnification is otherwise discretionary. Pursuant to Section 145 of the Delaware Law, a corporation generally has the power to indemnify its present and former directors, officers, employees and agents against expenses incurred by them in connection with any suit to which they are, or are threatened to be made, a party by reason of their serving in such positions so long as they acted in good faith and in a manner they reasonably believed to be in, or not opposed to, the best interest of the corporation, and with respect to any criminal action, they had no reasonable cause to believe their conduct was unlawful. The Company believes that these provisions are necessary to attract and retain qualified persons as directors and officers. These provisions do not eliminate the directors' duty of care, and, in appropriate circumstances, equitable remedies such as injunctive or other forms of non-monetary relief will remain available under Delaware law. In addition, each director will continue to be subject to liability for breach of the directors' duty of loyalty to the Company, for acts or omissions not in good faith or involving intentional misconduct, for knowing violations of law, for acts or omissions that the director believes to be contrary to the best interests of the Company or its stockholders, for any transaction from which the director derived an improper personal benefit, for acts or omissions involving a reckless disregard for the directors' duty to Isis or its stockholders when the director was aware or should have been aware of a risk of serious injury to the Company or its stockholders, for acts or omissions that constitute an unexcused pattern of inattention that amounts to an abdication of the director's duty to the Company or its stockholders, for improper transactions between the director and the Company and for improper distributions to stockholders and loans to directors and officers. The provision also does not affect a director's responsibilities under any other law, such as the federal securities law or state or federal environmental laws.

The Company has entered into indemnity agreements with each of its directors and executive officers that require the Company to indemnify such persons against expenses, judgments, fines, settlements and other amounts incurred (including expenses of a derivative action) in connection with any proceeding, whether actual or threatened, to which any such person may be made a party by reason of the fact that such person is or was a director or an executive officer of the Company or any of its affiliated enterprises, provided such person acted in good faith and in a manner such persons reasonably believed to be in, or not opposed to, the best interests of the Company and, with respect to any criminal proceeding, has no reasonable cause to believe his conduct was unlawful. The indemnification agreements also set forth procedures that will apply in the event of a claim for indemnification thereunder.

The Company has an insurance policy covering the officers and directors of the Company with respect to certain liabilities, including liabilities arising under the Securities Act or otherwise.

3

UNDERTAKINGS

1. The undersigned registrant hereby undertakes:

(a) To file, during any period in which offers or sales are being made, a post-effective amendment to this registration statement:

(i) To include any prospectus required by section 10(a)(3) of the Securities Act;

(ii) To reflect in the prospectus any facts or events arising after the effective date of the registration statement (or the most recent post-effective amendment thereof) which, individually or in the aggregate, represent a fundamental change in the information set forth in the registration statement. Notwithstanding the foregoing, any increase or decrease in volume of securities offered (if the total dollar value of securities offered would not exceed that which was registered) and any deviation from the low or high end of the estimated maximum offering range may be reflected in the form of prospectus filed with the Commission pursuant to Rule 424(b) (§ 230.424(b) of this chapter) if, in the aggregate, the changes in volume and price represent no more than a 20% change in the maximum aggregate offering price set forth in the "Calculation of Registration Fee" table in the effective registration statement.

(iii) To include any material information with respect to the plan of distribution not previously disclosed in the registration statement or any material change to such information in the registration statement;

Provided, however, that paragraphs (a)(i) and (a)(ii) do not apply if the information required to be included in a post-effective amendment by those paragraphs is contained in periodic reports filed by the issuer pursuant to section 13 or section 15(d) of the Exchange Act that are incorporated by reference herein.

(b) That, for the purpose of determining any liability under the Securities Act, each such post-effective amendment shall be deemed to be a new registration statement relating to the securities offered herein, and the offering of such securities at that time shall be deemed to be the initial bona fide offering thereof.

(c) To remove from registration by means of a post-effective amendment any of the securities being registered which remain unsold at the termination of the offering.

2.

The undersigned registrant hereby undertakes that, for purposes of determining any liability under the Securities Act, each filing of the registrant's annual report pursuant to Section 13(a) or Section 15(d) of the Exchange Act (and, where applicable, each filing of an employee benefit plan's annual report pursuant to section 15(d) of the Exchange Act) that is incorporated by reference in the Registration Statement shall be deemed to be a new registration statement relating to the securities offered herein, and the offering of such securities at that time shall be deemed to be the initial bona fide offering thereof.

3.

Insofar as indemnification for liabilities arising under the Securities Act may be permitted to directors, officers and controlling persons of the registrant pursuant to the foregoing provisions, or otherwise, the registrant has been advised that in the opinion of the Securities and Exchange Commission such indemnification is against public policy as expressed in the Securities Act and is, therefore, unenforceable. In the event that a claim for indemnification against such liabilities (other than the payment by the registrant of expenses incurred or paid by a director, officer or controlling person of the registrant in the successful defense of any action, suit or proceeding) is asserted by such director, officer or controlling person in connection with the securities being registered, the registrant will, unless in the opinion of its counsel the matter has been settled by controlling precedent, submit to a court of appropriate jurisdiction the question whether such indemnification by it is against public policy as expressed in the Securities Act and will be governed by the final adjudication of such issue.

4

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 April 20, 2001.

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. Croke and B. Lynne Parshall, and each or any one of them, his true and lawful attorney-in-fact and agent, with full power of substitution and resubstitution, for him and in his 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 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 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

Chairman of the Board, Chief Executive Officer
and President
(Principal Executive Officer)

April 20, 2001

Stanley T. Croke, M.D., Ph.D.

/s/ B. LYNNE PARSHALL

Executive Vice President and Chief Financial
Officer Principal Financial and Accounting
Officer

April 20, 2001

B. Lynne Parshall

/s/ FREDERICK T. MUTO

Frederick T. Muto

Director

April 20, 2001

5

/s/ CHRISTOPHER F. O. GABRIELI

Christopher F. O. Gabrieli

Director

April 20, 2001

/s/ WILLIAM R. MILLER

William R. Miller

Director

April 20, 2001

Director

April , 2001

Mark B. Skaletsky

/s/ JOSEPH H. WENDER

Joseph H. Wender

Director

April 20, 2001

6

EXHIBITS

Exhibit Number

Description

- | Exhibit Number | Description |
|----------------|--|
| 5.1 | Opinion of Grantland E. Bryce |
| 23.1 | Consent of Ernst & Young LLP, Independent Auditors |
| 23.2 | Consent of Grantland E. Bryce is contained in Exhibit 5.1 to this Registration Statement |
| 24 | Power of Attorney is contained on the signature pages. |
| 99.1 | 2000 Broad Based Equity Incentive Plan |

7

QuickLinks

[INCORPORATION OF CERTAIN DOCUMENTS BY REFERENCE](#)

[DESCRIPTION OF SECURITIES](#)

[INTERESTS OF NAMED EXPERTS AND COUNSEL](#)

[INDEMNIFICATION OF DIRECTORS AND OFFICERS](#)

[UNDERTAKINGS](#)

[SIGNATURES](#)

[POWER OF ATTORNEY](#)

[EXHIBITS](#)

April 16, 2001

Isis Pharmaceuticals, Inc.
2292 Faraday Avenue
Carlsbad, CA 92008

Ladies and Gentlemen:

You have requested my 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 an aggregate of 2,000,000 shares of the Company's Common Stock, \$.001 par value (the "Shares"), issuable pursuant to its 2000 Broad Based Equity Incentive Plan (the "Equity Plan") as described in the Registration Statement.

In connection with this opinion, I have examined and relied upon the Registration Statement, the Company's Amended and Restated Certificate of Incorporation and Bylaws and the originals or copies certified to my satisfaction, of such records, documents, certificates, memoranda and other instruments as in my judgment are necessary or appropriate to enable me to render the opinion expressed below.

On the basis of the foregoing, and in reliance thereon, I am of the opinion that the Shares, when issued and sold in accordance with the Equity Plan, the Registration Statement and related prospectus, will be validly issued, fully paid and nonassessable.

I consent to the reference to myself under the caption "Interests of Named Experts and Counsel" in the Registration Statement and to the filing of this opinion as an exhibit to the Registration Statement.

Very truly yours,

/s/ Grantland E. Bryce

Grantland E. Bryce
Vice President, General Counsel

CONSENT OF ERNST & YOUNG LLP, INDEPENDENT AUDITORS

We consent to the incorporation by reference in the Registration Statement (Form S-8) pertaining to the 2000 Broad Based Equity Incentive Plan of ISIS Pharmaceuticals, Inc. of our report dated February 2, 2001, with respect to the financial statements of ISIS Pharmaceuticals, Inc., included in its Annual Report (form 10-K) for the year ended December 31, 2000, filed with the Securities and Exchange Commission.

/s/ ERNST & YOUNG, LLP

San Diego, California
April 16, 2001

Isis Pharmaceuticals, Inc. 2000 Broad-Based Equity Incentive Plan

Adopted January 6, 2000
Amended December 8, 2000

TABLE OF CONTENTS

	<u>Page</u>
1. Purposes	1
2. Definitions	1
3. Administration	3
4. Shares Subject to the Plan	4
5. Eligibility	4
6. Option Provisions	5
7. Provisions of Stock Awards other than Options	7
8. Covenants of the Company	8
9. Use of Proceeds from Stock	9
10. Miscellaneous	9
11. Adjustments upon Changes in Stock	10
12. Amendment of the Plan and Stock Awards	10
13. Termination or Suspension of the Plan	11
14. Effective Date of Plan	11
15. Choice of Law	11

Isis Pharmaceuticals, Inc.
2000 Broad-Based Equity Incentive Plan
Adopted January 6, 2000

1. Purposes.

(a) **Eligible Stock Award Recipients.** The persons eligible to receive Stock Awards are the Employees, Directors and Consultants of the Company and its Affiliates.

(b) **Available Stock Awards.** The purpose of the Plan is to provide a means by which eligible recipients of Stock Awards may be given an opportunity to benefit from increases in value of the Common Stock through the granting of the following Stock Awards: (i) Supplemental Stock Options, (ii) stock bonuses and (iii) rights to acquire restricted stock.

(c) **General Purpose.** The Company, by means of the Plan, seeks to retain the services of the group of persons eligible to receive Stock Awards, to secure and retain the services of new members of this group and to provide incentives for such persons to exert maximum efforts for the success of the Company and its Affiliates.

2. Definitions.

(a) "**Affiliate**" means any parent corporation or subsidiary corporation of the Company, whether now or hereafter existing, as those terms are defined in Sections 424(e) and (f), respectively, of the Code.

(b) "**Board**" means the Board of Directors of the Company.

(c) "**Code**" means the Internal Revenue Code of 1986, as amended.

(d) "**Committee**" means a committee of one or more members of the Board appointed by the Board in accordance with subsection 3(c).

(e) "**Common Stock**" means the common stock of the Company.

(f) "**Company**" means Isis Pharmaceuticals, Inc., a Delaware corporation.

(g) "**Consultant**" means any person, including an advisor, (i) engaged by the Company or an Affiliate to render consulting or advisory services and who is compensated for such services or (ii) who is a member of the Board of Directors of an Affiliate. However, the term "Consultant" shall not include either Directors who are not compensated by the Company for their services as Directors or Directors who are merely paid a director's fee by the Company for their services as Directors.

(h) "**Continuous Service**" means that the Participant's service with the Company or an Affiliate, whether as an Employee, Director or Consultant, is not interrupted or terminated. The Participant's Continuous Service shall not be deemed to have terminated merely because of a change in the capacity in which the Participant renders service to the Company or an Affiliate as an Employee, Consultant or Director or a change in the entity for which the Participant renders such service, provided that there is no interruption or termination of the Participant's Continuous Service. For example, a change in status from an Employee of the Company to a Consultant of an Affiliate or a Director will not constitute an interruption of Continuous Service. The Board or the chief executive officer of the Company, in that party's sole discretion, may determine whether Continuous Service shall be considered interrupted in the case of any leave of absence approved by that party, including sick leave, military leave or any other personal leave.

1

(i) "**Covered Employee**" means the chief executive officer and the four (4) other highest compensated officers of the Company for whom total compensation is required to be reported to shareholders under the Exchange Act, as determined for purposes of Section 162(m) of the Code.

(j) "**Director**" means a member of the Board of Directors of the Company.

(k) "**Disability**" means the permanent and total disability of a person within the meaning of Section 22(e)(3) of the Code.

(l) "**Employee**" means any person employed by the Company or an Affiliate. Mere service as a Director or payment of a director's fee by the Company or an Affiliate shall not be sufficient to constitute "employment" by the Company or an Affiliate.

(m) "**Exchange Act**" means the Securities Exchange Act of 1934, as amended.

(n) "**Fair Market Value**" means, as of any date, the value of the Common Stock determined as follows:

(i) If the Common Stock is listed on any established stock exchange or traded on the Nasdaq National Market or the Nasdaq SmallCap Market, the Fair Market Value of a share of Common Stock shall be the closing sales price for such stock (or the closing bid, if no sales were reported) as quoted on such exchange or market (or the exchange or market with the greatest volume of trading in the Common Stock) on the date of grant, or if the date of grant is not a market trading day, then the last market trading day prior to the date of grant, as reported in *The Wall Street Journal* or such other source as the Board deems reliable.

(ii) In the absence of such markets for the Common Stock, the Fair Market Value shall be determined in good faith by the Board.

(o) "**Non-Employee Director**" means a Director who either (i) is not a current Employee or Officer of the Company or its parent or a subsidiary, does not receive compensation (directly or indirectly) from the Company or its parent or a subsidiary for services rendered as a consultant or in any capacity other than as a Director (except for an amount as to which disclosure would not be required under Item 404(a) of Regulation S-K promulgated pursuant to the Securities Act ("Regulation S-K")), does not possess an interest in any other transaction as to which disclosure would be required under Item 404(a) of Regulation S-K and is not engaged in a business relationship as to which disclosure would be required under Item 404(b) of Regulation S-K; or (ii) is otherwise considered a "non-employee director" for purposes of Rule 16b-3.

(p) "**Officer**" means a person who possesses the authority of an "officer" as that term is used in Rule 4460(i)(1)(A) of the Rules of the National Association of Securities Dealers, Inc. For purposes of the Plan, a person in the position of "Vice President" or higher shall be classified as an "Officer" unless the Board or Committee expressly finds that such person does not possess the authority of an "officer" as that term is used in Rule 4460(i)(1)(A) of the Rules of the National Association of Securities Dealers, Inc.

(q) "**Option**" means a Supplemental Stock Option granted pursuant to the Plan.

(r) "**Optionholder**" means a person to whom an Option is granted pursuant to the Plan or, if applicable, such other person who holds an outstanding Option.

(s) "**Outside Director**" means a Director who either (i) is not a current employee of the Company or an "affiliated corporation" (within the meaning of Treasury Regulations promulgated under Section 162(m) of the Code), is not a former employee of the Company or an "affiliated corporation" receiving compensation for prior services (other than benefits under a tax qualified pension plan), was not an officer of the Company or an "affiliated corporation" at any time and is not currently receiving direct or indirect remuneration from the Company or an "affiliated corporation" for services in any

2

capacity other than as a Director or (ii) is otherwise considered an "outside director" for purposes of Section 162(m) of the Code.

(t) "**Participant**" means a person to whom a Stock Award is granted pursuant to the Plan or, if applicable, such other person who holds an outstanding Stock Award.

(u) "**Plan**" means this Isis Pharmaceuticals, Inc. 2000 Broad-Based Equity Incentive Plan.

(v) "**Rule 16b-3**" means Rule 16b-3 promulgated under the Exchange Act or any successor to Rule 16b-3, as in effect from time to time.

(w) "**Securities Act**" means the Securities Act of 1933, as amended.

(x) "**Stock Award**" means any right granted under the Plan, including an Option, a stock bonus and a right to acquire restricted stock.

(y) "**Stock Award Agreement**" means a written agreement between the Company and a holder of a Stock Award evidencing the terms and conditions of an individual Stock Award grant. Each Stock Award Agreement shall be subject to the terms and conditions of the Plan.

(z) "**Supplemental Stock Option**" means an Option not intended to qualify as an "incentive stock option" within the meaning of Section 422 of the Code and the regulations promulgated thereunder.

(aa) "**Ten Percent Shareholder**" means a person who owns (or is deemed to own pursuant to Section 424(d) of the Code) stock possessing more than ten percent (10%) of the total combined voting power of all classes of stock of the Company or of any of its Affiliates.

(bb) "**Terms of Supplemental Stock Option**" means a written agreement between the Company and an Optionholder evidencing the terms and conditions of an individual Option grant. Each Terms of Supplemental Stock Option shall be subject to the terms and conditions of the Plan.

3. Administration.

(a) **Administration by Board.** The Board shall administer the Plan unless and until the Board delegates administration to a Committee, as provided in subsection 3(c).

(b) **Powers of Board.** The Board shall have the power, subject to, and within the limitations of, the express provisions of the Plan:

(i) To determine from time to time which of the persons eligible under the Plan shall be granted Stock Awards; when and how each Stock Award shall be granted; what type or combination of types of Stock Award shall be granted; the provisions of each Stock Award granted (which need not be identical), including the time or times when a person shall be permitted to receive Common Stock pursuant to a Stock Award; and the number of shares of Common Stock with respect to which a Stock Award shall be granted to each such person.

(ii) To construe and interpret the Plan and Stock Awards granted under it, and to establish, amend and revoke rules and regulations for its administration. The Board, in the exercise of this power, may correct any defect, omission or inconsistency in the Plan or in any Stock Award Agreement, in a manner and to the extent it shall deem necessary or expedient to make the Plan fully effective.

(iii) To amend the Plan or a Stock Award as provided in Section 12.

(iv) Generally, to exercise such powers and to perform such acts as the Board deems necessary or expedient to promote the best interests of the Company which are not in conflict with the provisions of the Plan.

3

(c) Delegation to Committee.

(i) **General.** The Board may delegate administration of the Plan to a Committee or Committees of one (1) or more members of the Board, and the term "Committee" shall apply to any person or persons to whom such authority has been delegated. If administration is delegated to a Committee, the Committee shall have, in connection with the administration of the Plan, the powers theretofore possessed by the Board, including the power to delegate to a subcommittee any of the administrative powers the Committee is authorized to exercise (and references in this Plan to the Board shall thereafter be to the Committee or subcommittee), subject, however, to such resolutions, not inconsistent with the provisions of the Plan, as may be adopted from time to time by the Board. The Board may abolish the Committee at any time and revert to the Board the administration of the Plan.

(ii) **Committee Composition when Common Stock is Publicly Traded.** At such time as the Common Stock is publicly traded, in the discretion of the Board, a Committee may consist solely of two or more Outside Directors, in accordance with Section 162(m) of the Code, and/or solely of two or more Non-Employee Directors, in accordance with Rule 16b-3. Within the scope of such authority, the Board or the Committee may (1) delegate to a committee of one or more members of the Board who are not Outside Directors the authority to grant Stock Awards to eligible persons who are either (a) not then Covered Employees and are not expected to be Covered Employees at the time of recognition of income resulting from such Stock Award or (b) not persons with respect to whom the Company wishes to comply with Section 162(m) of the Code and/or (2) delegate to a committee of one or more members of the Board who are not Non-Employee Directors the authority to grant Stock Awards to eligible persons who are not then subject to Section 16 of the Exchange Act.

(d) **Effect of Board's Decision.** All determinations, interpretations and constructions made by the Board in good faith shall not be subject to review by any person and shall be final, binding and conclusive on all persons.

4. Shares Subject to the Plan.

(a) **Share Reserve.** Subject to the provisions of Section 11 relating to adjustments upon changes in Common Stock, the Common Stock that may be issued pursuant to Stock Awards shall not exceed in the aggregate 3,990,000 shares of Common Stock.

(b) **Reversion of Shares to the Share Reserve.** If any Stock Award shall for any reason expire or otherwise terminate, in whole or in part, without having been exercised in full, the shares of Common Stock not acquired under such Stock Award shall revert to and again become available for issuance under the Plan.

(c) **Source of Shares.** The shares of Common Stock subject to the Plan may be unissued shares or reacquired shares, bought on the market or otherwise.

5. Eligibility.

(a) **Eligibility for Specific Stock Awards.** Stock Awards may be granted to Employees, Directors and Consultants.

(b) **Restrictions on Eligibility.** Notwithstanding the foregoing, the aggregate number of shares issued pursuant to Stock Awards granted to Officers and Directors cannot exceed forty percent (40%) of the number of shares reserved for issuance under the Plan as determined at the time of each such issuance to an Officer or Director, except that there shall be excluded from this calculation shares issued to Officers not previously employed by the Company pursuant to Stock Awards granted as an inducement essential to such individuals entering into employment contracts with the Company.

4

(c) **Consultants.**

(i) A Consultant shall not be eligible for the grant of a Stock Award if, at the time of grant, a Form S-8 Registration Statement under the Securities Act ("Form S-8") is not available to register either the offer or the sale of the Company's securities to such Consultant because of the nature of the services that the Consultant is providing to the Company, or because the Consultant is not a natural person, or as otherwise provided by the rules governing the use of Form S-8, unless the Company determines both (i) that such grant (A) shall be registered in another manner under the Securities Act (*e.g.*, on a Form S-3 Registration Statement) or (B) does not require registration under the Securities Act in order to comply with the requirements of the Securities Act, if applicable, and (ii) that such grant complies with the securities laws of all other relevant jurisdictions.

(ii) Form S-8 generally is available to consultants and advisors only if (i) they are natural persons; (ii) they provide bona fide services to the issuer, its parents, its majority-owned subsidiaries or majority-owned subsidiaries of the issuer's parent; and (iii) the services are not in connection with the offer or sale of securities in a capital-raising transaction, and do not directly or indirectly promote or maintain a market for the issuer's securities.

6. Option Provisions.

Each Option shall be in such form and shall contain such terms and conditions as the Board shall deem appropriate. The provisions of separate Options need not be identical, but each Option shall include (through incorporation of provisions hereof by reference in the Option or otherwise) the substance of each of the following provisions:

(a) **Term.** The term of an Option shall be the term determined by the Board, either at the time of grant of the Option or as the Option may be amended thereafter.

(b) **Consideration.** The purchase price of Common Stock acquired pursuant to an Option shall be paid, to the extent permitted by applicable statutes and regulations, either (i) in cash at the time the Option is exercised or (ii) at the discretion of the Board at the time of the grant of the Option (or subsequently in the case of a Supplemental Stock Option) (1) by delivery to the Company of other Common Stock, (2) according to a deferred payment or other similar arrangement with the Optionholder or (3) in any other form of legal consideration that may be acceptable to the Board. Unless otherwise specifically provided in the Option, the purchase price of Common Stock acquired pursuant to an Option that is paid by delivery to the Company of other Common Stock acquired, directly or indirectly from the Company, shall be paid only by shares of the Common Stock of the Company that have been held for more than six (6) months (or such longer or shorter period of time required to avoid a charge to earnings for financial accounting purposes). At any time that the Company is incorporated in Delaware, payment of the Common Stock's "par value," as defined in the Delaware General Corporation Law, shall not be made by deferred payment.

In the case of any deferred payment arrangement, interest shall be compounded at least annually and shall be charged at the minimum rate of interest necessary to avoid the treatment as interest, under any applicable provisions of the Code, of any amounts other than amounts stated to be interest under the deferred payment arrangement.

(c) **Transferability of a Supplemental Stock Option.** A Supplemental Stock Option shall be transferable to the extent provided in the Terms of Supplemental Stock Option. If the Supplemental Stock Option does not provide for transferability, then the Supplemental Stock Option shall not be transferable except by will or by the laws of descent and distribution and shall be exercisable during the lifetime of the Optionholder only by the Optionholder. Notwithstanding the foregoing, the Optionholder may, by delivering written notice to the Company, in a form satisfactory to the Company,

5

designate a third party who, in the event of the death of the Optionholder, shall thereafter be entitled to exercise the Option.

(d) **Vesting Generally.** The total number of shares of Common Stock subject to an Option may, but need not, vest and therefore become exercisable in periodic installments that may, but need not, be equal. The Option may be subject to such other terms and conditions on the time or times when it may be exercised (which may be based on performance or other criteria) as the Board may deem appropriate. The vesting provisions of individual Options may vary. The provisions of this subsection 6(e) are subject to any Option provisions governing the minimum number of shares of Common Stock as to which an Option may be exercised.

(e) **Termination of Continuous Service.** In the event an Optionholder's Continuous Service terminates (other than upon the Optionholder's death or Disability), the Optionholder may exercise his or her Option (to the extent that the Optionholder was entitled to exercise such Option as of the date of termination) but only within such period of time ending on the earlier of (i) the date three (3) months following the termination of the Optionholder's Continuous Service (or such longer or shorter period specified in the Terms of Supplemental Stock Option), or (ii) the expiration of the term of the Option as set forth in the Terms of Supplemental Stock Option. If, after termination, the Optionholder does not exercise his or her Option within the time specified in the Terms of Supplemental Stock Option, the Option shall terminate.

(f) **Extension of Termination Date.** An Optionholder's Terms of Supplemental Stock Option may also provide that if the exercise of the Option following the termination of the Optionholder's Continuous Service (other than upon the Optionholder's death or Disability) would be prohibited at any time solely because the issuance of shares of Common Stock would violate the registration requirements under the Securities Act, then the Option shall terminate on the earlier of (i) the expiration of the term of the Option set forth in the Terms of Supplemental Stock Option, or (ii) the expiration of a period of three (3) months after the termination of the Optionholder's Continuous Service during which the exercise of the Option would not be in violation of such registration requirements.

(g) **Disability of Optionholder.** In the event that an Optionholder's Continuous Service terminates as a result of the Optionholder's Disability, the Optionholder may exercise his or her Option (to the extent that the Optionholder was entitled to exercise such Option as of the date of termination), but only within such period of time ending on the earlier of (i) the date twelve (12) months following such termination (or such longer or shorter period specified in the Terms of Supplemental Stock Option) or (ii) the expiration of the term of the Option as set forth in the Terms of Supplemental Stock Option. If, after termination, the Optionholder does not exercise his or her Option within the time specified herein, the Option shall terminate.

(h) **Death of Optionholder.** In the event (i) an Optionholder's Continuous Service terminates as a result of the Optionholder's death or (ii) the Optionholder dies within the period (if any) specified in the Terms of Supplemental Stock Option after the termination of the Optionholder's Continuous Service for a reason other than death, then the Option may be exercised (to the extent the Optionholder was entitled to exercise such Option as of the date of death) by the Optionholder's estate, by a person who acquired the right to exercise the Option by bequest or inheritance or by a person designated to exercise the Option upon the Optionholder's death pursuant to subsection 6(d), but only within the period ending on the earlier of (1) the date eighteen (18) months following the date of death (or such longer or shorter period specified in the Terms of Supplemental Stock Option) or (2) the expiration of the term of such Option as set forth in the Terms of Supplemental Stock Option. If, after death, the Option is not exercised within the time specified herein, the Option shall terminate.

6

(i) **Early Exercise.** The Option may, but need not, include a provision whereby the Optionholder may elect at any time before the Optionholder's Continuous Service terminates to exercise the Option as to any part or all of the shares of Common Stock subject to the Option prior to the full vesting of the Option. Any unvested shares of Common Stock so purchased may be subject to a repurchase option in favor of the Company or to any other restriction the Board determines to be appropriate. The Company will not exercise its repurchase option until at least six (6) months (or such longer or shorter period of time required to avoid a charge to earnings for financial accounting purposes) have elapsed following exercise of the Option unless the Board otherwise specifically provides in the Option.

(j) **Re-Load Options.**

(i) Without in any way limiting the authority of the Board to make or not to make grants of Options hereunder, the Board shall have the authority (but not an obligation) to include as part of any Terms of Supplemental Stock Option a provision entitling the Optionholder to a further Option (a "Re-Load Option") in the event the Optionholder exercises the Option evidenced by the Terms of Supplemental Stock Option, in whole or in part, by surrendering other shares of Common Stock in accordance with this Plan and the terms and conditions of the Terms of Supplemental Stock Option. Unless otherwise specifically provided in the Option, the Optionholder shall not surrender shares of Common Stock acquired, directly or indirectly from the Company, unless such shares have been held for more than six (6) months (or such longer or shorter period of time required to avoid a charge to earnings for financial accounting purposes).

(ii) Any such Re-Load Option shall (1) provide for a number of shares of Common Stock equal to the number of shares of Common Stock surrendered as part or all of the exercise price of such Option; (2) have an expiration date which is the same as the expiration date of the Option the exercise of which gave rise to such Re-Load Option; and (3) have an exercise price which is equal to one hundred percent (100%) of the Fair Market Value of the Common Stock subject to the Re-Load Option on the date of exercise of the original Option. Notwithstanding the foregoing, a Re-Load Option shall be subject to the same exercise price and term provisions heretofore described for Options under the Plan.

(iii) There shall be no Re-Load Options on a Re-Load Option. Any such Re-Load Option shall be subject to the availability of sufficient shares of Common Stock under subsection 4(a) and shall be subject to such other terms and conditions as the Board may determine which are not inconsistent with the express provisions of the Plan regarding the terms of Options.

7. Provisions of Stock Awards other than Options.

(a) **Stock Bonus Awards.** Each stock bonus agreement shall be in such form and shall contain such terms and conditions as the Board shall deem appropriate. The terms and conditions of stock bonus agreements may change from time to time, and the terms and conditions of separate stock bonus agreements need not be identical, but each stock bonus agreement shall include (through incorporation of provisions hereof by reference in the agreement or otherwise) the substance of each of the following provisions:

(i) **Consideration.** A stock bonus may be awarded in consideration for past services actually rendered to the Company or an Affiliate for its benefit.

(ii) **Vesting.** Shares of Common Stock awarded under the stock bonus agreement may, but need not, be subject to a share repurchase option in favor of the Company in accordance with a vesting schedule to be determined by the Board.

(iii) **Termination of Participant's Continuous Service.** In the event a Participant's Continuous Service terminates, the Company may reacquire any or all of the shares of Common Stock held by

7

the Participant which have not vested as of the date of termination under the terms of the stock bonus agreement.

(iv) **Transferability.** Rights to acquire shares of Common Stock under the stock bonus agreement shall be transferable by the Participant only upon such terms and conditions as are set forth in the stock bonus agreement, as the Board shall determine in its discretion, so long as Common Stock awarded under the stock bonus agreement remains subject to the terms of the stock bonus agreement.

(b) **Restricted Stock Awards.** Each restricted stock purchase agreement shall be in such form and shall contain such terms and conditions as the Board shall deem appropriate. The terms and conditions of the restricted stock purchase agreements may change from time to time, and the terms and conditions of separate restricted stock purchase agreements need not be identical, but each restricted stock purchase agreement shall include (through incorporation of provisions hereof by reference in the agreement or otherwise) the substance of each of the following provisions:

(i) **Purchase Price.** The purchase price under each restricted stock purchase agreement shall be such amount as the Board shall determine and designate in such restricted stock purchase agreement. The purchase price shall not be less than eighty-five percent (85%) of the Common Stock's Fair Market Value on the date such award is made or at the time the purchase is consummated.

(ii) **Consideration.** The purchase price of Common Stock acquired pursuant to the restricted stock purchase agreement shall be paid either: (i) in cash at the time of purchase; (ii) at the discretion of the Board, according to a deferred payment or other similar arrangement with the Participant; or (iii) in any other form of legal consideration that may be acceptable to the Board in its discretion; provided, however, that at any time that the Company is

incorporated in Delaware, then payment of the Common Stock's "par value," as defined in the Delaware General Corporation Law, shall not be made by deferred payment.

(iii) **Vesting.** Shares of Common Stock acquired under the restricted stock purchase agreement may, but need not, be subject to a share repurchase option in favor of the Company in accordance with a vesting schedule to be determined by the Board.

(iv) **Termination of Participant's Continuous Service.** In the event a Participant's Continuous Service terminates, the Company may repurchase or otherwise reacquire any or all of the shares of Common Stock held by the Participant which have not vested as of the date of termination under the terms of the restricted stock purchase agreement.

(v) **Transferability.** Rights to acquire shares of Common Stock under the restricted stock purchase agreement shall be transferable by the Participant only upon such terms and conditions as are set forth in the restricted stock purchase agreement, as the Board shall determine in its discretion, so long as Common Stock awarded under the restricted stock purchase agreement remains subject to the terms of the restricted stock purchase agreement.

8. Covenants of the Company.

(a) **Availability of Shares.** During the terms of the Stock Awards, the Company shall keep available at all times the number of shares of Common Stock required to satisfy such Stock Awards.

(b) **Securities Law Compliance.** The Company shall seek to obtain from each regulatory commission or agency having jurisdiction over the Plan such authority as may be required to grant Stock Awards and to issue and sell shares of Common Stock upon exercise of the Stock Awards; provided, however, that this undertaking shall not require the Company to register under the Securities

8

Act the Plan, any Stock Award or any Common Stock issued or issuable pursuant to any such Stock Award. If, after reasonable efforts, the Company is unable to obtain from any such regulatory commission or agency the authority which counsel for the Company deems necessary for the lawful issuance and sale of Common Stock under the Plan, the Company shall be relieved from any liability for failure to issue and sell Common Stock upon exercise of such Stock Awards unless and until such authority is obtained.

9. Use of Proceeds from Stock.

Proceeds from the sale of Common Stock pursuant to Stock Awards shall constitute general funds of the Company.

10. Miscellaneous.

(a) **Acceleration of Exercisability and Vesting.** The Board shall have the power to accelerate the time at which a Stock Award may first be exercised or the time during which a Stock Award or any part thereof will vest in accordance with the Plan, notwithstanding the provisions in the Stock Award stating the time at which it may first be exercised or the time during which it will vest.

(b) **Shareholder Rights.** No Participant shall be deemed to be the holder of, or to have any of the rights of a holder with respect to, any shares of Common Stock subject to such Stock Award unless and until such Participant has satisfied all requirements for exercise of the Stock Award pursuant to its terms.

(c) **No Employment or other Service Rights.** Nothing in the Plan or any instrument executed or Stock Award granted pursuant thereto shall confer upon any Participant any right to continue to serve the Company or an Affiliate in the capacity in effect at the time the Stock Award was granted or shall affect the right of the Company or an Affiliate to terminate (i) the employment of an Employee with or without notice and with or without cause, (ii) the service of a Consultant pursuant to the terms of such Consultant's agreement with the Company or an Affiliate or (iii) the service of a Director pursuant to the Bylaws of the Company or an Affiliate, and any applicable provisions of the corporate law of the state in which the Company or the Affiliate is incorporated, as the case may be.

(d) **Investment Assurances.** The Company may require a Participant, as a condition of exercising or acquiring Common Stock under any Stock Award, (i) to give written assurances satisfactory to the Company as to the Participant's knowledge and experience in financial and business matters and/or to employ a purchaser representative reasonably satisfactory to the Company who is knowledgeable and experienced in financial and business matters and that he or she is capable of evaluating, alone or together with the purchaser representative, the merits and risks of exercising the Stock Award; and (ii) to give written assurances satisfactory to the Company stating that the Participant is acquiring Common Stock subject to the Stock Award for the Participant's own account and not with any present intention of selling or otherwise distributing the Common Stock. The foregoing requirements, and any assurances given pursuant to such requirements, shall be inoperative if (1) the issuance of the shares of Common Stock upon the exercise or acquisition of Common Stock under the Stock Award has been registered under a then currently effective registration statement under the Securities Act or (2) as to any particular requirement, a determination is made by counsel for the Company that such requirement need not be met in the circumstances under the then applicable securities laws. The Company may, upon advice of counsel to the Company, place legends on stock certificates issued under the Plan as such counsel deems necessary or appropriate in order to comply with applicable securities laws, including, but not limited to, legends restricting the transfer of the Common Stock.

(e) **Withholding Obligations.** To the extent provided by the terms of a Stock Award Agreement, the Participant may satisfy any federal, state or local tax withholding obligation relating to the exercise or acquisition of Common Stock under a Stock Award by any of the following means (in addition to

9

the Company's right to withhold from any compensation paid to the Participant by the Company) or by a combination of such means: (i) tendering a cash payment; (ii) authorizing the Company to withhold shares of Common Stock from the shares of Common Stock otherwise issuable to the Participant as a result of the exercise or acquisition of Common Stock under the Stock Award, provided, however, that no shares of Common Stock are withheld with a value exceeding the minimum amount of tax required to be withheld by law; or (iii) delivering to the Company owned and unencumbered shares of Common Stock.

11. Adjustments upon Changes in Stock.

(a) **Capitalization Adjustments.** If any change is made in the Common Stock subject to the Plan, or subject to any Stock Award, without the receipt of consideration by the Company (through merger, consolidation, reorganization, recapitalization, reincorporation, stock dividend, dividend in property other than cash, stock split, liquidating dividend, combination of shares, exchange of shares, change in corporate structure or other transaction not involving the receipt of consideration by the Company), the Plan will be appropriately adjusted in the class(es) and maximum number of securities subject to the Plan pursuant to subsection 4(a), and the outstanding Stock Awards will be appropriately adjusted in the class(es) and number of securities and price per share of Common Stock subject to such outstanding Stock Awards. The Board shall make such adjustments, and its determination shall be final, binding and conclusive. (The conversion of any convertible securities of the Company shall not be treated as a transaction "without receipt of consideration" by the Company.)

(b) **Change in Control—Dissolution or Liquidation.** In the event of a dissolution or liquidation of the Company, then all outstanding Stock Awards shall terminate immediately prior to such event.

(c) **Change in Control—Asset Sale, Merger, Consolidation or Reverse Merger.** In the event of (i) a sale, lease or other disposition of all or substantially all of the assets of the Company, (ii) a merger or consolidation in which the Company is not the surviving corporation or (iii) a reverse merger in which the Company is the surviving corporation but the shares of Common Stock outstanding immediately preceding the merger are converted by virtue of the merger into other property, whether in the form of securities, cash or otherwise, then any surviving corporation or acquiring corporation shall assume any Stock Awards outstanding under the Plan or shall substitute similar stock awards (including an award to acquire the same consideration paid to the shareholders in the transaction described in this subsection 11(c) for those outstanding under the Plan). In the event any surviving corporation or acquiring corporation refuses to assume such Stock Awards or to substitute similar stock awards for those outstanding under the Plan, then with respect to Stock Awards held by Participants whose Continuous Service has not terminated, the vesting of such Stock Awards (and, if applicable, the time during which such Stock Awards may be exercised) shall be accelerated in full, and the Stock Awards shall terminate if not exercised (if applicable) at or prior to such event. With respect to any other Stock Awards outstanding under the Plan, such Stock Awards shall terminate if not exercised (if applicable) prior to such event.

12. Amendment of the Plan and Stock Awards.

(a) **Amendment of Plan.** The Board at any time, and from time to time, may amend the Plan. However, except as provided in Section 11 relating to adjustments upon changes in Common Stock, no amendment shall be effective unless approved by the shareholders of the Company to the extent shareholder approval is necessary to satisfy the requirements of Section 422 of the Code, Rule 16b-3 or any Nasdaq or securities exchange listing requirements.

(b) **Shareholder Approval.** The Board may, in its sole discretion, submit any other amendment to the Plan for shareholder approval, including, but not limited to, amendments to the Plan intended to satisfy the requirements of Section 162(m) of the Code and the regulations thereunder regarding the

10

exclusion of performance-based compensation from the limit on corporate deductibility of compensation paid to certain executive officers.

(c) **Contemplated Amendments.** It is expressly contemplated that the Board may amend the Plan in any respect the Board deems necessary or advisable to provide eligible Employees with the maximum benefits provided or to be provided under the provisions of the Code and the regulations promulgated thereunder and/or to bring the Plan and/or Options into compliance therewith.

(d) **No Impairment of Rights.** Rights under any Stock Award granted before amendment of the Plan shall not be impaired by any amendment of the Plan unless (i) the Company requests the consent of the Participant and (ii) the Participant consents in writing.

(e) **Amendment of Stock Awards.** The Board at any time, and from time to time, may amend the terms of any one or more Stock Awards; provided, however, that the rights under any Stock Award shall not be impaired by any such amendment unless (i) the Company requests the consent of the Participant and (ii) the Participant consents in writing.

13. Termination or Suspension of the Plan.

(a) **Plan Term.** The Board may suspend or terminate the Plan at any time. Unless sooner terminated, the Plan shall terminate on the day before the tenth (10th) anniversary of the date the Plan is adopted by the Board or approved by the shareholders of the Company, whichever is earlier. No Stock Awards may be granted under the Plan while the Plan is suspended or after it is terminated.

(b) **No Impairment of Rights.** Suspension or termination of the Plan shall not impair rights and obligations under any Stock Award granted while the Plan is in effect except with the written consent of the Participant.

14. Effective Date of Plan.

The Plan shall become effective on January 6, 2000.

15. Choice of Law.

The law of the State of Delaware shall govern all questions concerning the construction, validity and interpretation of this Plan, without regard to such state's conflict of laws rules.

11

QuickLinks

[TABLE OF CONTENTS](#)
[Isis Pharmaceuticals, Inc. 2000 Broad-Based Equity Incentive Plan Adopted January 6, 2000](#)