

SECURITIES AND EXCHANGE COMMISSION  
WASHINGTON, D. C. 20549

FORM 8-K/A

CURRENT REPORT  
PURSUANT TO SECTION 13 OR 15(D) OF THE  
SECURITIES EXCHANGE ACT OF 1934

Date of report (Date of earliest event reported): JANUARY 14, 2001

ISIS PHARMACEUTICALS, INC.  
(Exact Name of Registrant as Specified in Charter)

DELAWARE  
(State or Other Jurisdiction of Incorporation)

000-19125  
(Commission File No.)

330336973  
(IRS Employer Identification No.)

2292 FARADAY AVENUE  
CARLSBAD, CA 92008  
(Address of Principal Executive Offices and Zip Code)

Registrant's telephone number, including area code: (760) 931-9200

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EXPLANATORY NOTE

THIS AMENDMENT TO THE FORM 8-K FILED JANUARY 28, 2000, IS BEING FILED SOLELY TO AMEND ITEM 7(c) BY THE ADDITION OF EXHIBIT 10.9.

ITEM 7. FINANCIAL STATEMENTS AND EXHIBITS.

(a) FINANCIAL STATEMENTS OF BUSINESSES ACQUIRED.

NOT APPLICABLE.

(b) PRO FORMA FINANCIAL INFORMATION.

NOT APPLICABLE.

(c) EXHIBITS.

EXHIBIT NO.	DESCRIPTION
10.1*+	Subscription, Joint Development and Operating Agreement, dated January 14, 2000, by and among Registrant, Elan Corporation, plc ("Elan"), Elan International Services, Ltd. ("EIS"), Elan Pharma International Ltd. ("Elan Pharma") and HepaSense, Ltd. ("HepaSense") (with certain confidential information deleted).
10.2*+	Securities Purchase Agreement, dated January 14, 2000, by and between Registrant and EIS.
10.3+	Convertible Promissory Note, dated January 14, 2000, by and between Registrant and EIS.
10.4+	Form of Warrants to Purchase Shares of Common Stock, of contingent date, by and between Registrant and EIS.

- 10.5+ Registration Rights Agreement, dated January 14, 2000, by and between Registrant and EIS.
- 10.6+ Registration Rights Agreement, dated January 14, 2000, by and among Registrant, EIS and HepaSense.
- 10.7\*+ License Agreement, dated January 14, 2000, by and between Elan and HepaSense.
- 10.8\*+ License Agreement, dated January 14, 2000, by and between Registrant and HepaSense.

1.

- 10.9 Certificate of Designation of the Series B Convertible Preferred Stock.

\* Confidential treatment has been requested with respect to certain portions of this exhibit. Omitted portions have been filed separately with the Securities and Exchange Commission.

+ Filed as an exhibit to Registrant's Report on Form 8-K dated January 28, 2000 and incorporated herein by reference.

2.

SIGNATURE

Pursuant to the requirements of the Securities Exchange Act of 1934, as amended, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

ISIS PHARMACEUTICALS, INC.

Dated: October 5, 2001

By: /s/ B. Lynne Parshall

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B. LYNNE PARSHALL  
Executive Vice President,  
Chief Financial Officer and Secretary

3.

CERTIFICATE OF DESIGNATION  
OF THE  
SERIES B CONVERTIBLE PREFERRED STOCK  
(PAR VALUE \$.001 PER SHARE)  
OF  
ISIS PHARMACEUTICALS, INC.

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PURSUANT TO SECTION 151 OF THE  
GENERAL CORPORATION LAW OF THE STATE OF DELAWARE  
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ISIS PHARMACEUTICALS, INC., a company organized and existing under the General Corporation Law of the State of Delaware (the "Company"), in accordance with the provisions of Section 103 thereof, and pursuant to Section 151 thereof, DOES HEREBY CERTIFY:

That the Restated Certificate of Incorporation of the Company (the "Restated Certificate") authorizes the creation of up to 15,000,000 shares of the Company's preferred stock, par value \$.001 per share, 120,150 shares of which have been designated Series A Preferred Stock (the "Series A Preferred Stock") pursuant to the Certificate of Designation of the Series A Convertible Preferred Stock filed with the Secretary of State of Delaware on April 19, 1999 (the "Series A Certificate"); and

That pursuant to the authority conferred upon the Board of Directors (the "Board") by the Restated Certificate, the Board on December 27, 1999, approved the creation, issuance and the voting powers of shares of Series B Preferred Stock to be issued in one series and adopted the following resolution creating a series of 16,620 shares of Series B Preferred Stock designated as set forth below:

RESOLVED, that pursuant to the authority expressly granted to and vested in the Board by provisions of the Restated Certificate of the Company and the General Corporation Law of the State of Delaware, the issuance of a series of Preferred Stock, which shall consist of 16,620 shares of the shares of Preferred Stock which the Company now has authority to issue, be, and the same hereby is, authorized, and the Board hereby fixes the powers, designations, preferences and relative participating, optional or other special rights, and the qualifications, limitations or restrictions thereof, of the shares of such series (in addition to the powers, designations, preferences and relative participating, optional or other special rights, and the qualifications, limitations or restrictions thereof, set forth in the Restated Certificate which may be applicable to the Preferred Stock) authorized by this resolution as follows:

SECTION 1. DESIGNATION OF SERIES B PREFERRED STOCK. The designation of such series of Preferred Stock authorized by this resolution shall be Series B Convertible Preferred Stock (the "Series B Preferred Stock"). The Series B Preferred Stock is issuable solely in whole shares that shall entitle the holder thereof to participate in the distributions and to have the benefit of all

other rights of holders of Series B Preferred Stock, as set forth herein and in the Restated Certificate.

SECTION 2. DIVIDEND RIGHTS OF SERIES B PREFERRED STOCK.

(a) When and if the Board shall declare a dividend or distribution payable with respect to the then-outstanding shares of Common Stock of the Company, other than any such dividend or distribution payable in shares of Common Stock or other securities of the Company (which is provided for in Sections 4(f) and (g)), the holders of the Series B Preferred Stock shall be entitled to the amount of dividends per share that would be payable on the largest number of whole shares of Common Stock into which a holder's aggregate shares of Series B Preferred Stock could then be converted pursuant to Section 4(a) hereof without regard to the provisions of Section 5 (such number to be determined as of the record date for the determination of holders of Common Stock entitled to receive such dividend, and, if the record date is prior to June 30, 2002, for purposes of determining the number of shares of Common Stock

into which the Series B Preferred Stock could then be converted, the Series B Conversion Price will be calculated in accordance with Section 4(c)(i) for the 60 trading days ending two business days prior to the record date).

(b) In addition to Section 2(a) above, the Series B Preferred Stock shall be entitled to a mandatory dividend equal to 5.0% per year of \$1,000 per share (the "Series B Original Issue Price") (as adjusted for any combinations, consolidations, stock distributions, stock dividends or other recapitalizations with respect to such shares) plus accrued dividends thereon, compounded on a semi-annual basis. Such dividend shall be payable solely by the issuance of additional shares of Common Stock upon conversion of the Series B Preferred Stock into Common Stock pursuant to Section 4 hereof; provided that, in the event the Company exercises the Redemption Right (as defined in Section 5(c)), such dividend shall be payable in cash upon such redemption in accordance with Section 5. The dividend to be paid to a holder under this Section 2(b) upon a conversion of the Series B Preferred Stock shall be equal to that number of shares Common Stock determined by dividing the total dividend accrued with respect such holder's Series B Preferred Stock by the Series B Conversion Price, determined in accordance with Section 4(c) hereof, then in effect. No dividends shall be payable under this Section 2(b) in the event the Exchange Right is exercised pursuant to Section 6.

### SECTION 3. SENIORITY; LIQUIDATION PREFERENCE.

(a) The Series B Preferred Stock shall rank PARI PASSU to the Company's currently outstanding Series A Preferred Stock and senior to or PARI PASSU with any future class or series of Preferred Stock issued by the Company and senior to the Company's Common Stock.

(b) In the event of any voluntary or involuntary liquidation, dissolution or winding up of the Company, other than a Significant Transaction (as defined below) (collectively, a "Liquidation"), the holders of Series B Preferred Stock and Series A Preferred Stock then outstanding shall be entitled to be paid, pro rata per share, out of the assets of the Company legally available for distribution to its stockholders, whether from capital, surplus or earnings, before any payment shall be made in respect of any other class or series of stock ranking junior to the Series B Preferred Stock and Series A Preferred Stock, an amount equal to the sum of (i)

2.

the Series A Original Issue Price (as defined in the Series A Certificate), plus any accrued but unpaid dividends, including without limitation any dividends payable upon conversion of the Series A Preferred Stock pursuant to the Series A Certificate (the "Series A Preferred Stock Liquidation Preference") and (ii) the Series B Original Issue Price (each as adjusted for any combinations, consolidations, stock distributions, stock dividends or other recapitalizations with respect to such shares), plus any accrued but unpaid dividends, including without limitation any dividends payable upon conversion of the Series B Preferred Stock pursuant to Section 2(b) (the "Series B Preferred Stock Liquidation Preference" and, together with the Series A Preferred Stock Liquidation Preference, the "Aggregate Preferred Liquidation Preference"). If, upon a Liquidation, the assets of the Company available for distribution to its stockholders shall be insufficient to pay the holders of the Series B Preferred Stock and the Series A Preferred Stock the Aggregate Preferred Liquidation Preference, then the entire assets of the Company legally available for distribution shall be distributed pro rata among the holders of the Series B Preferred Stock and the Series A Preferred Stock in proportion to the percentage of the Aggregate Preferred Liquidation Preference each such holder would otherwise be entitled to receive. After setting apart or paying in full the Aggregate Preferred Liquidation Preference, the holders of the Series B Preferred Stock and the Series A Preferred Stock will not be entitled to any further participation in any distribution of the assets of the Company, and the entire remaining assets of the Company legally available for distribution, if any, shall be distributed among the holders of all securities of the Company ranking junior in liquidation to the Series A Preferred Stock and the Series B Preferred Stock (including, without limitation, the Common Stock), in proportion to the shares of such junior securities then held by them.

### SECTION 4. CONVERSION PRIVILEGES.

(a) RIGHTS OF CONVERSION. Subject to the other provisions of this Certificate of Designation, each share of Series B Preferred Stock shall be convertible, without payment of any additional consideration by the holder thereof and at the option of such holder, into such number of fully paid and nonassessable shares of Common Stock as is determined by dividing the Series B Original Issue Price, plus accrued but unpaid cash dividends under Section 2(a) and accrued dividends under Section 2(b), by the Series B Conversion Price (as

defined below) in effect at the time of conversion, at any time and from time to time after June 30, 2002, at the office of the Company or any transfer agent for such stock.

(b) AUTOMATIC CONVERSION.

(i) In the event that a Significant Transaction (as defined below) occurs, then, in such event, without giving effect to any Preferred Liquidation Preference, the Series B Preferred Stock shall automatically, and without the requirement of further action by the Company or the holders, be converted into such number of fully paid and nonassessable shares of Common Stock determined by dividing the Series B Original Issue Price, plus accrued but unpaid dividends under Section 2(a) and accrued dividends under Section 2(b), by the Series B Conversion Price then in effect. For purposes of this Certificate of Designation, "Significant Transaction" shall mean (A) a reorganization, merger or consolidation in which immediately after (by virtue of securities issued as consideration for such transaction) the former shareholders of the Company do not hold at least 50% of the voting power of the surviving or acquiring entity, (B) an acquisition of all outstanding capital stock of the Company, (C) a liquidation of the Company or

3.

a winding down of its business, or (D) a sale or other transfer of all or substantially all of the Company's assets, but shall not include (1) a commencement of any bankruptcy or insolvency proceedings, whether voluntary or involuntary, (2) a filing for reorganization or relief under bankruptcy law, (3) a consent to the appointment of a receiver, liquidator or trustee for the Company or its assets, (4) a making of a general assignment by the Company for the benefit of its creditors or (5) any other similar corporate action.

(ii) Subject to the provisions of Sections 5 and 6, upon January 14, 2006, the Series A Preferred Stock shall automatically, and without the requirement of further action by the Company or the holders, be converted into such number of fully paid and nonassessable shares of Common Stock determined by dividing the Series B Original Issue Price, plus accrued but unpaid dividends under Section 2(a) and accrued dividends under Section 2(b), by the Series B Conversion Price then in effect. Any shares of Series B Preferred Stock that are not automatically converted into shares of the Company's Common Stock as a result of the provisions of Section 5 shall remain issued and outstanding unless converted pursuant to the provisions of Section 4(a) or redeemed pursuant to the provisions of Section 5.

(c) SERIES B CONVERSION PRICE. The price at which shares of Common Stock shall be deliverable upon conversion of Series B Preferred Stock (the "Series B Conversion Price") (i) for purposes of Sections 4(a) and 4(b)(ii) shall be equal to 125% of the average closing price of the Company's Common Stock on the Nasdaq National Market (or any other national securities exchange on which the Common Stock is then traded) per share for the 60 trading days ending two business days prior to June 30, 2002, subject to adjustment as set forth below, and (ii) for purposes of Section 4(b)(i) shall be equal to (A) if prior to June 30, 2002, 120% of the average closing price of the Company's Common Stock on the Nasdaq National Market (or any other national securities exchange on which the Common Stock is then traded) per share for the 60 trading days ending two business days prior to the date of first public announcement of the Significant Transaction, or (B) if on or after June 30, 2002, 125% of the average closing price of the Company's Common Stock on the Nasdaq National Market (or any other national securities exchange on which the Common Stock is then traded) per share for the 60 trading days ending two business days prior to the date of first public announcement of the Significant Transaction.

(d) MECHANICS OF CONVERSION. Before any holder of Series B Preferred Stock shall be entitled to convert the same into shares of Common Stock, such holder shall surrender the certificate or certificates thereof, duly endorsed, at the office of the Company or of any transfer agent for such stock, and shall give written notice to the Company at such office that such holder elects to convert the same and shall state therein the name or names in which such holder wishes the certificate or certificates for shares of Common Stock to be issued. The Company shall, as soon as practicable thereafter, issue and deliver at such office to such holder of Series B Preferred Stock or its nominee or nominees, a certificate or certificates for the number of shares of Common Stock to which such holder shall be entitled as aforesaid, together with cash in lieu of any fractional shares. Such conversion shall be deemed to have been made immediately prior to the close of business on the date of surrender of the shares of Series B Preferred Stock to be converted. The person or persons entitled to receive the shares of Common Stock issuable upon such conversion shall be treated for all purposes as the record holder or holders of such shares of Common Stock on such date.

(e) ADJUSTMENT FOR STOCK SPLITS AND COMBINATIONS. If the Company shall at any time or from time to time after the date that the first share of Series B Preferred Stock is issued (the "Original Issue Date") effect a subdivision of the outstanding Common Stock without a corresponding subdivision of the Series B Preferred Stock, the Series B Conversion Price in effect immediately before that subdivision shall be proportionately decreased. Conversely, if the Company shall at any time or from time to time after the Original Issue Date combine the outstanding shares of Common Stock into a smaller number of shares without a corresponding combination of the Series B Preferred Stock, the Series B Conversion Price in effect immediately before the combination shall be proportionately increased. Any adjustment under this Section 4(e) shall become effective at the close of business on the date the subdivision or combination becomes effective.

(f) ADJUSTMENT FOR COMMON STOCK DIVIDENDS AND DISTRIBUTIONS. If the Company at any time or from time to time after the Original Issue Date makes, or fixes a record date for the determination of holders of Common Stock entitled to receive, a dividend or other distribution payable in additional shares of Common Stock, in each such event the Series B Conversion Price that is then in effect shall be decreased as of the time of such issuance or, in the event such record date is fixed, as of the close of business on such record date, by multiplying the Series B Conversion Price then in effect by a fraction (i) the numerator of which is the total number of shares of Common Stock issued and outstanding immediately prior to the time of such issuance or the close of business on such record date, and (ii) the denominator of which is the total number of shares of Common Stock issued and outstanding immediately prior to the time of such issuance or the close of business on such record date plus the number of shares of Common Stock issuable in payment of such dividend or distribution; provided, however, that if such record date is fixed and such dividend is not fully paid or if such distribution is not fully made on the date fixed therefor, the Series B Conversion Price shall be recomputed accordingly as of the close of business on such record date and thereafter the Series B Conversion Price shall be adjusted pursuant to this Section 4(f) to reflect the actual payment of such dividend or distribution.

(g) ADJUSTMENTS FOR OTHER DIVIDENDS AND DISTRIBUTIONS. If the Company at any time or from time to time after the Original Issue Date makes, or fixes a record date for the determination of holders of Common Stock entitled to receive, a dividend or other distribution payable in securities of the Company other than shares of Common Stock, in each such event provision shall be made so that the holders of the Series B Preferred Stock shall receive upon conversion thereof, in addition to the number of shares of Common Stock receivable thereupon, the amount of other securities of the Company which they would have received had their Series B Preferred Stock been converted into Common Stock on the date of such event and had they thereafter, during the period from the date of such event to and including the conversion date, retained such securities receivable by them as aforesaid during such period, subject to all other adjustments called for during such period under this Section 4 with respect to the rights of the holders of the Series B Preferred Stock or with respect to such other securities by their terms.

(h) ADJUSTMENT FOR RECLASSIFICATION, EXCHANGE AND SUBSTITUTION. If at any time or from time to time after the Original Issue Date, the Common Stock issuable upon the conversion of the Series B Preferred Stock is changed into the same or a different number of shares of any class or classes of stock, whether by recapitalization, reclassification or otherwise (other than a

subdivision or combination of shares or stock dividend or a reorganization, merger, consolidation or sale of assets provided for elsewhere in this Section 4), in any such event each holder of Series B Preferred Stock shall have the right thereafter to convert such stock into the kind and amount of stock and other securities and property receivable upon such recapitalization, reclassification or other change by holders of the maximum number of shares of Common Stock into which such shares of Series B Preferred Stock could have been converted immediately prior to such recapitalization, reclassification or change, all subject to further adjustment as provided herein or with respect to such other securities or property by the terms thereof.

(i) REORGANIZATIONS, MERGERS, CONSOLIDATIONS OR SALES OF ASSETS. If at any time or from time to time after the Original Issue Date, there is a

capital reorganization of the Common Stock (other than a Signification Transaction or a subdivision or combination of shares or stock dividend or a reorganization, merger, consolidation or sale of assets provided for elsewhere in this Section 4), as a part of such capital reorganization, provision shall be made so that the holders of the Series B Preferred Stock shall thereafter be entitled to receive upon conversion of the Series B Preferred Stock the number of shares of stock or other securities or property of the Company to which a holder of the number of shares of Common Stock deliverable upon conversion would have been entitled on such capital reorganization, subject to adjustment in respect of such stock or securities by the terms thereof. In any such case, appropriate adjustment shall be made in the application of the provisions of this Section 4 with respect to the rights of the holders of Series B Preferred Stock after the capital reorganization to the end that the provisions of this Section 4 (including adjustment of the Series B Conversion Price then in effect and the number of shares issuable upon conversion of the Series A Preferred Stock) shall be applicable after that event and be as nearly equivalent as practicable.

(j) CERTIFICATES AS TO ADJUSTMENTS. Upon the occurrence of each adjustment or readjustment of the number of shares of Common Stock issuable upon conversion of a share of Series B Preferred Stock pursuant to this Section 4, the Company at its expense shall promptly compute such adjustment or readjustment in accordance with the terms hereof and prepare and furnish to each holder of Series B Preferred Stock a certificate setting forth such adjustment or readjustment and showing in detail the facts upon which such adjustment or readjustment is based. The Company shall, upon the written request at any time of any holder of Series B Preferred Stock, furnish or cause to be furnished to such holder a like certificate prepared by the Company setting forth (i) such adjustments and readjustments, (ii) the Series B Conversion Price at the time in effect, and (iii) the number of shares of Common Stock and the amount, if any, of other property which at the time would be received upon the conversion of the Series B Preferred Stock.

(k) NOTICES OF RECORD DATE. In the event of any taking by the Company of a record of the holders of any class of securities for the purpose of determining the holders thereof who are entitled to receive any dividend (other than a cash dividend) or other distribution, any security or right convertible into or entitling the holder thereof to receive additional shares of Common Stock, or any right to subscribe for, purchase or otherwise acquire any shares of stock of any class or any other securities or property, or to receive any other right, the Company shall mail to each holder of Series B Preferred Stock at least 10 days prior to the date specified therein, a notice specifying the date on which any such record is to be taken for the purpose of

6.

such dividend, distribution, security or right, and the amount and character of such dividend, distribution, security or right.

(l) ISSUE TAXES. The holders of Series B Preferred Stock shall pay any and all issue, transfer and other taxes that may be payable in respect of any issue or delivery of shares of Common Stock on conversion of shares of Series B Preferred Stock pursuant hereto.

(m) RESERVATION OF STOCK ISSUABLE UPON CONVERSION. The Company shall at all times reserve and keep available out of its authorized but unissued shares of Common Stock, solely for the purpose of effecting the conversion of the shares of the Series B Preferred Stock, such number of its shares of Common Stock as shall from time to time be sufficient to effect the conversion of all outstanding shares of the Series B Preferred Stock; and if at any time the number of authorized but unissued shares of Common Stock shall not be sufficient to effect the conversion of all then outstanding shares of the Series B Preferred Stock, the Company will take such corporate action as may, in the opinion of its counsel, be necessary to increase its authorized but unissued shares of Common Stock to such number of shares as shall be sufficient for such purpose, including, without limitation, engaging in best efforts to obtain the requisite stockholder approval of any necessary amendment to the Restated Certificate. All shares of Common Stock which are issuable upon such conversion shall, when issued, be duly and legally issued, fully paid and nonassessable and free of all taxes, liens and charges.

(n) FRACTIONAL SHARES. No fractional share shall be issued upon the conversion of any share or shares of Series B Preferred Stock. All shares of Common Stock (including fractions thereof) issuable upon conversion of more than one share of Series B Preferred Stock by a holder thereof shall be aggregated for purposes of determining whether the conversion would result in the issuance of any fractional share. If, after the aforementioned aggregation, the conversion would result in the issuance of a fraction of a share of Common

Stock, the Company shall, in lieu of issuing any fractional share, pay the holder otherwise entitled to such fraction a sum in cash equal to such fraction multiplied by the closing price of the Company's Common Stock on the Nasdaq National Market (or any other national securities exchange on which the Common Stock is then traded) on the day immediately preceding the conversion.

(o) NOTICES. Any notice required by the provisions of this Section 4 shall be in writing and shall be deemed effectively given: (i) upon personal delivery to the party to be notified, (ii) when telephonically confirmed if sent by telex or facsimile, (iii) five days after having been sent by registered or certified mail, return receipt requested, postage prepaid, or (iv) one day after deposit with a nationally recognized overnight courier, specifying next day delivery, with written verification of receipt. All notices shall be addressed to each holder of record at the address of such holder appearing on the books of the Company.

#### SECTION 5. LIMITATION ON ISSUANCE OF SHARES UPON CONVERSION; REDEMPTION.

(a) The following definitions shall apply to this Certificate of Designation:

(i) "Maximum Share Amount" shall mean the number of shares of the Company's Common Stock equal to 19.99% of the Company's Common Stock then outstanding;

7.

(ii) "Excess Shares" shall mean Common Stock of the Company which, upon issuance, results in the beneficial ownership (as defined in Rule 13(d)-3 of the Securities Exchange Act of 1934) by a holder of shares of Common Stock in excess of the Maximum Share Amount;

(iii) "Exchange Rules" shall mean the rules or regulations of Nasdaq or any other principal securities market upon which the Common Stock of the Company is or becomes traded.

(b) Except as provided in Section 5(c) hereof, the Company shall not be obligated to issue upon conversion of the Series B Preferred Stock, in the aggregate, Excess Shares if such issuance in excess of the Maximum Shares Amount would constitute a breach or violation of the Company's obligations under the Exchange Rules.

(c) To the extent the Company will be required, or it appears likely to the Board of Directors of the Company that the Company will be required, to issue any Excess Shares, the Company shall promptly use its best efforts to obtain stockholder approval in accordance with Delaware law, the applicable rules of the Securities and Exchange Commission and the Exchange Rules. In the event the Company does not obtain stockholder approval, the Company shall have the right, at its option (the "Redemption Right"), to redeem, out of funds legally available therefor, all or any part of the Excess Shares at a redemption price, payable in cash, equal to the Series B Original Issue Price per share together with accrued dividends on any such shares that are redeemed (the "Redemption Price"). The Company may exercise the Redemption Right by providing notice by mail, first class postage prepaid, to each holder of Series B Preferred Stock of record (at the close of business on the business day preceding the day on which notice is given) of the Series B Preferred Stock to be redeemed, at the address last shown on the records of the Company for such holder, notifying such holder of the redemption to be effected, specifying the number of shares to be redeemed from such holder, the date that the redemption is to occur (the "Redemption Date"), the place at which payment may be obtained and calling upon such holder to surrender to the Company, in the manner and at the place designated, such holder's certificate or certificates representing the shares to be redeemed (the "Redemption Notice"). On or after the Redemption Date, each holder of Series B Preferred Stock to be redeemed shall surrender to the Company the certificate or certificates representing such shares in the manner and at the place designated in the Redemption Notice, and thereupon the Redemption Price of such shares shall be payable to the order of the person whose name appears on such certificate or certificates as the owner thereof and each surrendered certificate shall be cancelled. In the event less than all of the shares represented by any such certificate are redeemed, a new certificate shall be issued representing the unredeemed shares. From and after the Redemption Date, unless there shall have been a default in payment of the Redemption Price, all rights of the holders of shares of Series B Preferred Stock designated for redemption in the Redemption Notice as holders of Series B Preferred Stock (except the right to receive the Redemption Price without interest upon surrender of their certificate or certificates and except as provided in Section 6(c)) shall cease with respect to such shares, and such

shares shall not thereafter be transferred on the books of the Company or be deemed to be outstanding for any purpose whatsoever.

8.

#### SECTION 6. EXCHANGE RIGHT.

(a) At any time beginning on the date hereof, provided that no shares of Series B Preferred Stock representing the shares initially issued and sold by the Company to Elan International Services, Ltd., a Bermuda corporation ("EIS") and its affiliates, together with those issued or issuable in respect of dividends provided for in Section 1 above, have been converted as provided in Section 4(a) or (b)(ii) above, the holders of the Series B Preferred Stock (by act of the holders of a majority of the Series B Preferred Stock) shall have the right to exchange their shares of Series B Preferred Stock (the "Exchange Right") with the Company for non-voting convertible preferred shares of HepaSense Ltd., a Bermuda corporation ("Newco"), held by the Company, together with all dividends or distributions made thereon (or, if the Company has converted its non-voting convertible preferred shares of Newco into common shares of Newco, the Exchange Right shall apply to the common shares of Newco received by the Company upon such conversion, together with all dividends or distributions made thereon), representing, on a fully-diluted basis, 30.097% of the aggregate issued and outstanding capital stock of Newco, so that, after giving effect to the exercise of the Exchange Right, such holders will own 49.995% of such issued and outstanding capital stock of Newco on a fully-diluted basis.

(b) In order to exercise the Exchange Right, the holders shall provide written notice thereof to the Company, setting forth (i) the fact that such holders intend to exercise the Exchange Right, and (ii) the proposed date for such exercise (the "Exercise Date"), which shall be between 10 and 30 days after the date of such notice. Such notice shall be irrevocable. On the Exercise Date, (y) the holders shall tender their shares of Series B Preferred Stock to the Company for cancellation, and (z) the Company shall cause to be delivered to EIS, acting on behalf of such holders, such shares of Newco. The holders and the Company shall take all other necessary or appropriate actions in connection with or to effect such closing.

(c) If any shares of Series B Preferred Stock are converted into shares of Common Stock pursuant to Section 4(a) or (b)(ii), the Exchange Right shall be terminated and be of no further force and effect with respect to such shares or with respect to those shares of Series B Preferred Stock issued as dividends pursuant to Section 2(b). If all or any shares of the Series B Preferred Stock are converted to shares of Common Stock pursuant to Section 4(b)(i) upon the occurrence of a Significant Transaction, the Exchange Right shall be preserved for its full term as provided in Section 6(a), except that, to exercise the Exchange Right, EIS shall be obligated to tender the consideration received by EIS upon the automatic conversion of the Series B Preferred Stock in connection with such Significant Transaction. If the Company exercises the Redemption Right with respect to any shares of Series B Preferred Stock, the Exchange Right shall be preserved for its full six-year term, except that, to exercise the Exchange Right, EIS shall be obligated to tender the consideration received by EIS upon the redemption of any Excess Shares in connection with the Company's exercise of its Redemption Right.

SECTION 7. VOTING RIGHTS. Holders of Series B Preferred Stock shall not be entitled to vote together with holders of Common Stock, including with respect to the election of directors of the Company, or as a separate class, except as otherwise provided by the General Corporation Law of the State of Delaware ("DGCL") and in this Section 7. To the extent that, under the DGCL, the vote of the holders of the Series B Preferred Stock, voting separately as a class or series as applicable, is required to authorize a given action of the Company, the affirmative vote or

9.

consent of the holders of at least a majority of the shares of the Series B Preferred Stock represented at a duly held meeting at which a quorum is present or by written consent of a majority of the shares of Series B Preferred Stock (except as otherwise may be required under the DGCL) shall constitute the approval of such action by the class. Holders of the Series B Preferred Stock shall be entitled to notice of all shareholder meetings or written consents (and copies of proxy materials and other information sent to shareholders) with respect to which they would be entitled as of right under the DGCL which notice would be provided pursuant to the Company's Bylaws and the DGCL.

SECTION 8. PROTECTIVE PROVISIONS. So long as any shares of Series B Preferred Stock are outstanding, the Company shall not, without first obtaining the approval (by vote or written consent, as provided by law) of the holders of at least a majority of the then outstanding shares of Series B Preferred Stock, voting as a separate class, amend its Certificate of Incorporation so as to adversely affect the rights, preferences or privileges of the Series B Preferred Stock or any holder thereof, including, without limitation, by creating any series of Preferred Stock (or issuing shares under any such series) that is senior in right payment upon liquidation, in respect of dividends or otherwise to the Series B Preferred Stock, or change the rights of the holders of the Series B Preferred Stock in any other respect; provided, however, that the creation of any series of Preferred Stock (or issuance of shares under any such series) that is PARI PASSU in right payment upon liquidation, in respect of dividends or otherwise with the Series B Preferred Stock shall not be deemed to adversely affect the rights, preferences or privileges of the Series B Preferred Stock or any holder thereof or change the rights of the holders of the Series B Preferred Stock in any other respect.

SECTION 9. STATUS OF CONVERTED, REDEEMED OR EXCHANGED STOCK. In the event any shares of Series B Preferred Stock shall be converted pursuant to Section 4 hereof, redeemed pursuant to Section 5 hereof or exchanged pursuant to Section 6 hereof, the shares so converted, redeemed or exchanged shall be cancelled and shall not be reissuable by the Company.

10.

IN WITNESS WHEREOF, Isis Pharmaceuticals, Inc. has caused this Certificate of Designation to be signed by its Chief Executive Officer and attested by its Secretary this \_\_\_\_ day of January, 2000.

ISIS PHARMACEUTICALS, INC.

By:

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Stanley T. Crooke, M.D., Ph.D.  
Chief Executive Officer

Attest:

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B. Lynne Parshall  
Secretary

11.