SECURITIES AND EXCHANGE COMMISSION

WASHINGTON, D.C. 20549

FORM 8-K

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, 2000

ISIS PHARMACEUTICALS, INC.
(Exact name of registrant as specified in its charter)

DELAWARE
(State or other jurisdiction of incorporation)

000-19125	33-0336973
(Commission File No.)	(IRS Employer Identification No.)

2292 FARADAY AVENUE
CARLSBAD, CALIFORNIA 92008
(Address of principal executive offices and zip code)

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

ITEM 2. ACQUISITION OR DISPOSITION OF ASSETS

On January 14, 2000 Isis Pharmaceuticals, Inc., a Delaware Corporation, ("Isis" or the "Company") and Elan Corporation, plc ("Elan") formed a joint venture to develop an antisense drug, ISIS 14803, to treat patients chronically infected with Hepatitis C virus (HCV). The joint venture, HepaSense Ltd. ("HepaSense"), a Bermuda limited company, is initially owned 80.1% by Isis and 19.9% by Elan International Services Ltd. ("EIS"). Isis and Elan each contributed certain rights to antisense oligonucleotide and ambulatory drug delivery technology to the joint venture. In addition, Isis contributed rights to a proprietary oligonucleotide, which will be the first designated oligonucleotide for development by HepaSense. Isis and Elan will provide development and manufacturing services to HepaSense and will be entitled to royalties on milestone payments and royalties received by HepaSense for products incorporating the first or additionally designated oligonucleotides. HepaSense will subcontract with other parties, which may include Isis and Elan, to perform any research and development it will require.

In conjunction with the joint venture, EIS purchased 12,015 shares of Isis' Series B Convertible Exchangeable Preferred Stock for $12,015,000. The preferred stock bears a 5% dividend payable in preferred stock and is convertible into Isis Common Stock at an agreed premium or is exchangeable for preferred shares of HepaSense owned by Isis which represent 30.1% of the outstanding capital stock of HepaSense.

At any time after June 30, 2002, the preferred stock (including accrued dividends) will be convertible at EIS' option into shares of Isis' common stock at 125% of the 60-trading day average closing price of Isis' common stock. In the event of a liquidation of Isis or certain transactions involving a change of control of Isis, the agreement provides for automatic conversion of the preferred stock on terms similar to those set forth above.

Isis is not obligated to issue shares representing more than 19.99% of it's then outstanding common stock upon conversion of the preferred stock if it would result in a violation of the rules of any securities market or exchange upon which the common stock is traded.

At any time the holders of the preferred stock may exchange their preferred stock with Isis for preferred shares of HepaSense held by Isis that represent 30.1% of the total outstanding capital stock of HepaSense. The exchange right will terminate if any of the preferred stock is converted into Isis' common stock, unless such conversion occurs as a result of a liquidation or certain transactions involving a change of control of Isis.

EIS will purchase $7.5 million of Isis Common Stock in the first quarter of 2000 and potentially an additional $7.5 million of common stock upon completion of a mutually agreed milestone. Both tranches of common stock will be priced at a premium to Isis

market price. Isis will issue 5 year warrants to EIS upon the purchase of each tranche in an amount equal to 5% of the shares of Isis Common Stock purchased by EIS in the respective tranche. The warrants will be priced at an agreed premium to Isis market price.

Isis contributed $12.015 million to HepaSense as the purchase price for 6,001 shares of HepaSense Common Stock and 3,612 shares of HepaSense Preferred Stock together representing 80.1% of the outstanding capital stock of HepaSense.

Until June 30, 2002, EIS will, at Isis request, purchase convertible debt of Isis in an amount equal to Isis' share of the budgeted funding for HepaSense. The convertible debt will have a term of 6 years, bear interest at the rate of 12% and be convertible into Isis Common Stock at a premium. Isis may repay the convertible debt in cash or Isis stock. Isis will use the proceeds of the sale of the convertible debt to provide additional development funding to HepaSense.

EIS will have certain registration rights with respect to the Isis Common Stock and the Isis Common Stock issuable upon conversion of the Isis Preferred Stock, the warrants and the convertible debt.

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.

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* 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.

SIGNATURE

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

ISIS PHARMACEUTICALS, INC.

Dated: January 27, 2000

By: /s/ B. LYNNE PARSHALL

B. Lynne Parshall
Executive Vice President

INDEX TO EXHIBITS

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EXHIBIT 10.1

TEXT OMITTED AND FILED SEPARATELY
"CONFIDENTIAL TREATMENT REQUESTED
UNDER 17 C.F.R. SECTIONS 200.80(B)(4),
200.83 AND 240.24B-2."

SUBSCRIPTION, JOINT DEVELOPMENT AND OPERATING AGREEMENT

ELAN CORPORATION, PLC
(ACTING THROUGH ITS DIVISION ELAN PHARMACEUTICAL TECHNOLOGIES)

AND

ELAN INTERNATIONAL SERVICES, LTD.

AND

ELAN PHARMA INTERNATIONAL LIMITED

AND

ISIS PHARMACEUTICALS, INC.

AND

HEPASENSE LTD.

JANUARY 14, 2000

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THIS SUBSCRIPTION, JOINT DEVELOPMENT AND OPERATING AGREEMENT made this 14th day of January, 2000

BETWEEN:

(1) ELAN CORPORATION, PLC, a public limited company incorporated under the laws of Ireland, acting through its division ELAN PHARMACEUTICAL TECHNOLOGIES and having its registered office at Lincoln House, Lincoln Place, Dublin 2, Ireland ("ELAN, PLC");

(2) ELAN INTERNATIONAL SERVICES, LTD., a Bermuda exempted limited liability company incorporated under the laws of Bermuda, and having its registered office at Clarendon House, 2 Church St., Hamilton, Bermuda ("EIS");

(3) ELAN PHARMA INTERNATIONAL LIMITED, a private limited company incorporated under the laws of Ireland, and having its registered office at WIL House, Shannon Business Park, Shannon, County Clare, Ireland ("EPIL");

(4) ISIS PHARMACEUTICALS, INC. a corporation duly incorporated and validly existing under the laws of Delaware and having its principal place of business at 2292 Faraday Avenue, Carlsbad, CA 92008, United States of America ("ISIS"); and

(5) HEPASENSE LTD., a Bermuda exempted limited liability company incorporated under the laws of Bermuda, and having its registered office at Clarendon House, 2 Church St., Hamilton, Bermuda ("HEPASENSE").

RECITALS:

A. HepaSense desires to issue and sell to the Shareholders (as defined below), and the Shareholders desire to purchase from HepaSense, for aggregate consideration of fifteen million United States Dollars (US$15,000,000), apportioned between them as set forth herein, shares of HepaSense's common shares, par value $1.00 per share (the "COMMON SHARES") and shares of HepaSense's preferred shares, par value $1.00 per share (the "PREFERRED SHARES").

B. As of the date hereof, Elan Pharmaceutical Technologies, a division of Elan ("EPT") and EPIL have entered into a license agreement with HepaSense, and Isis has entered into a license agreement with HepaSense, in connection with the license to HepaSense of the Elan Intellectual Property and the Isis Intellectual Property, respectively (each as defined below).

C. Elan and Isis have agreed to co-operate in the research, development and commercialization of the Products (as defined below) based on their respective technologies.

D. Elan and Isis have agreed to enter into this Agreement for the purpose of recording the terms and conditions regulating their relationship with each other, with respect to the Licensed Technologies and with HepaSense.

NOW IT IS HEREBY AGREED AS FOLLOWS:

CLAUSE 1

DEFINITIONS

1.1 In this Agreement, the following terms shall, where not inconsistent with the context, have the following meanings respectively.

"ADDITIONAL PRODUCTS" shall mean the pharmaceutical formulation incorporating an Additional Oligonucleotide and incorporated within or packaged with the System.

"ADDITIONAL OLIGONUCLEOTIDES" shall mean another Oligonucleotide from the Isis portfolio of Oligonucleotides nominated by Isis and accepted by Elan to be incorporated within or packaged with the System for commercialization. For the avoidance of doubt, the Parties acknowledge that any Additional Oligonucleotide shall be at least at the same stage of development as the Designated Oligonucleotide, i.e., shall be ready for clinical testing.

"AFFILIATE" of any Person (in the case of a legal entity) shall mean any other Person controlling, controlled or under the common control of such first Person, as the case may be. For the purposes of this definition, "control" shall mean direct or indirect ownership of fifty percent (50%) or more of the stock or shares entitled to vote for the election of directors or capital interests representing at least 50% of the equity thereof and "controlling" and "controlled" shall be construed accordingly. HepaSense is not an Affiliate of Elan or EIS.

"AGREEMENT" shall mean this agreement (which expression shall be deemed to include the Recitals and the Schedules hereto).

"BOARD" shall mean the board of directors of HepaSense.

"BUSINESS" shall mean the business specified in the Business Plan.

"BUSINESS PLAN" shall mean the business plan and program of development to be agreed by Elan and Isis pursuant to Clause 6, with respect to the research, development, and commercialization of the Products that shall contain, among other things, to the extent practicable, the research and development objectives, desired Product specifications, clinical indications, preliminary clinical trial designs (Phase I/II), development timelines, budgeted costs and the relative responsibilities of Isis and Elan as it relates to the implementation of the Business Plan.

"CLOSING DATE" shall mean the date upon which the Definitive Documents are executed and delivered by the Parties and the transactions effected thereby are closed.

"COMMON SHARES EQUIVALENTS" shall mean any options, warrants, rights or any other securities convertible, exercisable or exchangeable, in whole or in part, for or into Common Shares.

"CERTIFICATE OF DESIGNATIONS" shall mean that certain certificate of designations, preferences and rights of Series B Preferred Shares of Isis issued on the date hereof.

"CHANGE OF CONTROL" shall mean, with respect to a Party, the acquisition of fifty percent (50%) or more of its voting securities, the ability, by contract or otherwise, to control the board of directors or management of any such entity, or a sale of all or substantially all of the business of such Party to which the Transaction Documents relate, whether by merger, sale of stock, sale of assets or otherwise.

"CONVERTIBLE NOTE" shall mean that certain convertible promissory note, of even date herewith, by and between Isis and EIS.

"DEFINITIVE DOCUMENTS" shall mean this Agreement, the Funding Agreement, the Elan License Agreement, the Isis License Agreement, the Convertible Note, the Isis Securities Purchase Agreement, the Registration Rights Agreements, the Certificate of Designations and associated documentation of even date herewith, by and between Isis, Elan, EIS and HepaSense, as applicable.

"DESIGNATED OLIGONUCLEOTIDE" shall mean Isis 14803.

"DIRECTORS" shall mean, at any time, the directors of HepaSense.

"EIS DIRECTOR" has the meaning set forth in Clause 5.

"ELAN" shall mean Elan, plc and EPIL.

"ELAN IMPROVEMENTS" has the meaning assigned thereto in the Elan License Agreement.

"ELAN INTELLECTUAL PROPERTY" has the meaning assigned thereto in the Elan License Agreement.

"ELAN KNOW-HOW" has the meaning assigned thereto in the Elan License Agreement.

"ELAN LICENSE AGREEMENT" shall mean the license agreement between Elan and HepaSense, of even date herewith, attached hereto in Schedule 1.

"ELAN PATENT RIGHTS" has the meaning assigned thereto in the Elan License Agreement.

"ELAN RIGHT OF FIRST NEGOTIATION" shall have the meaning provided in Clause 8.3 hereof.

"ENCUMBRANCE" shall mean any liens, charges, encumbrances, equities, claims, options, proxies, pledges, security interests, or other similar rights of any nature.

"EXCHANGE RIGHT" has the meaning assigned to such term in the Certificate of Designations in effect on the date hereof.

"EXCHANGE ACT" shall mean the Securities Exchange Act of 1934, as amended.

"FDA" shall mean the United States Food and Drug Administration or any successors or agency the approval of which is necessary to market a product in the United States of America.

"FIELD" shall mean the administration of the Designated Oligonucleotide by all routes of administration. Upon nomination by Isis and acceptance by Elan of an Additional Oligonucleotide, the parties shall amend the definition of the Field to include the administration of the Additional Oligonucleotide by such means of administration as agreed to by the parties.

Notwithstanding the foregoing, the Parties acknowledge and agree that, pursuant to existing agreement among Elan, Isis and Orasense Ltd, both Isis and Elan and their Affiliates may be subject to certain restrictions concerning the development and commercialization of products comprised upon the Oral administration of any Oligonucleotide.

"FINANCIAL YEAR" shall mean each year commencing on January 1 (or in the case of the first Financial Year, the date hereof) and expiring on December 31 of each year.

"FULLY DILUTED COMMON SHARES" shall mean all of the issued and outstanding Common Shares, assuming the conversion, exercise or exchange of all outstanding Common Shares Equivalents.

"FUNDING AGREEMENT" shall mean the Funding Agreement, dated as of the date hereof, between EIS and Isis.

"HCV" shall mean the hepatitis C virus.

"HEPASENSE BYE-LAWS" shall mean the Memorandum of Association and Bye-Laws of HepaSense Ltd.

"HEPASENSE INTELLECTUAL PROPERTY" shall mean HepaSense Patents and HepaSense Know How. In addition to the foregoing, any enhancement or improvement relating to both the System and the Isis Know-How or Isis Patents developed by any of the Parties individually or jointly pursuant to the Project or by a third party (under contract with HepaSense) pursuant to the Project shall, except as limited by agreements with third parties, be deemed to be HepaSense Intellectual Property.

"HEPASENSE KNOW-HOW" shall mean any and all rights owned, licensed or controlled by HepaSense to any scientific, pharmaceutical or technical information, data, discovery, invention (whether patentable or not), technique, process, procedure, system, formulation or design that is not generally known to the public arising out of the conduct of the Project by any person that does not constitute Elan Improvements or Isis Improvements.

"HEPASENSE PATENTS" shall mean any and all patents and patent applications arising out of the conduct of the Project by any person that does not constitute Elan Improvements or Isis Improvements and all rights therein, and including all extensions, continuations, continuations-in-part, divisionals, patents-of-additions, re-examinations, re-issues, supplementary protection certificates and foreign counterparts thereto owned or licensed to HepaSense.

"ISIS DIRECTORS" has the meaning set forth in Clause 5.

"ISIS FIELD" has the meaning assigned thereto in the Isis License Agreement.

"ISIS IMPROVEMENTS" has the meaning assigned thereto in the Isis License Agreement.

"ISIS INTELLECTUAL PROPERTY" has the meaning assigned thereto in the Isis License Agreement.

"ISIS KNOW-HOW" has the meaning assigned thereto in the Isis License Agreement.

"ISIS LICENSE AGREEMENT" shall mean the license agreement between Isis and HepaSense, of even date herewith, attached hereto in Schedule 2.

"ISIS PATENT RIGHTS" has the meaning assigned thereto in the Isis License Agreement.

"ISIS SECURITIES PURCHASE AGREEMENT" shall mean that certain securities purchase agreement, of even date herewith, by and between Isis and EIS.

"ISIS 14803" shall mean the Oligonucleotide described in Exhibit A to the Isis License Agreement.

"LICENSE AGREEMENTS" shall mean the Elan License Agreement and the Isis License Agreement.

"LICENSED TECHNOLOGIES" shall mean, collectively, the Elan Intellectual Property and the Isis Intellectual Property.

"OLIGONUCLEOTIDE" shall mean any single stranded, [*] oligonucleotide including those [*] used as a human therapeutic and/or prophylactic compound containing between [*] nucleotides and/or nucleosides including oligonucleotide analogs which may include [*]. For purposes of this agreement, Oligonucleotide shall specifically exclude oligonucleotides used in gene therapy except [*] an oligonucleotide, oligonucleotides used as [*] or oligonucleotides used as adjuvants. Oligonucleotide shall also specifically exclude polymers in which the linkages are amide based, such as peptides and proteins and shall also exclude [*].

"ORAL" shall mean administration by way of the mouth for the purpose of topical or systemic delivery by way of the alimentary canal.

"PARTICIPANT" shall mean Isis or Elan, as the case may be, and "PARTICIPANTS" shall mean both of the Participants together.

"PARTY" shall mean Elan, Isis, or HepaSense, as the case may be, and "PARTIES" shall mean all three together.

*CONFIDENTIAL TREATMENT REQUESTED

"PERSON" shall mean an individual, partnership, corporation, limited liability company, business trust, joint stock company, trust, unincorporated association, joint venture, governmental entity or authority or other entity of whatever nature.

"PERMITTED TRANSFEREE" shall mean any Affiliate or subsidiary of Elan, EIS or Isis, to whom this Agreement may be assigned, in whole or in part, pursuant to the terms hereof or in the case of Elan/EIS, a special purpose financing entity created by Elan or EIS or their respective affiliates.

"PRODUCT" shall mean the pharmaceutical formulation incorporating the Designated Oligonucleotide for [*] within the Field, including, without limitation, the incorporation of the Designated Oligonucleotide within or packaged with the System.

"PROJECT" shall mean all activity as undertaken by or on behalf of HepaSense in order to develop the Products in accordance with the Business Plan.

"REGISTRATION RIGHTS AGREEMENTS" shall mean the Registration Rights Agreements of even date herewith relating to HepaSense and Isis, respectively.

"REGULATORY APPLICATION" shall mean any regulatory application or any other application for marketing approval for a Product, which HepaSense will file in any country of the Territory, including any supplements or amendments thereto.

"REGULATORY APPROVAL" shall mean the final approval to market a Product in any country of the Territory, and any other approval which is required to launch the Product in the normal course of business. "RHA" shall mean any relevant government health authority (or successor agency thereof) in any country of the Territory whose approval is necessary to market a Product in the relevant country of the Territory.

"RESEARCH AND DEVELOPMENT TERM" shall mean shall mean the period commencing on the Closing Date and continuing for a period of [*] thereafter.

"SECURITIES ACT" shall mean the Securities Act of 1933, as amended.

"SHARES" shall mean the shares of Common Shares and shares of Preferred Shares of HepaSense.

"SHAREHOLDER" shall mean any of EIS, Isis, any Permitted Transferee or any other Person who subsequently becomes bound by this Agreement as a holder of the Shares, and "SHAREHOLDERS" shall mean all of the Shareholders together.

*CONFIDENTIAL TREATMENT REQUESTED

"SUBSIDIARY" shall mean any company that is a subsidiary of HepaSense within the meaning of applicable laws.

"SUBSTITUTE OLIGONUCLEOTIDE" shall have the meaning set forth in Clause 8 hereof.

"SYSTEM" shall mean an ambulatory drug delivery system for direct attachment to the body of a patient having a flexible diaphragm drug reservoir, which is capable of delivering factory pre-programmed continuous amounts of drug upon activation as disclosed and described in the Elan Patents set forth in Schedule 1 to the Elan License Agreement.

"TECHNOLOGICAL COMPETITOR OF ELAN" shall mean any entity which has a significant program for the development of drug delivery systems and which is active in promoting and contracting the use of such drug delivery systems to third parties, a listing of which is contained on Schedule 2B to the Elan License Agreement, as the same shall be updated and revised on an annual basis by mutual consent of the Parties.

"TECHNOLOGICAL COMPETITOR OF ISIS" shall mean any entity which has a significant program for the discovery and development of antisense drugs, a listing of which is contained on Schedule 2 to the Elan License Agreement, as the same shall be updated and revised on an annual basis by mutual consent of the Parties.

"TERM" shall mean the term of this Agreement.

"TERRITORY" shall mean all of the countries of the world.

"UNITED STATES DOLLAR" and "US$" and "$" shall mean the lawful currency of the United States of America.

1.2 In addition, the following definitions have the meanings in the Clauses corresponding thereto, as set forth below.

DEFINITION	CLAUSE
"AAA"	20.6
"Buyout Option"	20.7
"Closing"	4.2
"Common Shares"	Recital
"Confidential Information"	22.1
"Co-sale Notice"	17.4
"Elan Valuation"	20.8

"Expert"	19.3
"Isis Employee Director"	5.1.4
"Isis Valuation"	20.8
"Management Committee"	5.2.1
"Notice of Exercise"	17.3
"Notice of Intention"	17.3
"Offered Shares"	17.3
"Offering Price"	17.3
"Preferred Shares"	Recital
"Purchase Price"	20.8
"R&D Committee"	5.2.2
"Remaining Shareholders"	17.4
"Relevant Event"	20.2
"Selling Shareholder"	17.3
"Tag-Along Right"	17.4
"Transaction Proposal"	17.3
"Transfer"	17.1
"Transferee Terms"	17.4
"Transferring Shareholder"	17.4

1.3 Words importing the singular shall include the plural and vice versa.

1.4 Unless the context otherwise requires, reference to a recital, article, paragraph, provision, clause or schedule is to a recital, article, paragraph, provision, clause or schedule of or to this Agreement.

1.5 Reference to a statute or statutory provision includes a reference to it as from time to time amended, extended or re-enacted.

1.6 The headings in this Agreement are inserted for convenience only and do not affect its construction.

1.7 Unless the context or subject otherwise requires, references to words in one gender include references to the other genders.

1.8 Capitalized terms used but not defined herein shall have the meanings ascribed in the Definitive Documents, if defined therein.

CLAUSE 2

BUSINESS

2.1 The primary objective of the Agreement is to regulate the business of the development, testing, registration, manufacture, commercialization and licensing of Products in the Territory and to achieve the other objectives set out in this

Agreement. The focus of the Business will be to develop the Products using the Elan Intellectual Property, the Isis Intellectual Property and the HepaSense Intellectual Property to agreed-upon specifications and timelines.

2.2 The central management and control of HepaSense shall be exercised in Bermuda and shall be vested in the Directors and such Persons as they may delegate the exercise of their powers in accordance with the HepaSense Bye-Laws. The Participants agree to conduct the Business in such a manner as to ensure that HepaSense is liable to taxation in Bermuda and not in any other jurisdiction. The Participants shall use their best endeavours to ensure that to the extent required the sole residence of HepaSense in Bermuda, all meetings of the Directors are held in Bermuda or other jurisdictions outside the United States and generally to ensure that HepaSense is treated as resident for taxation purposes in Bermuda.

CLAUSE 3

REPRESENTATIONS AND WARRANTIES

3.1 REPRESENTATIONS AND WARRANTIES OF HEPASENSE: HepaSense hereby represents and warrants to each of the Shareholders as follows, as of the date hereof:

3.1.1 ORGANIZATION: HepaSense is an exempted company duly organized, validly existing and in good standing under the laws of Bermuda, and has all the requisite corporate power and authority to own and lease its properties, to carry on its business as presently conducted and as proposed to be conducted.

3.1.2 CAPITALIZATION: As of the date hereof, the authorized capital stock of HepaSense consists of 6,001 Common Shares and 6,000 Preferred Shares. Prior to the date hereof, no shares of capital stock of HepaSense have been issued.

3.1.3 AUTHORIZATION: The execution, delivery and performance by HepaSense of this Agreement, including the issuance of the Shares, have been duly authorized by all requisite corporate actions; this Agreement has been duly executed and delivered by HepaSense and is the valid and binding obligation of HepaSense, enforceable against it in accordance with its terms except as limited by applicable bankruptcy, insolvency, reorganization, moratorium and other laws of general application affecting the enforcement of creditors' rights generally, and except as enforcement of rights to indemnity and contribution hereunder may be limited by United States federal or state securities laws or principles of public policy. The Shares, when issued as contemplated hereby, will be validly issued and outstanding, fully paid and non-assessable and not subject to preemptive or any other similar rights of the Shareholders or others.

3.1.4 NO CONFLICTS: The execution, delivery and performance by HepaSense of this Agreement, the issuance, sale and delivery of the Shares, and compliance with the provisions hereof by HepaSense, will not:

(i) violate any provision of applicable law, statute, rule or regulation applicable to HepaSense or any ruling, writ, injunction, order, judgement or decree of any court, arbitrator, administrative agency or other governmental body applicable to HepaSense or any of its properties or assets;

(ii) conflict with or result in any breach of any of the terms, conditions or provisions of, or constitute (with notice or lapse of time or both) a default (or give rise to any right of termination, cancellation or acceleration) under its charter or organizational documents or any material contract to which HepaSense is a party, except where such violation, conflict or breach would not, individually or in the aggregate, have a material adverse effect on HepaSense; or

(iii) result in the creation of, any Encumbrance upon any of the properties or assets of HepaSense.

3.1.5 APPROVALS: As of the date hereof, no permit, authorization, consent or approval of or by, or any notification of or filing with, any Person is required in connection with the execution, delivery or performance of this Agreement by HepaSense. HepaSense has full authority to conduct its business as contemplated in the Business Plan and the Definitive Documents.

3.1.6 DISCLOSURE: This Agreement does not contain any untrue statement of a material fact or omit to state any material fact necessary to make the statements contained herein not misleading. HepaSense is not aware of any material contingency, event or circumstance relating to its business or prospects, which could have a material adverse effect thereon, in order for the disclosure herein relating to HepaSense not to be misleading in any material respect.

3.1.7 NO BUSINESS; NO LIABILITIES: HepaSense has not conducted any business or incurred any liabilities or obligations prior to the date hereof, except solely in connection with its organization and formation.

3.2 REPRESENTATIONS AND WARRANTIES OF THE SHAREHOLDERS: Each of the Shareholders hereby severally represents and warrants to HepaSense as follows as of the date hereof:

3.2.1 ORGANIZATION: Such Shareholder is a corporation duly organized and validly existing under the laws of its jurisdiction of organization and has all the requisite corporate power and authority to own and lease its respective properties, to carry on its respective business as presently conducted and as proposed to be conducted and to carry out the transactions contemplated hereby.

3.2.2 AUTHORITY: Such Shareholder has full legal right, power and authority to enter into this Agreement and to perform its obligations hereunder, which have been duly authorized by all requisite corporate action. This Agreement is the valid and binding obligation of such Shareholder, enforceable against it in accordance with its terms except as limited by applicable bankruptcy, insolvency, reorganization, moratorium and other laws of general application affecting the enforcement of creditors' rights generally, and except as enforcement of rights to indemnity and contribution hereunder may be limited by United States federal or state securities laws or principles of public policy.

3.2.3 NO CONFLICTS: The execution, delivery and performance by such Shareholder of this Agreement, purchase of the Shares, and compliance with the provisions hereof by such Shareholder will not:

(i) violate any provision of applicable law, statute, rule or regulation known by and applicable to such Shareholder or any ruling, writ, injunction, order, judgement or decree of any court, arbitrator, administrative agency or other governmental body applicable to such Shareholder or any of its properties or assets;

(ii) conflict with or result in any breach of any of the terms, conditions or provisions of, or constitute (with notice or lapse of time or both) a default (or give rise to any right of termination, cancellation or acceleration) under the charter or organizational documents of such Shareholder or any material contract to which such Shareholder is a party, except where such violation, conflict or breach would not, individually or in the aggregate, have a material adverse effect on such Shareholder; or

(iii) result in the creation of, any Encumbrance upon any of the properties or assets of such Shareholder.

3.2.4 APPROVALS: As of the date hereof, no permit, authorization, consent or approval of or by, or any notification of or filing with, any Person is required in connection with the execution, delivery or performance of this Agreement by such Shareholder.

3.2.5 INVESTMENT REPRESENTATIONS: Such Shareholder is sophisticated in transactions of this type and capable of evaluating the merits and risks of its investment in HepaSense. Such Shareholder has not been formed solely for the purpose of making this investment and such Shareholder is acquiring the Common Shares and Preferred Shares for investment for its own account, not as a nominee or agent, and not with the view to, or for resale in connection with, any distribution of any part thereof. Such Shareholder understands that the Shares have not been registered under the Securities Act or applicable state and foreign securities laws by reason of a specific exemption from the registration provisions of the Securities Act and applicable state and foreign securities laws, the availability of which depends upon, among other things, the bona fide nature of the investment intent and the accuracy of such Shareholders' representations as expressed herein. Such Shareholder understands that no public market now exists for any of the Shares and that there is no assurance that a public market will ever exist for such Shares.

CLAUSE 4

AUTHORIZATION AND CLOSING

4.1 HepaSense has authorized the issuance to (i) EIS of 2,388 Preferred Shares and (ii) Isis of 6,001 Common Shares and 3,612 Preferred Shares, issuable as provided in Clause 4.3 hereof.

4.2 Isis and EIS hereby subscribe for the number of Shares set forth in Clause 4.1 and shall pay to HepaSense in consideration therefore, by wire transfer of immediately available funds (to a bank account established by HepaSense in connection with Completion) the subscription amounts each as provided in Clause 4.4.1.

4.3 The closing (the "CLOSING") shall take place at the offices of Brock Silverstein LLC at 800 Third Avenue, New York, New York 10022 on the date hereof or such other places if any, as the Parties may agree and shall occur contemporaneously with the closing under the Isis Securities Purchase Agreement.

4.4 At the Closing, each of the Shareholders shall take or (to the extent within its powers) cause to be taken the following steps at directors and shareholder meetings of HepaSense, or such other meetings or locations, as appropriate:

4.4.1 HepaSense shall issue and sell to EIS, and EIS shall purchase from HepaSense, upon the terms and subject to the conditions set forth herein, 2,388 Preferred Shares for an aggregate purchase price of US$2,985,000.

HepaSense shall issue and sell to Isis, and Isis shall purchase from HepaSense, upon the terms and conditions set forth herein, (i) 6,001 Common Shares for an aggregate purchase price of US$7,500,000 and (ii) 3,612 Preferred Shares for an aggregate purchase price of US$4,515,000;

4.4.2 the Parties shall execute and deliver to each other, as applicable, certificates in respect of the Common Shares and Preferred Shares described above and any other certificates, resolutions or documents which the Parties shall reasonably require;

4.4.3 the adoption by HepaSense of HepaSense Bye-Laws;

4.4.4 the appointment of Kevin Insley, B. Lynne Parshall, F. Andrew Dorr, M.D., Dawn Griffiths and Stephen Rossiter as Directors of HepaSense;

4.4.5 the resignation of all directors and the secretary of HepaSense holding office prior to the execution of this Agreement and delivery of written confirmation under seal by each Person so resigning that he has no claim or right of action against HepaSense and that HepaSense is not in any way obligated or indebted to him; and

4.4.6 the transfer to HepaSense of the share register.

4.5 EXEMPTION FROM REGISTRATION:

The Shares will be issued under an exemption or exemptions from registration under the Securities Act. Accordingly, the certificates evidencing the Shares shall, upon issuance, contain the following legend:

THE SECURITIES REPRESENTED HEREBY HAVE NOT BEEN REGISTERED UNDER THE SECURITIES ACT OF 1933, AS AMENDED, OR ANY SECURITIES LAWS OF A STATE OR OTHER JURISDICTION AND MAY NOT UNDER ANY CIRCUMSTANCES BE SOLD, TRANSFERRED, OR OTHERWISE DISPOSED OF (OTHER THAN TO AN AFFILIATE OF THE ORIGINAL HOLDER OR AS OTHERWISE PERMITTED IN THE AGREEMENT PURSUANT TO WHICH THEY WERE ISSUED) EXCEPT PURSUANT TO (i) AN EFFECTIVE REGISTRATION STATEMENT UNDER THE SECURITIES ACT AND ANY APPLICABLE STATE SECURITIES OR BLUE SKY LAWS, OR (ii) TO THE EXTENT APPLICABLE, RULE 144 UNDER THE SECURITIES ACT (OR ANY SIMILAR RULE UNDER THE SECURITIES ACT RELATING TO THE DISPOSITION OF SECURITIES) TOGETHER WITH AN OPINION OF COUNSEL

REASONABLY SATISFACTORY TO THE CORPORATION THAT REGISTRATION IS NOT REQUIRED UNDER SUCH ACT OR APPLICABLE STATE SECURITIES LAWS.

4.6 HepaSense shall use reasonable efforts to file any documents that require filing with the Registrar of Companies in Bermuda within the prescribed time limits. EIS and Isis shall provide all reasonable co-operation to HepaSense in relation to the matters set forth in this Clause 4.6.

4.7. In the event that EIS exercises the Exchange Right, HepaSense shall, immediately upon such exercise, take all necessary steps to ensure that EIS is duly and validly issued and has full legal right, title and interest in and to the Preferred Shares exchanged therefor. The Parties acknowledge that such Preferred Shares have been pledged to EIS pursuant to the Isis Securities Purchase Agreement and that EIS has physical possession of such Preferred Shares; upon such exercise, EIS shall be entitled to keep and retain such Preferred Shares, which shall be owned by EIS as provided above. In connection with the foregoing, HepaSense and the Participants shall take all necessary or appropriate steps to ensure such ownership by EIS.

CLAUSE 5

DIRECTORS; MANAGEMENT AND R&D COMMITTEES

5.1. DIRECTORS:

5.1.1 Prior to the exercise of the Exchange Right, the Board shall be composed of five Directors.

Isis shall have the right to nominate four directors of HepaSense, provided that two such directors are residents of Bermuda, ("ISIS DIRECTORS") and EIS shall have the right to nominate one Director of HepaSense ("EIS DIRECTOR") which Director, save as further provided herein, shall only be entitled to 15% of the votes of the Board.

In the event that the Exchange Right is exercised by EIS within 2 years following the Closing Date, the EIS Director shall only be entitled to 15% of the votes of the Board until the expiry of 2 years from the Closing Date.

In the event that the Exchange Right is exercised by EIS at any time after two years following the Closing Date or upon the expiry of 2 years following the Closing Date where the Exchange Right has been exercised by EIS within 2 years following the Closing Date, each of Isis, and EIS shall cause the Board to be reconfigured so that an equal number of Directors are designated by EIS and Isis and that each of the Directors has equal voting power.

5.1.2 If EIS removes the EIS Director, or Isis removes any of the Isis Directors, EIS or Isis, as the case may be, shall indemnify the other Shareholder against any claim by such removed Director arising from such removal.

5.1.3 The Directors shall meet not less than three times in each Financial Year and all Board meetings shall be held in Bermuda or otherwise by teleconference in accordance with the HepaSense Bye Laws or as otherwise required by to the laws of Bermuda and to ensure the sole residence of HepaSense in Bermuda.

5.1.4 At any such meeting, the presence of the EIS Director and at least one Isis Director who at the time of the meeting is an employee of Isis (an "Isis Employee Director") shall be required to constitute a quorum and, subject to Clause 17 hereof, the affirmative vote of a majority of the Directors present at a meeting at which such a quorum is present shall constitute an action of the Directors; provided, however, that the EIS Director and Isis Employee Director also vote in favor of such action. In the event of any meeting being inquorate, the meeting shall be adjourned for a period of seven days. A notice shall be sent to the EIS Director and the Isis Directors specifying the date, time and place where such adjourned meeting is to be held and reconvened.

5.1.5 On the Closing Date, Isis may appoint one of the Isis Directors to be the chairman of HepaSense. The chairman of HepaSense shall hold office until:

(i) the first meeting of the Board following the exercise by EIS of the Exchange Right, where the Exchange Right has been exercised by EIS after two years following the Closing Date; or

(ii) the first meeting of the Board following the expiry of 2 years following the Closing Date where the Exchange Right has been exercised by EIS within 2 years following the Closing Date

(in each case the "CHAIRMAN STATUS BOARD MEETING")

After the Chairman Status Board Meeting, each of EIS and Isis, beginning with EIS at the Chairman Status Board Meeting, shall have the right, exercisable alternatively, of nominating one Director to be chairman of HepaSense for a term of one year.

If the chairman is unable to attend any meeting of the Board held prior to the Chairman Status Board Meeting, the Isis Directors shall be entitled to appoint another Isis Director to act as chairman in his place at the meeting.

If the chairman of HepaSense is unable to attend any meeting of the Board

held after the Chairman Status Board Meeting, the Directors shall be entitled to appoint another Director to act as chairman of HepaSense in his place at the meeting.

5.1.6 In case of an equality of votes at a meeting of the Board, the chairman of HepaSense shall not be entitled to a second or casting vote. In the event of continued deadlock, the Board shall resolve the deadlock pursuant to the provisions set forth in Clause 18.

5.2 MANAGEMENT AND R&D COMMITTEES:

5.2.1 The Directors shall appoint a management committee (the "MANAGEMENT COMMITTEE") to perform certain operational functions, such delegation to be consistent with the Directors' right to delegate powers pursuant to the HepaSense Memorandum of Association of Bye-Laws. The Management Committee shall initially consist of four members, two of whom will be nominated by EIS and two of whom will be nominated by Isis, and each of whom shall be entitled to one vote, whether or not present at any Management Committee meeting during which such operational functions are discussed. Except as otherwise provided herein or in the License Agreements, decisions of the Management Committee shall require approval by at least one EIS nominee on the Management Committee and one Isis nominee on the Management Committee. Each of EIS and Isis shall be entitled to remove any of their nominees to the Management Committee and appoint a replacement in place of any nominees so removed.

5.2.2 The Management Committee shall appoint a research and development committee (the "R&D COMMITTEE") which shall initially be comprised of four members, two of whom will be nominated by Elan and two of whom will be nominated by Isis, and each of whom shall have one vote, whether or not present at an R&D Committee meeting during which research and development issues are discussed. Decisions of the R&D Committee shall require approval by at least one Elan nominee on the R&D Committee and one Isis nominee on the R&D Committee. Each of Elan and Isis shall be entitled to remove any of their nominees to the R&D Committee and appoint a replacement in place of any nominees so removed.

5.2.3 The Management Committee shall be responsible for, inter alia, devising, implementing and reviewing strategy for the business of HepaSense, and the operation of HepaSense, and in particular, devising HepaSense's strategy for research and development and to monitor and supervise the implementation of HepaSense's strategy for research and development.

5.2.4 The R&D Committee shall be responsible for:

5.2.4.1 designing that portion of the Business Plan that relates to the Project for consideration by the Management Committee;

5.2.4.2 establishing a joint Project team consisting of an equal number of team members from Elan and Isis, including one Project leader from each of Elan and Isis; and

5.2.4.3 implementing such portion of the Business Plan that relates to the Project, as approved by the Management Committee.

5.2.5 In the event of any dispute amongst the R&D Committee, the R&D Committee shall refer such dispute to the Management Committee whose decision on the dispute shall be binding on the R&D Committee. If the Management Committee cannot resolve the matter after 15 days or such other period as may be agreed by the Management Committee, the dispute will be referred to a designated senior officer of each of Elan and Isis, and thereafter, in the event of continued deadlock, pursuant to the deadlock provisions to be set forth in Clause 19, involving inter alia, the referral of the dispute to an expert, whose decision, however, will ultimately be non-binding on the Participants. This process shall also apply to any dispute within the Management Committee.

CLAUSE 6

THE BUSINESS PLAN AND REVIEWS

6.1 The Directors shall meet together as soon as reasonably practicable after the Closing Date hereof and shall agree upon and approve the Business Plan for the current Financial Year within 60 days of the Closing Date.

6.2. The Business Plan shall be subject to ongoing review by the Directors and the approval of the EIS Director and the Isis Directors on a quarterly basis.

6.3. Neither Participant shall be obliged to provide funding to HepaSense in the absence of quarterly approval of the Business Plan and a determination by each Participant, in its sole discretion, that Subsequent Funding (as such term is defined in the Funding Agreement) shall be provided for the development of the Products.

CLAUSE 7

RESEARCH AND DEVELOPMENT WORK

7.1 During the Research Term, HepaSense will diligently pursue the research and development of the Elan Intellectual Property, Isis Intellectual Property and

HepaSense Intellectual in accordance with the Research and Development Program. The "RESEARCH AND DEVELOPMENT PROGRAM" will be the program the development of the Product in the Field, including without limitation, in vivo toxicology, stability, formulation, optimization, clinical and regulatory activities. Such work shall be agreed to and conducted by Elan, Isis and/or a third party Isis under contract with HepaSense as provided in the Business Plan.

7.2 Subject to the provisions of Clause 6.3, Isis and Elan shall provide at their discretion respective such research and development services as is requested by HepaSense in accordance with the provisions in the License Agreements; provided, however, that HepaSense shall not perform any pre-clinical research or development work. HepaSense shall pay Isis and Elan for any development work carried out by them on behalf of HepaSense at the end of each month during the Research and Development Program, subject to the proper vouching of research and development work and expenses. An invoice shall be issued to HepaSense by Isis or Elan, as applicable, by the 15th day of the month following the month in which work was performed. The payments by HepaSense to Isis or Elan shall be calculated by reference to the fully burdened actual costs incurred by Isis and Elan [*] in carrying out such research and development work, on a fully allocated basis. Research and development activities that are outsourced to third party providers shall be charged to HepaSense at [*].

7.3 Elan and Isis shall permit HepaSense or its duly authorized representative on reasonable notice and at any reasonable time during normal business hours to have access to inspect and audit the accounts and records of Elan or Isis and any other book, record, voucher, receipt or invoice relating to the calculation or the cost of the Research and Development Program and to the accuracy of the reports which accompanied them. Any such inspection of Elan's or Isis's records, as the case may be, shall be at the expense of HepaSense, except that if such inspection reveals an overpayment in the amount paid to Elan or Isis, as the case may be, for the Research and Development Program hereunder in any Financial Year of 5% or more of the amount due to Elan or Isis, as the case may be, then the expense of such inspection shall be borne solely by Elan or Isis, as the case may be, instead of by HepaSense. Any surplus over the sum properly payable by HepaSense to Elan or Isis, as the case may be, shall be paid promptly by Elan or Isis, as the case may be, to HepaSense. If such inspection reveals a deficit in the amount of the sum properly payable to Elan or Isis, as the case may be, by HepaSense, HepaSense shall pay the deficit to Elan or Isis, as the case may be.

7.4 Should HepaSense determine that the Designated Oligonucleotide is not suitable for administration via the System, HepaSense, at its option may either (i) further develop and commercialize the Designated Oligonucleotide in a Product via another route of administration within the Field or (ii) request Isis to designate a substitute Oligonucleotide. In the event HepaSense requests that Isis designate a

*CONFIDENTIAL TREATMENT REQUESTED

substitute Oligonucleotide, the Parties shall review in good faith and designate for in-licensing to HepaSense, subject to then existing contractual obligations, another Oligonucleotide from the Isis portfolio of Oligonucleotides with comparable commercial potential, or designate an Oligonucleotide for in-licensing or acquisition of the rights from one or more third parties to such Oligonucleotide (the "SUBSTITUTE OLIGONUCLEOTIDE"). In either case, the Parties shall promptly negotiate in good faith such amendments as are required to this Agreement, such as amending the provisions regulating non-competition under Clause 4 of the License Agreements, and to the research and development budgeted costs for the Project.

7.5 Except as otherwise provided herein and as provided in the Isis License Agreement, upon designation of an Isis Oligonucleotide as a Substitute Oligonucleotide, (i) all rights to ISIS 14803 shall revert to Isis and (ii) all provisions contained herein and in the Isis License Agreement other than in the preceding clause (i) relating to the ISIS 14803 shall be deemed to apply to the Substitute Oligonucleotide as if it were the Designated Oligonucleotide, unless otherwise amended in accordance with Clause 7.4.

CLAUSE 8

COMMERCIALIZATION

8.1 HepaSense shall diligently pursue the research, development, prosecution and commercialization of the Product as provided in the Business Plan. During the Research Term, Elan and Isis shall meet to discuss the commercial strategy for HepaSense commercialization of the Product and the further exploitation of the HepaSense Intellectual Property. For example, Isis and Elan shall discuss strategy and terms relating to product and clinical development, corporate partnering, licensing and supply agreements. It is contemplated that Isis, through its representatives on the Management Committee, shall locate and negotiate with independent third party marketing partners for Product. In the course of such representation, Isis shall keep HepaSense and Elan fully informed of its efforts and progress with respect to the foregoing.

8.2 In the event HepaSense successfully commercializes the Product, Isis may, from time to time nominate, subject to Elan's consent, from the Isis portfolio of Oligonucleotides additional Oligonucleotides to be designated as Additional Oligonucleotides for incorporation in Additional Products. It is contemplated that Isis shall locate and negotiate with independent third party marketing partners for Isis Products. Isis shall keep HepaSense and Elan apprised of its efforts and progress with respect to the foregoing; provided, however, that any such information shall be kept confidential and shall not be disclosed to the Elan

Pharmaceuticals division of Elan, plc (excluding senior executive personnel of Elan).

8.3 Notwithstanding anything set forth herein, at such time as HepaSense intends to commercialize the Product, Elan shall have the right of first negotiation with respect to the world-wide commercialization of the Product (the "ELAN FIRST RIGHT OF NEGOTIATION"). Such right of first negotiation shall be exercised as follows:

8.3.1 If HepaSense intends to commercialize or enter into an agreement with an independent third party to commercialize the Product, then HepaSense immediately shall notify Elan in writing that Elan may elect to enter into negotiations referred to in this Clause 8.3. Elan shall indicate its desire to enter into such negotiations pursuant to this Clause 8.3 by delivering written notice to HepaSense within forty-five (45) days of Elan's receipt of the written notification from HepaSense to Elan. If Elan elects to enter into such negotiations, the Parties shall negotiate in good faith the terms of an applicable agreement.

8.3.2 If, despite such good faith negotiations, Elan and HepaSense do not reach agreement on the terms of such an agreement within six (6) months from the notification in writing by HepaSense to Elan, then HepaSense shall be free to offer a third party (other than a Technological Competitor of Elan unless consented to by Elan which consent may be withheld for any reason and otherwise subject to the terms and conditions of this Agreement) terms to commercialize the Product in the Territory, which terms when taken as a whole, are more favorable to HepaSense than the principal terms of the last written proposal offered to HepaSense by Elan, or by HepaSense to Elan, as the case may be; provided, however, that in the event the stage of development or data available in connection with the Product shall change materially, the Elan Right of First Negotiation shall be revived.

8.4 Subject to the rights of Elan with respect to the Product, HepaSense shall not be permitted to contract the commercialization of the Product or any other Product without the prior written consent of Elan and Isis, which consent will not be unreasonably withheld or delayed; provided that such reasonableness standard, in the case of Elan, shall not be applicable in the case of a proposed sublicense to any Technological Competitor of Elan and in the case of Isis, shall not be applicable in the case of a proposed sublicense to any Technological Competitor of Isis.

CLAUSE 9

OWNERSHIP OF INTELLECTUAL PROPERTY RIGHTS/NON-COMPETITION

9.1 The Parties acknowledge and agree to be bound by the provisions of Clause 3 of the Elan License Agreement and Clause 3 of the Isis License Agreement set forth the agreement between the parties thereto in relation to the ownership of the Elan Intellectual Property, the Isis Intellectual Property and the HepaSense Intellectual property respectively.

9.2 The Parties acknowledge and agree to be bound by the provisions the provisions of Clause 4 of the Elan License Agreement and the provisions of Clause 4 of the Isis License Agreement which set forth the agreement between the parties thereto in relation to the non-competition obligations of Elan and Isis, respectively.

CLAUSE 10

SUBLICENSE AND ASSIGNMENT RIGHTS

10.1 HepaSense shall not assign any of its rights under the HepaSense Intellectual Property without the prior written consent of Elan and Isis.

10.2 HepaSense shall not sublicense any of its rights under the License Agreements for the Licensed Technologies and/or the HepaSense Intellectual Property without the prior written consent of Elan and Isis, which consent shall not be unreasonably withheld or delayed; provided, however, that the consent of Elan may be withheld in Elan's sole discretion in the case of a proposed sublicense of such rights to a Technological Competitor of Elan.

CLAUSE 11

INTELLECTUAL PROPERTY RIGHTS

11.1 Elan, at its expense and sole discretion may (i) secure the grant of any patent applications within the Elan Patents that relate to the Field; (ii) file and prosecute patent applications on patentable inventions and discoveries within the Elan Improvements that relate to the Field; (iii) defend all such applications against third party oppositions; and (iv) maintain in force any issued letters patent within the Elan Patents that relate to the Field (including any letters patent that may issue covering any such Elan Improvements that relate to the Field). Elan shall have the right in its sole discretion to control such filing, prosecution, defense and maintenance provided that HepaSense and Isis at their request shall be provided with copies of all documents relating to such filing, prosecution, defense and maintenance in sufficient time to review such documents and comment thereon prior to filing.

11.2 Isis, at its expense and sole discretion, may (i) secure the grant of any patent applications within the Isis Patents that relate to the Field; (ii) file and prosecute

patent applications on patentable inventions and discoveries within the Isis Improvements that relate to the Field; (iii) defend all such applications against third party oppositions; and (iv) maintain in force any issued letters patent within the Isis Patents that relate to the Field (including any letters patent that may issue covering any such Isis Improvements that relate to the Field). Isis shall have the right in its sole discretion to control such filing, prosecution, defense and maintenance provided that Elan and HepaSense at their request shall be provided with copies of all documents relating to such filing, prosecution, defense and maintenance in sufficient time to review such documents and comment thereon prior to filing.

11.3 In the event that Elan does not intend to file for patent protection on patentable inventions or discoveries within the Elan Intellectual Property that relates to the Field in one or more countries in the Territory after providing written notice to HepaSense and Isis, HepaSense shall have the option at HepaSense's expense, upon the prior written approval of Elan which approval shall not be unreasonably withheld, to request Elan to file and prosecute such patent application(s). Upon such written request from HepaSense, Elan shall be responsible for preparing and prosecuting and otherwise seeking patent protection for such Elan Intellectual Property described in this Clause 11.3. Any such Elan Intellectual Property shall be owned by Elan but Elan shall grant a royalty free exclusive license to HepaSense for such Elan Intellectual Property in the Field. Such license shall be subject to the other terms and conditions set forth in this Agreement and the Elan License Agreement to HepaSense. The Parties shall have the right to remove their confidential information from any such patent application.

11.4 In the event that Isis does not intend to file for patent protection on patentable inventions or discoveries within the Isis Intellectual Property that relates to the Field in one or more countries in the Territory after providing written notice to HepaSense and Elan, HepaSense shall have the option at HepaSense's expense, upon the prior written approval of Isis which approval shall not be unreasonably withheld, to request Isis to file and prosecute such patent application(s). Upon such written request from HepaSense, Isis shall be responsible for preparing and prosecuting and otherwise seeking patent protection for such Isis Intellectual Property described in this Clause 11.4. Any such Isis Intellectual Property shall be owned by Isis but Isis shall grant a royalty free exclusive license to HepaSense such Isis Intellectual Property in the Field. Such license shall be subject to the other terms and conditions set forth in this Agreement and the Isis License Agreement to HepaSense. The Parties shall have the right to remove their confidential information from any such patent application.

11.5 HepaSense at its expense shall have the right but shall not be obligated (i) to file and prosecute patent applications on patentable inventions and discoveries within the HepaSense Intellectual Property; (ii) to defend all such applications against third party oppositions; and (iii) to maintain in force any issued letters patent within the HepaSense Patents (including any patents that issue on patentable

inventions and discoveries within the HepaSense Intellectual Property). HepaSense shall have the right to control such filing, prosecution, defense and maintenance provided that the other Parties shall be provided with copies of all documents relating to such filing, prosecution, defense, and maintenance in sufficient time to review such documents and comment thereon prior to filing. The Parties shall have the right to remove their confidential information from any such patent application.

11.6 In the event that HepaSense informs both Elan and Isis that it does not intend to file an application on the HepaSense Intellectual Property in or outside the Field, Elan shall have the right to file and prosecute such patent applications on inventions that Elan invents solely or which relate predominantly to the Elan Intellectual Property, and Isis shall have the right to file and prosecute such patent applications on inventions which Isis invents solely or which relate predominantly to the Isis Intellectual Property, and Elan and Isis agree to negotiate in good faith on the course of action to be taken with respect to HepaSense inventions that relate to both the Elan Intellectual Property and Isis Intellectual Property. The Parties shall have the right to remove their confidential information from any such patent application.

11.7 The Parties shall promptly inform each other in writing of any actual or alleged unauthorized use of any Elan Intellectual Property, the Isis Intellectual Property or the HepaSense Intellectual Property by a third party of which it becomes aware and provide the others with any available evidence of such unauthorized use.

11.8 At its option, as the case may be, Elan or Isis shall have the first option to enforce at its own expense and for its own benefit any unauthorized use of its respective Intellectual Property (the Elan Intellectual Property or the Isis Intellectual Property as the case may be) in the Field. At the enforcing party's request, the other Parties shall cooperate with such action. Should Elan or Isis decide not to enforce the Elan Intellectual Property or the Isis Intellectual Property respectively, against such unauthorized use in the Field, within a reasonable period but in any event within twenty (20) days after receiving written notice of such actual or alleged unauthorized use, HepaSense may in its discretion initiate such proceedings in its own name, at its expense and for its own benefit, and at such Party's request, Elan and Isis shall cooperate with such action. Any recovery remaining after the deduction by HepaSense of the reasonable expenses (including attorney's fees and expenses) incurred in relation to such enforcement proceeding shall belong to HepaSense. Alternatively, the Parties may agree to institute such proceedings in their joint names and shall reach agreement as to the proportion in which they shall share the proceeds of any such proceedings, and the expense of any costs not recovered, or the costs or damages payable to the third party. If the enforcement of the Elan Intellectual Property or the Isis Intellectual Property affects both the Field as well as other products being developed or commercialized by Isis or Elan or its commercial partners outside the Field, Isis or Elan shall endeavour to agree as to the manner in which the

proceedings should be instituted and as to the proportion in which they shall share the proceeds of any such proceedings, and the expense of any costs not recovered, or the costs or damages payable to the third party.

11.9 HepaSense shall have the first right but not the obligation to bring suit or otherwise take action against any unauthorized use of the HepaSense Intellectual Property. If any such alleged use occurs that gives rise to a cause of action both inside and outside the Field, HepaSense, in consultation with the other Parties, shall determine the course of action to be taken. In the event that HepaSense takes such action, HepaSense shall do so at its own cost and expense and all damages and monetary award recovered in or with respect to such action shall be the property of HepaSense. HepaSense shall keep Elan and Isis informed of any action in a timely manner so as to enable Isis and Elan to provide input in any such action and HepaSense shall reasonably take into consideration any such input. At HepaSense's request, the Parties shall cooperate with any such action at HepaSense's cost and expense.

11.10 In the event that HepaSense does not bring suit or otherwise take action against any unauthorized use of the HepaSense Intellectual Property (i) if only one Party determines to pursue such suit or take such action at its own cost and expense, it shall be entitled to all damages and monetary award recovered in or with respect to such action and (ii) if the other Parties pursue such suit or action outside of HepaSense, they shall negotiate in good faith an appropriate allocation of costs, expenses and recovery amounts. At the Party's request, HepaSense shall cooperate with any such action at the Party's cost and expense.

11.11 In the event that a claim or proceeding is brought against HepaSense by a third party alleging that the sale, distribution or use of a Product in the Territory constitutes the unauthorized use of the intellectual property rights of such Party, HepaSense shall promptly advise the other Parties of such threat or suit.

11.12 Save in respect of claims by HepaSense against either Party, or by an Independent Third Party against HepaSense, where Elan is in breach of a representation or warranty under Clause 7 of the Elan License Agreement or where Isis is in breach of a representation or warranty under Clause 7 of the Isis License Agreement, HepaSense shall indemnify, defend and hold harmless Elan or Isis, as the case may be, against all actions, losses, claims, demands, damages, costs and liabilities (including reasonable attorneys fees) relating directly or indirectly to all such claims or proceedings referred to in Clause 11.11, provided that Elan or Isis, as the case may be, shall not acknowledge to the third party or to any other person the validity of any claims of such a third party, and shall not compromise or settle any claim or proceedings relating thereto without the prior written consent to HepaSense, not to be unreasonably withheld or delayed. At its option, Elan or Isis, as the case may be, may elect to take over the conduct of such proceedings from HepaSense provided that HepaSense's indemnification obligations shall continue; the costs of defending such claim shall be borne by Elan or Isis, as the

case may be and such Party shall not compromise or settle any such claim or proceeding without the prior written consent of HepaSense, such consent not to be unreasonably withheld or delayed.

CLAUSE 12

CROSS LICENSING/EXPLOITATION OF PRODUCTS OUTSIDE THE FIELD

12.1 Solely for the purpose of and insofar as is necessary, in each case, for Elan to perform research and development work on behalf of HepaSense, HepaSense shall grant to Elan a non-exclusive, worldwide, royalty-free, fully paid-up license for the term of the Licenses:

12.1.1 to exploit the HepaSense Intellectual Property in the Field, and

12.1.2 subject to the terms and conditions of the Isis License, a sublicense to exploit the Isis Intellectual Property in the Field.

12.2 Solely for the purpose of and insofar as is necessary, in each case, for Isis to perform to conduct research and development work on behalf of HepaSense, HepaSense shall grant to Isis a non-exclusive, worldwide, royalty-free, fully paid-up license for the term of the Licenses:

12.2.1 to exploit the HepaSense Intellectual Property in the Field, and

12.2.2 subject to the terms and conditions of the Elan License, a sublicense to exploit the Elan Intellectual Property in the Field.

12.3 Subject to the provisions of this Clause 12, HepaSense hereby grants to each of Elan and Isis a license to the HepaSense Intellectual Property as follows:

12.3.1 HepaSense hereby grants to Elan a worldwide, perpetual, fully-paid and royalty-free license, with the right to sublicense, to the HepaSense Intellectual Property in all fields other than the Field or in connection with Isis proprietary Oligonucleotides on an as-is basis without recourse, representation or warranty whether express or implied, including warranties of merchantability or fitness for a particular purpose, or infringement of third party rights, and all such warranties are expressly disclaimed.

12.3.2 Subject to the rights of Elan pursuant to Clause 8.4 hereof, HepaSense hereby grants to Isis a worldwide, perpetual, fully-paid and royalty-free license, with the right to sublicense, to the HepaSense Intellectual Property as it relates to the Designated Oligonucleotide or any other Oligonucleotide for use outside the Field on an as-is basis without recourse, representation or warranty whether express or implied, including warranties of merchantability or fitness for

a particular purpose, or infringement of third party rights, and all such warranties are expressly disclaimed.

CLAUSE 13

REGULATORY

13.1 HepaSense shall keep the other Parties promptly and fully advised of HepaSense's regulatory activities, progress and procedures. HepaSense shall inform the other Parties of any dealings it shall have with an RHA, and shall furnish the other Parties with copies of all correspondence relating to the Products. The Parties shall collaborate to obtain any required regulatory approval of the RHA to market the Products.

13.2 HepaSense shall, at its own cost, file, prosecute and maintain any and all Regulatory Applications for the Product in the Territory in accordance with the Business Plan.

13.3 Any and all Regulatory Approvals obtained hereunder for any Product shall including without limitation, the DMF, shall be processed by and remain the property of HepaSense, provided that HepaSense shall allow Elan and Isis access thereto to enable Elan and Isis to fulfil their respective obligations and exercise their respective rights under this Agreement. HepaSense shall maintain such Regulatory Approvals at its own cost. All regulatory approvals and submissions relating to the System, including without limitation, the MAF, shall be processed by and be the property of Elan and at all times held in Elan's sole name; provided, however, that Elan will authorize HepaSense to reference its regulatory approval and submission, as described herein, with the FDA and such foreign agency to the extent necessary for HepaSense's regulatory purposes.

13.4 It is hereby acknowledged that there are inherent uncertainties involved in the registration of pharmaceutical products with the RHA's insofar as obtaining approval is concerned and such uncertainties form part of the business risk involved in undertaking the form of commercial collaboration as set forth in this Agreement.

CLAUSE 14

MANUFACTURING

14.1 Subject to the provisions of Clause 14.2, HepaSense shall be responsible for manufacturing, or having manufactured, all quantities of Products required for the development and commercialization of Products for use in the Field.

14.2 Elan shall, at its option, manufacture the System for HepaSense and meet its requirements, on standard commercial terms negotiated in good faith by

HepaSense and Elan or to subcontract the manufacture and supply of the System and HepaSense shall agree to utilize Elan as its sole supplier, subject to the customary terms and conditions contained in a supply agreement to be executed by the parties. Isis shall have the right to manufacture and supply of the Designated Oligonucleotide with respect to the Product, on standard commercial terms negotiated in good faith by HepaSense and Isis or subcontract the manufacture and supply of the Designated Oligonucleotide. In the event Elan or Isis subcontract such manufacture and supply, the amount charged to HepaSense shall be [*]. Any such supply agreement shall be negotiated and agreed by the Parties not later than the date of completion of Phase III (as such term is commonly used in connection with FDA applications) of the R&D Plan.

CLAUSE 15

TECHNICAL SERVICES AND ASSISTANCE

15.1 Whenever commercially and technically feasible, HepaSense shall contract with Isis or Elan, as the case may be, to perform such other services as HepaSense may require, other than those specifically dealt with hereunder or in the License Agreements. In determining which Party should provide such services, the Management Committee shall take into account the respective infrastructure, capabilities and experience of Elan and Isis. There shall be no obligation upon either of Isis or Elan to perform such services.

15.2 HepaSense shall, if the Participants so agree, conclude an administrative support agreement with Elan and/or Isis on such terms as the Parties thereto shall in good faith negotiate. The administrative services shall include one or more of the following administrative services as requested by HepaSense:

15.2.1 accounting, financial and other services;

15.2.2 tax services;

15.2.3 insurance services;

15.2.4 human resources services;

15.2.5 legal and company secretarial services;

15.2.6 patent and related intellectual property services; and

15.2.7 all such other services consistent with and of the same type as those services to be provided pursuant to this Agreement, as may be required.

*CONFIDENTIAL TREATMENT REQUESTED

The foregoing list of services shall not be deemed exhaustive and may be changed from time to time upon written request by HepaSense.

15.3 The Parties agree that each Party shall effect and maintain comprehensive general liability insurance in respect of all clinical trials and other activities performed by them on behalf of HepaSense. The Participants and HepaSense shall ensure that the industry standard insurance policies shall be in place for all activities to be carried out by HepaSense.

15.4 If Elan or Isis so requires, Isis or Elan, as the case may be, shall receive, at times and for periods mutually acceptable to the Parties, employees of the other Party (such employees to be acceptable to the receiving Party in the matter of qualification and competence) for instruction in respect of the Elan Intellectual Property or the Isis Intellectual Property, as the case may be, as necessary to further the Project.

15.5 The employees received by Elan or Isis, as the case may be, shall be subject to obligations of confidentiality no less stringent than those set out in Clause 20 and such employees shall observe the rules, regulations and systems adopted by the Party receiving the said employees for its own employees or visitors.

CLAUSE 16

AUDITORS, BANKERS, REGISTERED OFFICE, ACCOUNTING REFERENCE DATE; SECRETARY; COUNSEL

Unless otherwise agreed by the Participants and save as may be provided to the contrary herein:

16.1 the auditors of HepaSense shall be KMPG Peat Marwick of Vallis Building, Hamilton, Bermuda;

16.2 the bankers of HepaSense shall be Bank of Bermuda or such other bank as may be mutually agreed from time to time;

16.3 the accounting reference date of HepaSense shall be December 31st in each Financial Year; and

16.4 the secretary of HepaSense shall be I.S. Outerbridge or such other Person as may be appointed by the Directors from time to time.

CLAUSE 17

TRANSFERS OF SHARES;
RIGHT OF FIRST OFFER; TAG ALONG RIGHTS

GENERAL:

17.1 No Shareholder shall, directly or indirectly, sell or otherwise transfer (each, a "TRANSFER") any Shares held by it except as expressly permitted by and in accordance with the terms of this Agreement. HepaSense shall not, and shall not permit any transfer agent or registrar for any Shares to, transfer upon the books of HepaSense any Shares from any Shareholder to any transferee, in any manner, except in accordance with this Agreement, and any purported transfer not in compliance with this Agreement shall be void.

During the Research and Development Term, no Shareholder shall, directly or indirectly, sell or otherwise Transfer any of its legal and/or beneficial interest in the Shares held by it to any other Person. After completion of the Research and Development Term, a Shareholder may Transfer Shares provided such Shareholder complies with the provisions of Clauses 17.2 and 17.3.

Notwithstanding anything contained herein to the contrary, at all times, EIS and/or Isis shall have the right to Transfer any Shares to their Affiliates provided, however, that such assignment does not result in adverse tax consequences for any other Parties. EIS shall have the right to Transfer any Shares to a special purpose financing or similar entity established by Elan or EIS; provided, that such Affiliates or other Permitted Transferee to which such legal and/or beneficial interest in the Shares have been transferred shall agree to be expressly subject to and bound by all the limitations and provisions which are embodied in this Agreement.

17.2 No Shareholder shall, except with the prior written consent of the other Shareholder, create or permit to subsist any Encumbrance over or in, all or any of the Shares held by it (other than by a Transfer of such Shares in accordance with the provisions of this Agreement).

17.3 RIGHTS OF FIRST OFFER:

If at any time after the end of the Research and Development Term a Shareholder shall desire to Transfer any Shares owned by it (a "SELLING SHAREHOLDER"), in any transaction or series of related transactions (other than a Transfer to an Affiliate or subsidiary or in the case of EIS to a special purpose financing or similar entity established by EIS), then such Selling Shareholder shall deliver prior written notice of its desire to Transfer (a "NOTICE OF INTENTION") (i) to HepaSense and (ii) to the Shareholders who are not the Selling Shareholder (and any transferee thereof permitted hereunder, if any), as applicable, setting forth such Selling Shareholder's desire to make such Transfer, the number of Shares proposed to be

transferred (the "OFFERED SHARES") and the proposed form of transaction (the "TRANSACTION PROPOSAL"), together with any available documentation relating thereto, if any, and the price at which such Selling Shareholder proposes to Transfer the Offered Shares (the "OFFER PRICE"). The "Right of First Offer" provided for in this Clause 16 shall be subject to any "Tag Along Right" benefiting a Shareholder which may be provided for by Clause 16, subject to the exceptions set forth therein.

Upon receipt of the Notice of Intention, the Shareholders who are not the Selling Shareholder shall have the right to purchase at the Offer Price the Offered Shares, exercisable by the delivery of notice to the Selling Shareholder (the "NOTICE OF EXERCISE"), with a copy to HepaSense, within 10 business days from the date of receipt of the Notice of Intention. If no such Notice of Exercise has been delivered by the Shareholders who are not the Selling Shareholder within such 10-business day period, or such Notice of Exercise does not relate to all of the Offered Shares covered by the Notice of Intention, then the Selling Shareholder shall be entitled to Transfer all of the Offered Shares to the intended transferee. In the event that all of the Offered Shares are not purchased by the non-selling Shareholders, the Selling Shareholder shall sell the available Offered Shares within 30 days after the delivery of such Notice of Intention on terms no more favorable to a third party than those presented to the non-selling Shareholders. If such sale does not occur, the Offered Shares shall again be subject to the Right of First Offer set forth in Clause 17.3.

In the event that any of the Shareholders who are not the Selling Shareholder exercises their right to purchase all of the Offered Shares (in accordance with this Clause 16), then the Selling Shareholder shall sell all of the Offered Shares to such Shareholder(s), in the amounts set forth in the Notice of Intention, after not less than 10 business days and not more than 25 business days from the date of the delivery of the Notice of Exercise. In the event that more than one of the Shareholders who are not the Selling Shareholders wish to purchase the Offered Shares, the Offered Shares shall be allocated to such Shareholders on the basis of their pro rata equity interests in HepaSense.

The rights and obligations of each of the Shareholders pursuant to the Right of First Offer provided herein shall terminate upon the date that the Common Shares are registered under Section 12(b) or 12(g) of the Exchange Act.

At the closing of the purchase of all of the Offered Shares by the Shareholders who are not the Selling Shareholder (scheduled in accordance with Clause 16), the Selling Shareholder shall deliver certificates evidencing the Offered Shares being sold, duly endorsed, or accompanied by written instruments of transfer in form reasonably satisfactory to the Shareholders who are not the Selling Shareholder, duly executed by the Selling Shareholder, free and clear of any adverse claims, against payment of the purchase price therefor in cash, and such other customary documents as shall be necessary in connection therewith.

Notwithstanding any other provision of this Clause 17.3, a Change in Control of any Stockholder shall not trigger a "Right of First Offer" in favor of any other Stockholder.

17.4 TAG ALONG RIGHTS:

Subject to Clause 17.3, a Shareholder (the "TRANSFERRING SHAREHOLDER") shall not Transfer (either directly or indirectly), in any one transaction or series of related transactions, to any Person or group of Persons, any Shares, unless the terms and conditions of such Transfer shall include an offer to the other Shareholders (the "REMAINING SHAREHOLDERS"), to sell Shares at the same price and on the same terms and conditions as the Transferring Shareholder has agreed to sell its Shares (the "TAG ALONG RIGHT").

In the event a Transferring Shareholder proposes to Transfer any Shares in a transaction subject to this Clause 16.4, it shall notify, or cause to be notified, the Remaining Shareholders in writing of each such proposed Transfer. Such notice shall set forth: (i) the name of the transferee and the amount of Shares proposed to be transferred, (ii) the proposed amount and form of consideration and terms and conditions of payment offered by the transferee (the "TRANSFEREE TERMS") and (iii) that the transferee has been informed of the Tag Along Right provided for in this Clause 16, if such right is applicable, and the total number of Shares the transferee has agreed to purchase from the Shareholders in accordance with the terms hereof.

The Tag Along Right may be exercised by each of the Remaining Shareholders by delivery of a written notice to the Transferring Shareholder (the "CO-SALE NOTICE") within 10 business days following receipt of the notice specified in the preceding subsection. The Co-sale Notice shall state the number of Shares owned by such Remaining Shareholder which the Remaining Shareholder wishes to include in such Transfer; provided, however, that without the written consent of the Transferring Shareholder, the amount of such securities belonging to the Remaining Shareholder included in such Transfer may not be greater than such Remaining Shareholder's percentage beneficial ownership of Fully Diluted Common Shares multiplied by the total number of Fully Diluted Common Shares to be sold by both the Transferring Shareholder and all Remaining Shareholders. Upon receipt of a Co-sale Notice, the Transferring Shareholder shall be obligated to transfer at least the entire number of Shares set forth in the Co-sale Notice to the transferee on the Transferee Terms; provided, however, that the Transferring Shareholder shall not consummate the purchase and sale of any Shares hereunder if the transferee does not purchase all such Shares specified in all Co-sale Notices. If no Co-sale Notice has been delivered to the Transferring Shareholder prior to the expiration of the 10 business day period referred to above and if the provisions of this Section have been complied with in all respects, the Transferring Shareholder shall have the right for a 45 day calendar day period to Transfer

Shares to the transferee on the Transferee Terms without further notice to any other party, but after such 45-day period, no such Transfer may be made without again giving notice to the Remaining Shareholders of the proposed Transfer and complying with the requirements of this Clause 17.

At the closing of any Transfer of Shares subject to this Clause 17, the Transferring Shareholder, and the Remaining Shareholder, in the event such Tag Along Right is exercised, shall deliver certificates evidencing such securities as have been Transferred by each, duly endorsed, or accompanied by written instruments of transfer in form reasonably satisfactory to the transferee, free and clear of any adverse claim, against payment of the purchase price therefor.

Notwithstanding the foregoing, this Clause 17 shall not apply to any sale of Common Shares pursuant to an effective registration statement under the Securities Act in a bona fide public offering.

The rights and obligations of each of the Stockholders pursuant to the "Tag Along Right" provided herein shall terminate upon the date that the Common Shares are registered under Section 12(b) or 12(g) of the Exchange Act.

Notwithstanding any other provision of this Clause 17.4, a Change in Control of any Stockholder shall not trigger a "Tag Along Right" in favor of any other Stockholder.

CLAUSE 18

MATTERS REQUIRING STOCKHOLDERS' APPROVAL

18.1 In consideration of Isis and Elan agreeing to enter into the License Agreements, the Parties hereby agree that HepaSense shall not without the prior approval of the EIS Director and the Isis Employee Directors:

18.1.1. make a material determination outside the ordinary course of business, including, among other things, acquisitions or dispositions of intellectual property and licenses or sublicenses, change the domicile of, HepaSense from or discontinue jurisdiction HepaSense out of Bermuda, changes in the Business or the HepaSense budget as they relate to the Licensed Technologies; enter into joint ventures and similar arrangements as they relate to the Licensed Technologies and changes to the Business Plan as they relate to the Licensed Technologies;

18.1.2. issue any unissued Preferred Shares or unissued Common Shares, or create or issue any new shares (including a split of the Shares) or Common Shares Equivalents, except as expressly permitted by the HepaSense Memorandum of Association or Bye-Laws;

18.1.3. alter any rights attaching to any class of share in the capital of HepaSense or alter the HepaSense Memorandum of Association or Bye-Laws;

18.1.4. consolidate, sub-divide or convert any of HepaSense's share capital or in any way alter the rights attaching thereto;

18.1.5. dispose of all or substantially all of the assets of HepaSense;

18.1.6. do or permit or suffer to be done any act or thing whereby HepaSense may be wound up (whether voluntarily or compulsorily), save as otherwise expressly provided for in this Agreement;

18.1.7. enter into any contract or transaction except in the ordinary and proper course of the Business on arm's length terms;

18.1.8. subject to Clause 24.13, assign, license or sub-license any of the Elan Intellectual Property, Isis Intellectual Property or HepaSense Intellectual Property;

18.1.9. amend or vary the terms of the Isis License Agreement or the Elan License Agreement;

18.1.10. permit a person other than HepaSense to own a regulatory approval relating to the Product(s);

18.1.11. amend or vary the Business Plan or the HepaSense budget as they relate to the Licensed Technologies;

18.1.12. alter the number of Directors;

18.1.13. register any Shares of the Company for public trading with any governmental authority for public trading in any securities market; and

18.1.14. declare or pay any dividend or make any distribution, directly or indirectly, with respect to its capital stock; or issue, sell, exchange, deliver, redeem, purchase or otherwise acquire or dispose of any shares of its capital stock or other securities.

CLAUSE 19

DISPUTES

19.1 Should any dispute or difference arise between Elan and Isis, or between Elan or Isis and HepaSense, during the period that this Agreement is in force, other than a dispute or difference relating to (i) the interpretation of any provision of this

Agreement, (ii) the interpretation or application of law, or (iii) the ownership of any intellectual property, then any Party may forthwith give notice to the other Parties that it wishes such dispute or difference to be referred to the Chief Executive Officer of Isis and the President of EPT.

19.2 In any event of a notice being served in accordance with Clause 19.1, each of the Participants shall within 14 days of the service of such notice prepare and circulate to the designated senior officer of each of Elan and Isis a memorandum or other form of statement setting out its position on the matter in dispute and its reasons for adopting that position. Each memorandum or statement shall be considered by the designated senior officers of each of Elan and Isis who shall endeavour to resolve the dispute. If designated senior officers of each of Elan and Isis agree upon a resolution or disposition of the matter, they shall each sign a statement which sets out the terms of their agreement. The Participants agree that they shall exercise the voting rights and other powers available to them in relation to HepaSense to procure that the agreed terms are fully and promptly carried into effect.

CLAUSE 20

TERMINATION/CERTAIN CHANGES OF CONTROL

20.1 This Agreement shall govern the operation and existence of HepaSense until

20.1.1 terminated by written agreement of all Parties hereto; or

20.1.2 otherwise terminated in accordance with this Clause 20.

20.2 For the purpose of this Clause 20, a "RELEVANT EVENT" is committed or suffered by a Participant if:

20.2.1 it commits a breach of its material obligations under this Agreement or the applicable License Agreement and fails to remedy it within 60 days of being specifically required in writing to do so by the other Participant; provided, however, that if the breaching Participant has proposed a course of action to rectify the breach and is acting in good faith to rectify same but has not cured the breach by the 60th day, such period shall be extended by such period as is reasonably necessary to permit the breach to be rectified; or

20.2.2 a distress, execution, sequestration or other process is levied or enforced upon or sued out against a material part of its property which is not discharged or challenged within 30 days; or

20.2.3 it is unable to pay its debts in the normal course of business; or

20.2.4 it ceases wholly or substantially to carry on its business, otherwise than for the purpose of a reconstruction or amalgamation, without the prior written consent of the other Participant (such consent not to be unreasonably withheld); or

20.2.5 the appointment of a liquidator, receiver, administrator, examiner, trustee or similar officer of such Participant or over all or substantially all of its assets under the law of any applicable jurisdiction, including without limitation, the United States of America, Bermuda or Ireland; or

20.2.6 an application or petition for bankruptcy, corporate re-organization, composition, administration, examination, arrangement or any other procedure similar to any of the foregoing under the law of any applicable jurisdiction, including without limitation, the United States of America, Bermuda or Ireland, is filed, and is not discharged within 60 days, or a Participant applies for or consents to the appointment of a receiver, administrator, examiner or similar officer of it or of all or a material part of its assets, rights or revenues or the assets and/or the business of a Participant are for any reason seized, confiscated or condemned.

20.4 If either Participant commits a Relevant Event, the other Shareholder shall have in addition to all other legal and equitable rights and remedies hereunder, the right to terminate this Agreement upon 30 days' written notice.

20.5 In the event of a termination of the Elan License Agreement and/or the Isis License Agreement, both parties will negotiate in good faith to determine whether this Agreement should be terminated and if so, which provisions should survive termination.

20.6 The provisions of Clauses 1.1, 3, 5.1, 9, 10, 11.11, 11.12,12.3, 13.3, 18, 19, 20, 22, 23 and 24 shall survive the termination of this Agreement under Clause 20.5 or by mutual consent pursuant to Clause 20.1 in accordance with their terms; all other terms and provisions of this Agreement shall cease to have effect and be null and void upon the termination of this Agreement under Clause 20.5 or by mutual consent pursuant to Clause 20.1; provided, however, that so long as the License Agreements remain in effect Clauses 11.1 through 11.10 shall also survive.

20.7 [* *].

*CONFIDENTIAL TREATMENT REQUESTED

20.8 In the event that [*] pursuant to Clause 20.7 above, the Participants shall jointly select a nationally recognised investment banking firm as arbitrator to make such determination. In the event the Participants do not agree upon the selection of such investment banking firm, Elan may contact the presiding justice of the Supreme Court of the State of New York sitting in the City, County, and State of New York (the "PRESIDING JUSTICE") and request that an independent US-based nationally recognised investment banking firm which is knowledgeable of the pharmaceutical/biotechnology industry be appointed within 10 Business Days. The Presiding Justice shall endeavor to select an investment banking firm as arbitrator which is technically knowledgeable in the pharmaceutical/biotechnology industry (and which directly and through its Affiliates, has no business relationship with, or shareholding in, either of the Participants). Promptly upon being notified of the arbitrator's appointment, the Participants shall submit to the arbitrator details of their assessment of the [*] together with such information as they think necessary to validate their assessment. The arbitrator shall notify Isis of the fair market value assessed by Elan (the "ELAN VALUATION") and shall notify Elan of the fair market value assessed by Isis (the "ISIS VALUATION"). The Participants shall then be entitled to make further submissions to the arbitrator within five Business Days explaining [*], as the case may be, are unjustified. The arbitrator shall thereafter meet with Isis and Elan and shall thereafter choose either the [*] on the basis of [*]. The arbitrator shall use its best efforts to determine [*] within 30 Business Days of his appointment. The Participants shall bear the costs of the arbitrator equally provided that the arbitrator may, in its discretion, allocate all or a portion of such costs to one Party. Any decision of the arbitrator shall be final and binding.

20.9 Elan shall purchase the Shares beneficially owned by Isis by delivery of the Purchase Price in cash no later than the 15th Business Day following determination of the Purchase Price by the arbitrator.

20.10 The Shares so transferred shall be sold by Isis with effect from the date of such transfer free from any lien, charge or encumbrance, but with all rights and restrictions attaching thereto.

20.11 If Elan exercises the Buyout Option pursuant to Clause 20.7, above, HepaSense shall continue to develop Isis Products on terms which are substantially the same as those which would be provided to an third party negotiating on an arm's length basis.

*CONFIDENTIAL TREATMENT REQUESTED

20.12 If Elan exercises the Buyout Option pursuant to Clause 20.7, above, both parties will negotiate in good faith to agree to additional reasonable provisions and/or amendments to the License Agreements to protect the intellectual property rights of the Participants.

20.13 If Elan exercises the Buyout Option pursuant to Clause 20.7, above, the provisions of Clauses 1, 3, 10.2.6, 11.2 through 11.12, 12.3, 20.11, 20.12, 20.13, 22, 23 and 24 shall survive the termination of this Agreement under this Clause 20.13; all other terms and provisions of this Agreement shall cease to have effect and be null and void.

CLAUSE 21

SHARE RIGHTS

21.1 The provisions regulating the rights and obligations attaching to the Common Shares and the Preferred Shares are set out in the HepaSense Bye-Laws.

CLAUSE 22

CONFIDENTIALITY

22.1 The Parties and/or HepaSense acknowledge and agree that it may be necessary, from time to time, to disclose to each other confidential and/or proprietary information, including without limitation, inventions, works of authorship, trade secrets, specifications, designs, data, know-how and other information, relating to the Field, the Products, present or future products, the HepaSense Intellectual Property, the Elan Intellectual Property or the Isis Intellectual Property, as the case may be, methods, compounds, research projects, work in process, services, sales suppliers, customers, employees and/or business of the disclosing Party, whether in oral, written, graphic or electronic form (collectively "CONFIDENTIAL INFORMATION").

22.2 Any Confidential Information revealed by a Party to another Party shall be maintained as confidential and shall be used by the receiving Party exclusively for the purposes of fulfilling the receiving Party's rights and obligations under this Agreement, and for no other purpose. Confidential Information shall not include:

22.2.1 information that is generally available to the public;

22.2.2 information that is made public by the disclosing Party;

22.2.3 information that is independently developed by the receiving Party, as evidenced by such Party's records, without the aid, application or use of the disclosing Party's Confidential Information;

22.2.4 information that is published or otherwise becomes part of the public domain without any disclosure by the receiving Party, or on the part of the receiving Party's directors, officers, agents, representatives or employees;

22.2.5 information that becomes available to the receiving Party on a non-confidential basis, whether directly or indirectly, from a source other than the disclosing Party, which source did not acquire this information on a confidential basis; or

22.2.6 information which the receiving Party is required to disclose pursuant to:

(i) a valid order of a court or other governmental body or any political subdivision thereof or as otherwise required by law, rule or regulation; or

(ii) other requirement of law;

provided, however, that if the receiving Party becomes legally required to disclose any Confidential Information, the receiving Party shall give the disclosing Party prompt notice of such fact so that the disclosing Party may obtain a protective order or confidential treatment or other appropriate remedy concerning any such disclosure. The receiving Party shall fully co-operate with the disclosing Party in connection with the disclosing Party's efforts to obtain any such order or other remedy. If any such order or other remedy does not fully preclude disclosure, the receiving Party shall make such disclosure only to the extent that such disclosure is legally required; or

22.2.7 information which was already in the possession of the receiving Party at the time of receiving such information, as evidenced by its records, provided such information was not previously provided to the receiving party from a source which was under an obligation to keep such information confidential; or

22.2.8 information that is the subject of a written permission to disclose, without restriction or limitation, by the disclosing Party.

22.3 Each Party agrees to disclose Confidential Information of another Party only to those employees, representatives and agents requiring knowledge thereof in connection with their duties directly related to the fulfilling of the Party's obligations under this Agreement, so long as such persons are under an obligation of confidentiality no less stringent than as set forth herein. Each Party further agrees to inform all such employees, representatives and agents of the terms and provisions of this Clause and their duties hereunder and to obtain their consent hereto as a condition of receiving Confidential Information. Each Party agrees

that it will exercise the same degree of care and protection to preserve the proprietary and confidential nature of the Confidential Information disclosed by a Party, as the receiving Party would exercise to preserve its own Confidential Information. Each Party agrees that it will, upon request of another Party, return all documents and any copies thereof containing Confidential Information belonging to or disclosed by such other Party. Each Party shall promptly notify the other Parties upon discovery of any unauthorized use or disclosure of the other Parties' Confidential Information.

22.4 Notwithstanding the above, each Party may use or disclose Confidential Information disclosed to it by another Party to the extent such use or disclosure is reasonably necessary in filing or prosecuting patent applications, prosecuting or defending litigation, complying with patent applications, prosecuting or defending litigation, complying with applicable governmental regulations or otherwise submitting information to tax or other governmental authorities, conducting clinical trials, or granting a permitted sub-license or otherwise exercising its rights hereunder; provided, that if a Party is required to make any such disclosure of the other Party's Confidential Information, other than pursuant to a confidentiality agreement, such Party shall inform the third party recipient of the terms and provisions of this Agreement and their duties hereunder and shall obtain their consent hereto as a condition of releasing to the third party recipient the Confidential Information.

22.5 Any breach of this Clause 22 by any employee, representative or agent of a Party is considered a breach by the Party itself.

22.6 The provisions relating to confidentiality in this Clause 22 shall remain in effect during the Term and for a period of seven years following the termination of this Agreement.

22.7 The Parties agree that the obligations of this Clause 22 are necessary and reasonable in order to protect the Parties' respective businesses, and each Party expressly agrees that monetary damages would be inadequate to compensate a Party for any breach by the other Party of its covenants and agreements set forth herein. Accordingly, the Parties agree and acknowledge that any such violation or threatened violation will cause irreparable injury to a Party and that, in addition to any other remedies that may be available, in law or in equity or otherwise, any Party shall be entitled to obtain injunctive relief against the threatened breach of the provisions of this Clause 22, or a continuation of any such breach by the other Party, specific performance and other equitable relief to redress such breach together with its damages and reasonable counsel fees and expenses to enforce its rights hereunder, without the necessity of proving actual or express damages.

CLAUSE 23

COSTS

23.1 Each Shareholder shall bear its own legal and other costs incurred in relation to preparing and concluding this Agreement and the Definitive Documents.

23.2 All other costs, legal fees, registration fees and other expenses relating to the transactions contemplated hereby, including the costs and expenses incurred in relation to the incorporation of HepaSense, shall be borne by HepaSense.

CLAUSE 24

GENERAL

24.1 GOOD FAITH:

Each of the Parties hereto undertakes with the others to do all things reasonably within its power that are necessary or desirable to give effect to the spirit and intent of this Agreement.

24.2 FURTHER ASSURANCE:

At the request of any of the Parties, the other Party or Parties shall (and shall use reasonable efforts to procure that any other necessary parties shall) execute and perform all such documents, acts and things as may reasonably be required subsequent to the signing of this Agreement for assuring to or vesting in the requesting Party the full benefit of the terms hereof.

24.3 NO REPRESENTATION:

Each of the Parties hereto hereby acknowledges that in entering into this Agreement it has not relied on any representation or warranty except as expressly set forth herein or in any document referred to herein.

24.4 FORCE MAJEURE:

Neither Party to this Agreement shall be liable for delay in the performance of any of its obligations hereunder if such delay is caused by or results from causes beyond its reasonable control, including without limitation, acts of God, fires, strikes, acts of war (whether war be declared or not), insurrections, riots, civil commotions, strikes, lockouts or other labor disturbances or intervention of any relevant government authority, but any such delay or failure shall be remedied by such Party as soon as practicable.

24.5 RELATIONSHIP OF THE PARTIES:

Nothing contained in this Agreement is intended or is to be construed to constitute Elan/EIS and Isis as partners, or Elan/EIS as an employee or agent of Isis, or Isis as an employee or agent of Elan/EIS.

No Party hereto shall have any express or implied right or authority to assume or create any obligations on behalf of or in the name of another Party or to bind another Party to any contract, agreement or undertaking with any third party.

24.6 COUNTERPARTS:

This Agreement may be executed in any number of counterparts, each of which when so executed shall be deemed to be an original and all of which when taken together shall constitute this Agreement.

24.7 NOTICES:

Any notice to be given under this Agreement shall be sent in writing by registered or recorded delivery post or reputable overnight courier such as Federal Express or telecopied to:

Elan at:

Lincoln House, Lincoln Place, Dublin 2, Ireland
Attention: Vice President & General Counsel
Elan Pharmaceutical Technologies,
a division of Elan Corporation, plc
Telephone: 353-1-709-4000
Fax: 353-1-709-4124

and

Elan International Services, Ltd.
102 St. James Court
Flatts, Smiths FL04
Bermuda
Attention: President
Telephone: 441-292-9169
Fax: 441-292-2224

Isis at:

2292 Faraday Avenue
Carlsbad, CA 92008
Attention: B. Lynne Parshall, Esq.
Telephone: 760-603-2460
Fax: 760-931-9639

HepaSense Ltd. at:

102 St. James Court
Clarendon House
Church St.
Hamilton, Bermuda
Attention: Secretary
Telephone: 441-295-1422
Fax: 441-292-4720

or to such other address(es) as may from time to time be notified by any Party to the others hereunder. A copy of any notice served by a Participant on HepaSense shall also be delivered to the other Participant.

Any notice sent by mail shall be deemed to have been delivered within three Business Days after dispatch or delivery to the relevant courier and any notice sent by telecopy shall be deemed to have been delivered upon confirmation of receipt. Notices of change of address shall be effective upon receipt. Notices by telecopy shall also be sent by another method permitted hereunder.

24.8 GOVERNING LAW; ARBITRATION

24.8.1 This Agreement shall be governed by and construed in accordance with the laws of the State of New York.

24.8.2 Any dispute under this Agreement or the other Transaction Documents which is not settled by mutual consent (whether pursuant to the provisions in Clause 19 hereof or otherwise) shall be finally settled by binding arbitration, conducted in accordance with the Commercial Arbitration Rules of the American Arbitration Association by one (1) arbitrator appointed in accordance with said rules. Such arbitrator shall be reasonably satisfactory to each of the Parties; provided, that if the Parties are unable to agree upon the identity of such arbitrator within 15 days of demand by either Party, then either Party shall have the right to petition the Presiding Justice to appoint an arbitrator.

The arbitration shall be held in New York, New York and the arbitrator shall be an independent expert in pharmaceutical product development and marketing (including clinical development and regulatory affairs).

The arbitrator shall determine what discovery will be permitted, consistent with the goal of limiting the cost and time which the Parties must expend for discovery; provided the arbitrator shall permit such discovery as they deem necessary to permit an equitable resolution of the dispute.

Any written evidence originally in a language other than English shall be submitted in English translation accompanied by the original or a true copy thereof.

The costs of the arbitration, including administrative and arbitrators' fees, shall be shared equally by the Parties and each Party shall bear its own costs and attorneys' and witness' fees incurred in connection with the arbitration.

In rendering judgement, the arbitrator shall be instructed by the Parties that he shall be permitted to select solely from between the proposals for resolution of the relevant issue presented by each Party, and not any other proposal.

A disputed performance or suspended performances pending the resolution of the arbitration must be completed within thirty (30) days following the final decision of the arbitrators or such other reasonable period as the arbitrators determine in a written opinion.

Any arbitration under the Transaction Documents shall be completed within one year from the filing of notice of a request for such arbitration.

The arbitration proceedings and the decision shall not be made public without the joint consent of the Parties and each Party shall maintain the confidentiality of such proceedings and decision unless otherwise permitted by the other Party.

The Parties agree that the decision shall be the sole, exclusive and binding remedy between them regarding any and all disputes, controversies, claims and counterclaims presented to the arbitrators. Application may be made to any court having jurisdiction over the Party (or its assets) against whom the decision is rendered for a judicial recognition of the decision and an order of enforcement.

24.9 SEVERABILITY:

If any provision in this Agreement is agreed by the Parties to be, deemed to be or becomes invalid, illegal, void or unenforceable under any law that is applicable hereto, such provision will be deemed amended to conform to applicable laws so as to be valid and enforceable or, if it cannot be so amended without materially altering the intention of the Parties, it will be deleted, with effect from the date of

such agreement or such earlier date as the Parties may agree, and the validity, legality and enforceability of the remaining provisions of this Agreement shall not be impaired or affected in any way.

24.10 AMENDMENTS:

No amendment, modification or addition hereto shall be effective or binding on any Party unless set forth in writing and executed by a duly authorized representative of all Parties.

24.11 WAIVER:

No waiver of any right under this Agreement shall be deemed effective unless contained in a written document signed by the Party charged with such waiver, and no waiver of any breach or failure to perform shall be deemed to be a waiver of any future breach or failure to perform or of any other right arising under this Agreement.

24.12 ASSIGNMENT:

None of the Parties shall be permitted to assign its rights or obligations hereunder without the prior written consent of the other Parties except as follows:

24.12.1 Elan, EIS and/or Isis shall have the right to assign their rights and obligations hereunder to their Affiliates provided, however, that such assignment does not result in adverse tax consequences for any other Parties.

24.12.2 Elan and EIS shall have the right to assign their rights and obligations hereunder to a special purpose financing or similar entity established by Elan or EIS.

24.13 ASSIGNMENT OF HEPASENSE INTELLECTUAL PROPERTY:

Upon one month's prior notice in writing from Elan to HepaSense and Isis, HepaSense shall assign the HepaSense Intellectual Property from HepaSense to a wholly-owned subsidiary of HepaSense to be incorporated in Ireland, which company shall be newly incorporated by Elan to facilitate such assignment.

24.14 WHOLE AGREEMENT/NO EFFECT ON OTHER AGREEMENTS:

This Agreement (including the Schedules attached hereto) and the Definitive Documents set forth all of the agreements and understandings between the Parties with respect to the subject matter hereof, and supersedes and terminates all prior agreements and understandings between the Parties with respect to the subject matter hereof. There are no agreements or understandings with respect to the

subject matter hereof, either oral or written, between the Parties other than as set forth in this Agreement and the Definitive Documents.

In the event of any ambiguity or conflict arising between the terms of this Agreement and those of the HepaSense Bye-Laws, except with respect to the rights and obligations attaching to the Common Shares and the Preferred Shares in which respect the HepaSense Bye-Laws shall prevail, the terms of this Agreement.

No provision of this Agreement shall be construed so as to negate, modify or affect in any way the provisions of any other agreement between any of the Parties unless specifically referred to, and solely to the extent provided herein. In the event of a conflict between the provisions of this Agreement and the provisions of the License Agreements, the terms of this Agreement shall prevail unless this Agreement specifically provide otherwise.

24.15 SUCCESSORS:

This Agreement shall be binding upon and inure to the benefit of the Parties hereto, their successors and permitted assigns.

IN WITNESS WHEREOF, the Parties hereto have executed this Agreement on the day first set forth above.

SIGNED

BY:
---

for and on behalf of
ELAN CORPORATION, PLC

in the presence of:

SIGNED

BY:
---

for and on behalf of
ELAN INTERNATIONAL SERVICES, LTD.

in the presence of:

SIGNED

BY:
---

for and on behalf of
ELAN PHARMA INTERNATIONAL LIMITED

in the presence of:

SIGNED

BY:
---

for and on behalf of
ISIS PHARMACEUTICALS, INC.

in the presence of:

SIGNED

BY:
----

for and on behalf of
HEPASENSE LTD.

in the presence of:

SCHEDULE 1

ELAN LICENSE AGREEMENT

SCHEDULE 2

ISIS LICENSE AGREEMENT

SCHEDULE 3

SUBSCRIPTIONS

ISIS 6,001 Common Shares
3,612 Preferred Shares

EIS 2,388 Preferred Shares

EXHIBIT 10.2

TEXT OMITTED AND FILED SEPARATELY
"CONFIDENTIAL TREATMENT REQUESTED
UNDER 17 C.F.R. SECTIONS 200.80(B)(4),
200.83 AND 240.24b-2."

SECURITIES PURCHASE AGREEMENT

SECURITIES PURCHASE AGREEMENT (this "Agreement"), dated as of January 14, 2000, between ISIS PHARMACEUTICALS, INC., a Delaware corporation (the "Company"), and ELAN INTERNATIONAL SERVICES, LTD., a Bermuda exempted limited liability company ("EIS") and a wholly-owned subsidiary of Elan Corporation, plc, an Irish public limited company ("Elan").

R E C I T A L S:

A. The Company desires to issue and sell to EIS, and EIS desires to purchase from the Company, (i) 12,015 shares of a newly-created series of the Company's Preferred Stock, par value $.001 per share, designated "Series B Convertible Exchangeable Preferred Stock" (the "Series B Preferred Stock"), (ii) shares of the Company's Common Stock, par value $.001 per share (the "Common Stock"), in amounts and at the times determined pursuant to Section 1(b)(ii) and (iii) hereof (the "Common Shares" and together with all shares of the Series B Preferred Stock, the "Shares"), and (iii) warrants to purchase shares of Common Stock in amounts and at the times determined pursuant to Section 1(b)(ii) and (iii) hereof (the "Warrants"). In addition, EIS has agreed to lend certain funds to the Company pursuant to a convertible promissory note in the form attached hereto as Exhibit A (as may be amended at any time, the "Note" and, together with the Series B Preferred Stock, the Common Shares, and the Warrants, the "Securities"), with a maximum aggregate principal amount of U.S.$12,015,000, amounts in respect of which shall be disbursed in accordance with its terms and subject to the conditions contained herein and therein and in the Funding Agreement. The rights, preferences and privileges of the Series B Preferred Stock are as set forth in the Certificate of Designation of the Series B Convertible Preferred Stock, (the "Certificate of Designation"), the form of which is attached hereto as Exhibit B.

B. The Company and EIS have formed HepaSense Ltd., a Bermuda exempted limited liability company ("HepaSense"), and pursuant to the terms of a Subscription, Joint Development and Operating Agreement, dated as of the date hereof (as may be amended at any time, the "JDOA"), simultaneously with the transactions contemplated by this Agreement, the Company shall acquire from HepaSense, for an aggregate purchase price of $12,015,000, (i) 6,001 shares of HepaSense's voting common stock, par value US$1.00 per share (the "HepaSense Common Shares"), representing 100% of the outstanding shares of such class of stock, and (ii) 3,612 shares of HepaSense's non-voting, convertible preferred stock, par value US$1.00 per share (the "HepaSense Preferred Shares" and together with the HepaSense Common Shares, the "HepaSense Capital Shares"), representing 60.20% of the aggregate outstanding HepaSense Preferred Shares and, on a fully diluted basis, 30.097% of the outstanding HepaSense Capital Shares. EIS will acquire from HepaSense, for an aggregate purchase price of $2,985,000, 2,388 HepaSense Preferred Shares, representing 39.80% of the aggregate outstanding HepaSense Preferred Shares and, on a fully diluted basis, 19.898% of the outstanding HepaSense Capital Shares. Additionally, as of the date hereof, HepaSense has entered into license agreements with (i) Elan and its subsidiary, Elan Pharma International Limited (such agreement, as may be amended at any time, the "Elan License

Agreement"), and (ii) the Company (such agreement, as may be amended at any time, the "Company License Agreement" and, together with the Elan License Agreement, the "License Agreements").

C. The Company and EIS are executing and delivering on the date hereof a Registration Rights Agreement, in the form attached hereto as Exhibit C (as amended at any time, the "Company Registration Rights Agreement"), in respect of the Common Stock issued or issuable upon (i) conversion of the Series B Preferred Stock and/or the Note and exercise of the Warrants, and (ii) the Common Shares to be issued and purchased hereunder, and any other Common Stock issued to EIS or any of its affiliates or permitted transferees upon any stock split, stock dividend, recapitalization or similar event affecting the Securities. The Company, EIS and HepaSense are also executing and delivering on the date hereof a Registration Rights Agreement in the form attached hereto as Exhibit D (as amended at any time, the "HepaSense Registration Rights Agreement"), in respect of the purchase of HepaSense Common Shares and HepaSense Preferred Shares by the Company and EIS. Additionally, the Company and EIS are executing and delivering on the date hereof a Funding Agreement in the form attached hereto as Exhibit E (the "Funding Agreement;" and, together with this Agreement, the Certificate of Designation, the JDOA, the Company Registration Rights Agreement, the HepaSense Registration Rights Agreement, the License Agreements and each other document or instrument executed and delivered in connection with the transactions contemplated hereby and by the JDOA, the "Transactions Documents").

A G R E E M E N T:

The parties hereto agree as follows:

SECTION 1. Closing.

(a) Time and Place. The closing of the transactions contemplated hereby (the "Closing") shall occur on the date hereof (the "Closing Date"), at the offices of Brock Silverstein LLC, 800 Third Avenue, 21st Floor, New York, NY 10022.

(b) Issuance of Securities.

(i) At the Closing, the Company shall issue and sell to EIS, and EIS shall purchase from the Company, for an aggregate purchase price of US$12,015,000 (the "Preferred Stock Purchase Price"), 12,015 shares of Series B Preferred Stock.

(ii) On the sixtieth (60th) trading day after the Closing (the "First Subsequent Purchase Date"), the Company shall issue and sell to EIS, and EIS shall purchase from the Company, for an aggregate purchase price of US$7,500,000 ("First Common Stock Purchase Price"), (A) the number of shares of Common Stock determined by dividing the First Common Stock Purchase Price by [*] of the average closing price of the Common Stock for the [*] trading days ending two days prior such [*] trading day and (B) a Warrant to purchase a number of shares of Common Stock equal to [*] of the aggregate number of shares of Common Stock to be purchased by EIS pursuant to clause (ii)(A) above, pursuant to a warrant certificate in the form attached hereto as Exhibit F. The purchase by

*CONFIDENTIAL TREATMENT REQUESTED

EIS of the securities to be issued on the First Subsequent Purchase Date is conditioned upon EIS' obtaining requisite approval, if any, pursuant to the Mergers and Takeover (Control) Act 1978-1996 (Ireland) (the "Mergers Act").

(iii) On any day within 5 trading days after the receipt by EIS from the Company of notification of the occurrence of the Completion Date (the "Second Subsequent Purchase Date"), the Company shall issue and sell to EIS, and EIS shall purchase from the Company, for an aggregate purchase price of US$7,500,000 (the "Second Common Stock Purchase Price"), (A) the number of shares of Common Stock determined by dividing the Second Common Stock Purchase Price by [*] of the average closing price of the Common Stock for the 60 trading days ending two days prior to the Completion Date and (B) a Warrant to purchase a number of shares of Common Stock equal to 5% of the aggregate number of shares of Common Stock to be purchased by EIS pursuant to clause (iii)(A) above, pursuant to a warrant certificate in the form attached hereto as Exhibit G. "Completion Date" shall mean the date upon which a nine month toxicity study, with results sufficient to support a decision that ISIS 14803 has [*], has been completed. The purchase by EIS of the securities to be issued on the Second Subsequent Purchase Date is conditioned upon EIS' obtaining requisite approval, if any, pursuant to the Mergers Act.

(c) Convertible Note Facility. EIS shall lend the Company up to US$12,015,000, pursuant to the terms and conditions of the Note.

(d) Delivery.

(i) At the Closing:

(A) EIS shall pay the Preferred Stock Purchase Price by wire transfer to an account designated by the Company and the parties hereto shall execute and deliver to each other, as applicable: (I) a certificate or certificates for the Series B Preferred Stock; (II) the Note; (III) the Company Registration Rights Agreement; (IV) the HepaSense Registration Rights Agreement; (V) the JDOA; (VI) the Certificate of Designation, as filed with the Secretary of State of the State of Delaware; (VII) the License Agreements; (VIII) the Funding Agreement; (IX) a secretary certificate, in substantially the form of Exhibit H attached hereto; and (X) any other documents or instruments reasonably requested by a party hereto; and

(B) The Company shall cause to be delivered to EIS an opinion of counsel in the form attached hereto as Exhibit I;

(C) There shall have been delivered to EIS and the Company a legal opinion of Bermuda counsel to HepaSense with respect to the due organization of HepaSense and the valid issuance by HepaSense of shares of HepaSense Capital Shares to EIS and the Company.

(ii) On the First Subsequent Purchase Date, EIS shall pay the First Common Stock Purchase Price by wire transfer to an account designated by the Company and the parties hereto shall execute and deliver to each other, as applicable: (A) a certificate or certificates for the Common Stock to be purchased on the First Subsequent Purchase Date, as determined pursuant to Section 1(b)(ii) hereof; (B) the Warrant to be issued pursuant to Section 1(b)(ii) hereof; (C) a secretary certificate of the Company, in substantially the form of Exhibit H; and (D) any other documents or instruments reasonably requested by a party hereto;

(iii) On the Second Subsequent Purchase Date, EIS shall pay the Second Common Stock Purchase Price by wire transfer to an account designated by the Company and the parties hereto shall execute and deliver to each other, as applicable: (A) a certificate or certificates for the Common Stock to be purchased on the Second Subsequent Purchase Date, as determined pursuant to Section 1(b)(iii) hereof; (B) the Warrant to be issued pursuant to Section 1(b)(iii) hereof; (C) a secretary certificate of the Company, in substantially the form of Exhibit H; and (D) any other documents or instruments reasonably requested by a party hereto.

(e) Exemption from Registration. The Securities and any underlying shares of Common Stock will be issued under an exemption or exemptions from registration under the Securities Act of 1933, as amended (the "Securities Act"). Accordingly, the certificates evidencing the Series B Preferred Stock and the Common Shares, the Warrants, the Note and any shares of Common Stock or other securities issuable upon the exercise, conversion or exchange of any of the Securities shall, upon issuance, contain legends, substantially in the forms as follows:

THE SECURITIES REPRESENTED HEREBY HAVE NOT BEEN REGISTERED UNDER THE SECURITIES ACT OF 1933, AS AMENDED, AND MAY NOT UNDER ANY CIRCUMSTANCES BE SOLD, TRANSFERRED OR OTHERWISE DISPOSED OF WITHOUT AN EFFECTIVE REGISTRATION STATEMENT FOR SUCH SECURITIES UNDER THE SECURITIES ACT OF 1933, AS AMENDED, AND ANY APPLICABLE STATE SECURITIES LAWS OR AN OPINION OF COUNSEL SATISFACTORY TO THE COMPANY THAT REGISTRATION IS NOT REQUIRED UNDER SUCH ACT OR APPLICABLE STATE SECURITIES LAWS.

THE TRANSFER OF THE SECURITIES REPRESENTED BY THIS CERTIFICATE IS ALSO SUBJECT TO THE RESTRICTIONS CONTAINED IN THAT CERTAIN SECURITIES PURCHASE AGREEMENT, DATED AS OF JANUARY 14, 2000, BY AND BETWEEN ISIS PHARMACEUTICALS, INC. AND ELAN INTERNATIONAL SERVICES, LTD.

SECTION 2. Representations and Warranties of the Company. The Company hereby represents and warrants to EIS, as of the date hereof, as follows:

(a) Organization. The Company is duly organized, validly existing and in good standing under the laws of the State of Delaware and has all requisite corporate power and authority to own and lease its properties, to carry on its business as presently conducted and as proposed to be conducted and to consummate the transactions contemplated hereby. The Company is duly qualified as a foreign corporation and in good standing to do business in each jurisdiction in which the nature of the business conducted or the property owned by it requires such qualification, except where the failure to be so qualified would not, individually or in the aggregate, have a material adverse effect on the business, assets, liabilities (contingent or otherwise), operations, condition (financial or otherwise), or prospects of the Company (a "Company Material Adverse Effect").

(b) Capitalization. As of the Closing Date, the Company has reserved a sufficient number of shares of Common Stock: (i) for issuance upon conversion of the Series B Preferred Stock being purchased hereunder by EIS (including dividends in-kind thereon), (ii) for issuance upon exercise of the Warrants, and (iii) for issuance upon conversion of the Note (including interest payable thereon). The Shares, when issued against payment therefor in accordance with this Agreement, will be duly and validly issued, fully paid and nonassessable, will not be issued in violation of any preemptive or similar rights. The shares of Common Stock underlying the Series B Preferred Stock, the Note and the Warrants (the "Underlying Shares"), when issued upon conversion or exercise in accordance with the terms thereof, will be duly and validly issued, fully paid and nonassessable, and will not be issued in violation of any preemptive or similar rights.

(c) Authorization of Transactions Documents. The Company has full corporate power and authority to execute and deliver this Agreement and each of the other Transactions Documents to which it is a party, and to perform its obligations hereunder and thereunder. The execution, delivery and performance by the Company of this Agreement and each of the other Transactions Documents to which it is a party, including the issuance and sale of the Securities, have been duly authorized by all requisite corporate action by the Company and, when executed and delivered by the Company, this Agreement and each of the other Transactions Documents to which it is a party will be the valid and binding obligations of the Company, enforceable against the Company in accordance with their respective terms, except (A) that enforcement may be limited by (i) applicable bankruptcy, insolvency, reorganization, arrangement, moratorium or other similar laws affecting creditors' rights, and (ii) general equity principles and limitations on the availability of equitable relief, including specific performance, and (B) that any rights to indemnity or contribution hereunder or thereunder may be limited by state and federal securities laws and by public policy considerations.

(d) No Violation. The execution, delivery and performance by the Company of this Agreement and each other Transactions Document to which it is a party, including the issuance and sale of the Securities, and compliance with the provisions hereof and thereof by the Company, does not conflict with or constitute or result in a breach of or default under (or an event which with notice or passage of time or both would constitute a default) or give rise to any right of termination, cancellation or acceleration under (i) the Certificate of Incorporation, as amended, or by-laws, of the

Company, (ii) applicable law, statute, rule or regulation, or any ruling, writ, injunction, order, judgment or decree of any court, arbitrator, administrative agency or other governmental body applicable to the Company or any of its properties or assets, or (iii) any material contract or agreement affecting the Company, including any contract filed as an exhibit to the Company's Annual Report on Form 10-K for the year ended December 31, 1998 (the "1998 Form 10-K") or any subsequent interim quarterly report, except where such breach, default, termination, cancellation or acceleration would not, individually or in the aggregate, have a Company Material Adverse Effect.

(e) Approvals. Other than as may be necessary pursuant to the Mergers Act or applicable Bermuda Securities laws, no material permit, authorization, consent, approval, or order of or by, or any notification of or filing with, any person or entity (governmental or otherwise) is required in connection with the execution, delivery or performance of this Agreement or the Transactions Documents, including the issuance and sale of the Securities, by the Company, other than the filing of a Form D by the Company pursuant to Regulation D under the Securities Act ("Regulation D").

(f) SEC Filings. The Company has filed with the Securities and Exchange Commission (the "SEC") all forms, reports, schedules, statements, exhibits and other documents (collectively, the "SEC Filings") required to be filed by the Company on or before the date hereof. At the time filed, the SEC Filings, including without limitation, any financial statements, exhibits and schedules included therein or documents incorporated therein by reference (i) did not contain any untrue statement of a material fact or omit to state a material fact required to be stated therein or necessary in order to make the statements therein, in light of the circumstances under which they were made, not misleading and (ii) complied in all material respects with the applicable requirements of the Securities Act or the Securities Exchange Act of 1934, as amended (the "Exchange Act"), as the case may be.

(g) Financial Statements. The audited financial statements of the Company for the years ending December 31, 1997 and December 31, 1998, together with the related statements of operations, stockholders' equity (deficit) and cash flows for each of the two years then ended and the reports and opinions thereon of Ernst & Young LLP, contained in the Company's 1997 Form 10-K and 1998 Form 10-K and the Company's unaudited balance sheet for the period ending September 30, 1999, together with the related statements of operations, stockholders' equity (deficit) and cash flows for the quarter then ended (as set forth in the Company's Form 10-Q, for the quarterly period ending September 30, 1999), comply as to form in all material respects with applicable accounting requirements and the published rules and regulation of the SEC with respect thereto, and fairly present, in all material respects, the financial position of the Company and the results of its operations and its cash flows at such dates and for the periods then ended and were prepared in conformity in all material respects with generally accepted accounting principles applied on a consistent basis, subject, in the case of the unaudited financial statements for the quarterly period ending September 30, 1999, to normal year-end audit adjustments (which shall not be material in the aggregate) and the absence of footnote disclosures.

(h) Litigation. There is no legal, administrative, arbitration or other action or proceeding or to the Company's knowledge governmental investigation pending, or to the

Company's knowledge, threatened in writing against the Company, or any director, officer or employee of the Company that challenges the validity or performance of this Agreement or the other Transactions Documents to which the Company is a party.

(i) Absence of Certain Events. Since December 29, 1999, except as contemplated by the Transactions Documents, (A) the Company has not (i) made, paid or declared any dividend or distribution to any equity holder (in such capacity) or redeemed any of its capital stock, (ii) varied its business plan or practices, in any material respect, from past practices, (iii) entered into any financing, joint venture, license or similar arrangement that would limit or restrict its ability to perform its obligations hereunder and under each of the other Transactions Documents to which it is a party, or (iv) suffered or permitted to be incurred any liability or obligation or any lien or encumbrance against any of its properties or assets that would limit or restrict its ability to perform its obligations hereunder and under each of the other Transactions Documents to which it is a party, and (B) there has not been any change or development which has had, or in the Company's reasonable judgment is likely to have, a Company Material Adverse Effect.

(j) Disclosure. The representations and warranties set forth herein and in the other Transactions Documents, when viewed collectively, do not contain any untrue statement of a material fact or omit to state any material fact necessary to make the statements contained herein or therein not misleading in light of the circumstances in which they were made.

(k) Brokers or Finders. There have been no investment bankers, brokers or finders used by the Company in connection with the transactions contemplated by the Transactions Documents and no such persons or entities are entitled to a fee or compensation in respect thereof.

SECTION 3. Representation and Warranties of EIS. EIS hereby represents and warrants to the Company, as of the date hereof, as follows:

(a) Organization. EIS is duly organized, validly existing and in good standing under the laws of Bermuda and has all requisite corporate power and authority to own and lease its properties, to carry on its business as presently conducted and as proposed to be conducted and to consummate the transactions contemplated hereby. EIS is duly qualified as a foreign corporation and in good standing to do business in each jurisdiction in which the nature of the business conducted or the property owned by it requires such qualification, except where the failure to be so qualified would not, individually or in the aggregate, have a material adverse effect on the business, assets, liabilities (contingent or otherwise), operations, condition (financial or otherwise), or prospects of EIS (an "EIS Material Adverse Effect").

(b) Authorization of Transactions Documents. EIS has full corporate power and authority to execute and deliver this Agreement and each of the other Transactions Documents to which it is a party, and to perform its obligations hereunder and thereunder. The execution, delivery, and performance by EIS of this Agreement and each other Transactions Document to which it is a party, including the purchase and acceptance of the Securities, have been duly authorized by all requisite corporate action by EIS and, when executed and delivered by EIS, this Agreement and each of the other Transactions Documents to which it is a party, will be the valid and binding obligations

of EIS, enforceable against it in accordance with their respective terms, except (A) that enforcement may be limited by (i) applicable bankruptcy, insolvency, reorganization, arrangement, moratorium or other similar laws affecting creditors' rights, and (ii) general equity principles and limitations on the availability of equitable relief, including specific performance, and (B) that any rights to indemnity or contribution hereunder or thereunder may be limited by state and federal securities laws and by public policy considerations.

(c) No Violation. The execution, delivery and performance by EIS of this Agreement and each other Transactions Document to which it is a party, including the purchase and acceptance of the Securities, and compliance with provisions hereof and thereof by EIS, will not conflict with or constitute or result in a breach of or default under (or an event which with notice or passage of time or both would constitute a default) or give rise to any right of termination, cancellation or acceleration under (i) the Memorandum and Articles of Association of EIS, (ii) any applicable law, statute, rule or regulation, or any ruling, writ, injunction, order, judgment or decree of any court, arbitrator, administrative agency or other governmental body applicable to EIS or any of its properties or assets, or (iii) any material contract to which EIS is party, except where such breach, default, termination, cancellation or acceleration would not, individually or in the aggregate, have an EIS Material Adverse Effect.

(d) Approvals. Except for consent required under the Mergers Act, no material permit, authorization, consent, approval or order of or by, or any notification of or filing with, any person or entity (governmental or otherwise) is required in connection with the execution, delivery or performance of this Agreement or the Transactions Documents by EIS.

(e) Investment Representations.

(i) EIS is sophisticated in transactions of this type and capable of evaluating the merits and risks of the transactions described herein and in the other Transactions Documents to which it is a party, and has the capacity to protect its own interests. EIS has not been formed solely for the purpose of entering into the transactions described herein and therein and is acquiring the Securities (and the Underlying Shares) for investment for its own account, not as a nominee or agent, and not with the view to, or for resale, distribution or fractionalization thereof, in whole or in part, and no other person (other than Elan) has a direct or indirect interest, beneficial or otherwise in the Securities (or the Underlying Shares); provided, however, that EIS shall be permitted to convert or exchange such Securities in accordance with their terms.

(ii) EIS has not and does not intend to enter into any contract, undertaking, agreement or arrangement with any person or entity to sell, transfer or pledge the Securities (or the Underlying Shares), other than a transfer to a current affiliate or subsidiary or a special purpose financing or similar vehicle established by EIS or one of its affiliates.

(iii) EIS acknowledges its understanding that the private placement and sale of the Securities (and the Underlying Shares) is exempt from registration under the Securities Act by virtue of the provisions of Regulation D. In furtherance thereof, EIS represents and warrants that it is an "accredited investor" as that term is defined in Regulation D, has the financial ability to bear the economic risk of its investment, has adequate means for providing for its current needs and personal contingencies and has no need for liquidity with respect to its investment in the Company.

(iv) EIS agrees that it shall not sell or otherwise transfer any of the Securities (or the Underlying Shares) without registration under the Securities Act or pursuant to an opinion of counsel reasonably satisfactory to the Company that an exemption from registration is available, and fully understands and agrees that it must bear the total economic risk of its purchase for an indefinite period of time because, among other reasons, none of the Securities (or the Underlying Shares) have been registered under the Securities Act or under the securities laws of any applicable state or other jurisdiction and, therefore, cannot be resold, pledged, assigned or otherwise disposed of unless subsequently registered under the Securities Act and under the applicable securities laws of such states or jurisdictions or an exemption from such registration is available. EIS understands that the Company is under no obligation to register the Securities (or the Underlying Shares) on its behalf with the exception of certain registration rights with respect to certain of the Securities (and the Underlying Shares), as provided in the Company Registration Rights Agreement. EIS understands the lack of liquidity and restrictions on transfer of the Securities (and the Underlying Shares) and that this investment is suitable only for a person or entity of adequate financial means that has no need for liquidity of this investment and that can afford a total loss of its investment.

(f) Litigation. There is no legal, administrative, arbitration or other action or proceeding or governmental investigation pending, or to EIS's knowledge threatened, against EIS that challenges the validity or performance of this Agreement or the other Transactions Documents to which EIS is a party.

(g) Brokers or Finders. There have been no investment bankers, brokers or finders used by EIS in connection with the transactions contemplated by the Transactions Documents and no such persons or entities are entitled to a fee or compensation in respect thereof.

SECTION 4. Covenants of the Parties.

(a) Operating Covenants. From and after the Closing Date for so long as the Note is outstanding and until the earlier to occur of the exercise or expiration of the EIS Exchange Right (as such term is defined in Section 5 hereof), the Company shall not without the prior written consent of EIS: (i) sell, transfer, encumber, pledge or otherwise affect, in any respect, (A) any HepaSense Capital Shares owned by the Company, including, without limitation, those HepaSense Preferred Shares transferable to EIS upon exercise by EIS of the EIS Exchange Right, or (B) its ability to permit EIS to exercise the EIS Exchange Right in full, as provided herein or (ii) enter into any material transaction with a director, officer or beneficial owner of more than 20% of Common

Stock on other than an arm's length basis. From and after the Closing Date and until the earlier to occur of the exercise or expiration of the EIS Exchange Right, EIS shall not without the prior written consent of the Company encumber, pledge or otherwise affect, in any respect, any HepaSense Capital Shares owned by EIS.

(b) Fully-diluted Stock Ownership. Notwithstanding any other provision of this Agreement, in the event that EIS shall have determined that at any time it (together with its affiliates, if applicable) holds or has the right to receive Common Stock (or securities or rights, options or warrants exercisable, exchangeable or convertible for or into Common Stock) representing in the aggregate in excess of [*] of the Company's outstanding Common Stock on a fully diluted basis (assuming the exercise, exchange or conversion of such securities beneficially owned by EIS or its affiliates, but not the exercise, exchange or conversion of any other similar securities), EIS shall have the right to convert the Series B Preferred Stock and the shares issuable upon conversion of the Note into non-voting, convertible liquidation preferred stock of the Company such that EIS and its affiliates will not directly or indirectly own more than [*] of the Common Stock for a period of at least two years from the election of the conversions of the Series B Preferred Stock or the Note. In the event that EIS shall undertake to exercise such right, EIS shall retain the additional right to exchange such new class of equity security for Common Stock, in its discretion at any time after two years from the issuance date of the new securities pursuant to the terms of the underlying security. Each of the Company and EIS shall use commercially reasonable efforts to effect such transactions and any required subsequent conversions or adjustments to EIS's securities position, on a quarterly basis, within 10 business days of the end of each of EIS's fiscal quarters. The Company shall bear the fees and expenses in connection with the foregoing for the first such conversion by EIS; thereafter, EIS shall reimburse the Company for its reasonable legal fees and expenses, filing fees and other reasonable and documented costs and fees in connection with carrying out the foregoing.

(c) Use of Proceeds. The Company shall use the proceeds of (i) the issuance and sale of the Series B Preferred Stock solely to fund its initial capital contributions to, and funding of, HepaSense as described in the JDOA, and (ii) the issuance and funding of the Note solely to fund development amounts in connection with the business of HepaSense, as described in the Funding Agreement and, in each case, for no other purpose.

(d) Confidentiality; Non-Disclosure.

(i) Subject to clauses (ii) and (iii) below, from and after the date hereof, neither the Company nor EIS (nor their respective affiliates) shall disclose to any person or entity this Agreement or the other Transactions Documents or the contents thereof or the parties thereto, except that such parties may make such disclosure (x) to their directors, officers, employees and advisors, so long as they shall have advised such persons of the obligation of confidentiality herein and for whose breach or default the disclosing party shall be responsible, or (y) as required by applicable law, rule, regulation or judicial or administrative process, provided that the disclosing party uses reasonable efforts to obtain an order or ruling protecting the confidentiality of confidential information of the other party contained herein or therein. The parties shall be entitled to seek injunctive or other equitable

*CONFIDENTIAL TREATMENT REQUESTED

relief in respect of any breach or threatened breach of the foregoing covenant without the requirement of posting a bond or other collateral.

(ii) Prior to issuing any press release or public disclosure in respect of this Agreement or the transactions contemplated hereby, the party proposing such issuance shall obtain the consent of the other party to the contents thereof, which consent shall not be unreasonably withheld or delayed; it being understood that if such second party shall not have responded to such consent request within five business days, such consent shall be deemed given.

(iii) This Section 4(d) shall not be construed to prohibit disclosure by the receiving party of any information which has not been previously determined to be confidential by the disclosing party, or which shall have become publicly disclosed (other than by breach of the receiving party's obligations hereunder).

(e) Further Assurances. From and after the date hereof, each of the parties hereto agree to do or cause to be done such further acts and things and deliver or cause to be delivered to each other such additional assignments, agreements, powers and instruments, as each may reasonably require or deem advisable to carry into effect the purposes of this Agreement and the other Transactions Documents.

SECTION 5. Conversion and Exchange Rights. The Certificate of Designation sets forth certain rights of the holders of shares of Series B Preferred Stock to convert such shares of preferred stock into newly issued shares of Common Stock, or to exchange such shares of Series B Preferred Stock into (i) the shares of HepaSense Preferred Shares owned by the Company or (ii) if the HepaSense Preferred Shares issued to the Company on the date hereof are converted into HepaSense Common Shares, the HepaSense Common Shares received upon such conversion (the "EIS Exchange Right"), both on the terms and conditions set forth therein.

SECTION 6. Pledge of HepaSense Preferred Shares.

(a) In order to secure the Company's obligations pursuant to the EIS Exchange Right, except as provided in Section 6(e) hereof, the Company hereby pledges, assigns, grants and sets over to EIS, all of the Company's right, title and interest in and to all HepaSense Preferred Shares deliverable by the Company upon exercise of the EIS Exchange Right (including share distributions and dividends thereon, any security into which such HepaSense Preferred Shares shall be converted and all certificates representing such shares of capital stock and, issued as an addition to, in substitution or in exchange for, or on account of any such shares, now or hereafter acquired by the Company, the "Pledged Shares").

(b) The Company shall cause to be delivered to EIS all of the certificates evidencing the Pledged Shares together with duly executed stock power in favor of EIS, and cause to be filed with the Secretary of State of California an appropriate UCC-1 financing statement in respect of such pledge, assignment or setting over, and take all other necessary, appropriate and customary actions in connection therewith.

(c) During the term of this pledge, in the event the Company shall be entitled to receive by reason of its ownership of any of the Pledged Shares any:

(i) Stock certificates issued in connection with any increase or reduction in capital, reclassification, merger, consolidation, sale of assets, combination of shares, stock split, spin-off or split-off; or

(ii) Option, warrant or right, whether as an addition to or in substitution or exchange for any of the Pledged Shares or otherwise;

then, in each such case, the Company shall accept the same as agent of EIS or its permitted assign, in trust for EIS or its permitted assign and shall deliver the same immediately to EIS or its permitted assign in the exact form received with the Company's endorsement, to the extent necessary, or appropriate stock powers duly executed by the Company, to be held by EIS or its permitted assign as part of the Pledged Shares in accordance with the terms and conditions contained in this Section 6.

(d) The obligations of the Company under this Section 6 shall commence upon the date hereof and shall terminate and be of no further force and effect upon the expiration of the EIS Exchange Right. Upon the termination of the pledge of the Pledged Shares, (i) the security interests granted hereby shall terminate and all rights to the Pledged Shares shall revert to the Company, (ii) EIS or its permitted assignee shall (x) deliver to the Company all of the certificates evidencing the Pledged Shares (including the securities delivered pursuant to Section 6(c)(i) and 6(c)(ii) hereof) and (y) execute and deliver to the Company such documents as the Company shall reasonably request to evidence the termination of the security interest granted in this Section 6, including, without limitation, a UCC Form 3 termination statement.

(e) Such pledge shall be governed by the applicable provisions of the New York Uniform Commercial Code. Upon exercise of the EIS Exchange Right, EIS shall be entitled to keep and retain such share certificates, which shall then be owned by EIS in accordance with the terms thereof. Except as specifically provided in Section 6(c) hereof, until EIS exercises the EIS Exchange Right, the Company shall retain all rights in and to the Pledged Shares (including without limitation all voting, dividend, liquidation and other rights), subject only to this pledge and the JDOA.

SECTION 7. Survival Period. The representations and warranties of the Company and EIS contained herein shall survive for a period of two years from and after the date hereof.

SECTION 8. Notices. All notices, demands and requests of any kind to be delivered to any party in connection with this Agreement shall be in writing and shall be deemed to have been duly given if personally or hand delivered or if sent by an internationally-recognized overnight delivery or by registered or certified mail, return receipt requested and postage prepaid, or by facsimile transmission (with receipt confirmed by telephone) addressed as follows:

(i) if to the Company, to:

Isis Pharmaceuticals, Inc.
2292 Faraday Avenue
Carlsbad, CA 92008
Attn: B. Lynne Parshall
Tel.: 760-603-2460
Fax: 760-931-9639

with a copy to:
Cooley Godward LLP
4365 Executive Drive
San Diego, CA 92121
Attn: Julie Robinson, Esq.
Tel.: 619-550-6000
Fax: 619-453-3555

(ii) if to EIS, to:

Elan International Services, Ltd.
Flatts, Smiths Parish
Bermuda, FL 04
Attention: Director
Tel.: 441-292-9169
Fax: 441-292-2224

with a copy to:

Brock Silverstein LLC
800 Third Avenue
New York, New York 10022
Attention: Scott Rosenblatt, Esq.
Tel.: 212-371-2000
Fax: 212-371-5500

or to such other address as the party to whom notice is to be given may have furnished to the other party hereto in writing in accordance with provisions of this Section 8. Any such notice or communication shall be deemed to have been effectively given (i) in the case of personal or hand delivery, on the date of such delivery, (ii) in the case of an internationally-recognized overnight delivery service, on the second business day after the date when sent, (iii) in the case of mailing, on the fifth business day following that day on which the piece of mail containing such communication is posted, and (iv) in the case of facsimile transmission, on the date of telephone confirmation of receipt.

SECTION 9. Entire Agreement. This Agreement and the other Transactions Documents contain the entire understanding of the parties with respect to the subject matter hereof and thereof and supersede all prior agreements and understandings among the parties with respect thereto.

SECTION 10. Amendments. This Agreement may not be modified or amended, or any of the provisions hereof waived, except by written agreement of the Company and EIS dated after the date hereof.

SECTION 11. Counterparts and Facsimile. The Transactions Documents may be executed in any number of counterparts, and each such counterpart hereof shall be deemed to be an original instrument, but all such counterparts together shall constitute one agreement. Each of the Transactions Documents may be signed and delivered to the other party by facsimile transmission; such transmission shall be deemed a valid signature.

SECTION 12. Headings. The section and paragraph headings contained in this Agreement are for reference purposes only and shall not affect in any way the meaning or interpretation of this Agreement.

SECTION 13. Governing Law. This Agreement shall be governed by and construed in accordance with the laws of the State of New York, without giving effect to principles of conflicts of laws, except that all issues concerning the relative rights of the Company and its stockholders shall be governed by the Delaware General Corporation Law, without giving effect to the principles of conflicts of laws.

SECTION 14. Arbitration.

(a) Any dispute under the Transactions Documents which is not settled by mutual consent shall be finally settled by binding arbitration, conducted in accordance with the Commercial Arbitration Rules of the American Arbitration Association by one arbitrator appointed in accordance with said rules. Such arbitrator shall be reasonably satisfactory to each of the parties; provided, that if the parties are unable to agree upon the identity of such arbitrator within 15 days of demand by either party, then either party shall have the right to petition a presiding justice of the Supreme Court of New York, New York County, to appoint an arbitrator. The arbitration shall be held in New York, New York and the arbitrator shall be an independent expert in pharmaceutical product development and marketing (including clinical development and regulatory affairs).

(b) The arbitrator shall determine what discovery will be permitted, consistent with the goal of limiting the cost and time which the parties must expend for discovery; provided the arbitrator shall permit such discovery as he or she deems necessary to permit an equitable resolution of the dispute. Any written evidence originally in a language other than English shall be submitted in English translation accompanied by the original or a true copy thereof. The costs of the arbitration, including administrative and arbitrators' fees, shall be shared equally by the parties and each party shall bear its own costs and attorneys' and witness' fees incurred in connection with the arbitration.

(c) In rendering judgment, the arbitrator shall be instructed by the parties that he or she shall be permitted to select solely from between the proposals for resolution of the relevant issue presented by each party, and not any other proposal. A disputed performance or suspended performances pending the resolution of the arbitration must be completed within 30 days following the final decision of the arbitrators or such other reasonable period as the arbitrators determine in a written opinion.

(d) Any arbitration under the Transactions Documents shall be completed within one year from the filing of notice of a request for such arbitration. The arbitration proceedings and the decision shall not be made public without the joint consent of the parties and each party shall maintain the confidentiality of such proceedings and decision unless otherwise permitted by the other party.

(e) The parties agree that the decision shall be the sole, exclusive and binding remedy between them regarding any and all disputes, controversies, claims and counterclaims presented to the arbitrators. Application may be made to any court having jurisdiction over the party (or its assets) against whom the decision is rendered for a judicial recognition of the decision and an order of enforcement.

SECTION 15. Expenses. Each of the parties shall be responsible for its own costs and expenses incurred in connection with the transactions contemplated hereby and by the other Transactions Documents.

SECTION 16. Schedules, etc. All statements contained in any exhibit or schedule delivered by the parties hereto, or in connection with the transactions contemplated hereby, are an integral part of this Agreement and shall be deemed representations and warranties hereunder.

SECTION 17. Assignments and Transfers. This Agreement and all of the provisions hereof shall be binding upon and inure to the benefit of the parties hereto and their respective successors and permitted assigns. This Agreement, the shares of Series B Preferred Stock and the shares of Common Stock being purchased hereunder by EIS, the Note, the Warrants, and the shares of Common Stock underlying the Series B Preferred Stock, the Note and the Warrants may be transferred by EIS to its affiliates and subsidiaries, as well as any special purpose financing or similar vehicle established by EIS or its affiliates, provided, however, that EIS shall remain liable for its obligations hereunder after any such assignment. Other than as set forth above, no party shall transfer or assign this Agreement, the shares of Series B Preferred Stock and Common Shares being purchased hereunder by EIS, the Note, the Warrants, and the shares of Common Stock underlying the Series B Preferred Stock, the Note and the Warrants, or any interest therein, without the prior written consent of the other party; provided, however, that no consent shall be required in connection with any such transfer or assignment by a party pursuant to a sale of all or substantially all of the business of such party whether by merger, sale of stock, sale of assets or otherwise.

SECTION 18. Severability. In case any provision of this Agreement shall be invalid, illegal or unenforceable, the validity, legality and enforceability of the remaining provisions shall not be in any way affected or impaired thereby.

[Signature Page Follows.]

IN WITNESS WHEREOF, each of the undersigned has duly executed this Agreement as of the date first written above.

ISIS PHARMACEUTICALS, INC.

By:

B. Lynne Parshall
Executive Vice President

ELAN INTERNATIONAL SERVICES, LTD.

By:

Kevin Insley
President

EXHIBIT A
CONVERTIBLE PROMISSORY NOTE

EXHIBIT B
CERTIFICATE OF DESIGNATION

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EXHIBIT C
COMPANY REGISTRATION RIGHTS AGREEMENT

EXHIBIT D
HEPASENSE REGISTRATION RIGHTS AGREEMENT

EXHIBIT E
FUNDING AGREEMENT

EXHIBIT F
WARRANT CERTIFICATE
(FIRST SUBSEQUENT COMMON STOCK PURCHASE)

EXHIBIT G
WARRANT CERTIFICATE
(SECOND SUBSEQUENT COMMON STOCK PURCHASE)

EXHIBIT H
FORM OF SECRETARY'S CERTIFICATE

EXHIBIT I
OPINION OF COUNSEL TO ISIS

EXHIBIT 10.3

THIS CONVERTIBLE PROMISSORY NOTE AND THE SHARES OF COMMON STOCK ISSUABLE UPON CONVERSION HEREOF HAVE NOT BEEN REGISTERED UNDER THE SECURITIES ACT OF 1933, AS AMENDED, AND MAY NOT UNDER ANY CIRCUMSTANCES BE SOLD, TRANSFERRED OR OTHERWISE DISPOSED OF WITHOUT AN EFFECTIVE REGISTRATION STATEMENT FOR SUCH SECURITIES UNDER THE SECURITIES ACT OF 1933, AS AMENDED, AND ANY APPLICABLE STATE SECURITIES LAWS OR AN OPINION OF COUNSEL SATISFACTORY TO THE COMPANY THAT REGISTRATION IS NOT REQUIRED UNDER SUCH ACT OR APPLICABLE STATE SECURITIES LAWS.

THE TRANSFER OF THE SECURITIES REPRESENTED BY THIS CERTIFICATE IS ALSO SUBJECT TO THE RESTRICTIONS CONTAINED IN THAT CERTAIN SECURITIES PURCHASE AGREEMENT, DATED JANUARY 14, 2000, BY AND BETWEEN ISIS PHARMACEUTICALS, INC. AND ELAN INTERNATIONAL SERVICES, LTD.

ISIS PHARMACEUTICALS, INC.
CONVERTIBLE PROMISSORY NOTE

U.S. $12,015,000 JANUARY 14, 2000

The undersigned, ISIS PHARMACEUTICALS, INC., a Delaware corporation with offices at 2292 Faraday Avenue, Carlsbad, California 92008 (the "Company"), unconditionally promises to pay to ELAN INTERNATIONAL SERVICES, LTD., a Bermuda private limited company ("EIS"), or its permitted assigns, transferees and successors as provided herein (collectively, the "Holder"), on January 14, 2006 (the "Maturity Date"), at such place as may be designated by the Holder to the Company, the principal amount outstanding hereunder (not to exceed U.S.$12,015,000), together with interest thereon accrued at a rate per annum equal to the lesser of (i) 12.0%, and (ii) the maximum rate of interest permissible by applicable law, from and after the date of the initial disbursement of funds hereunder (the "Original Issue Date"), compounded on a semi-annual basis, the initial such compounding to commence on the date that is 180 days from and after the Original Issue Date and thereafter on each 180 day anniversary (each such date, a "Compounding Date").

SECTION 1. SECURITIES PURCHASE AGREEMENT AND FUNDING AGREEMENT.

This Note is issued pursuant to a Securities Purchase Agreement dated as of the date hereof, by and between the Company and EIS (as amended at any time, the "Securities Purchase Agreement"), and the Holder hereof is intended to be afforded the benefits thereof, including the representations and warranties set forth therein. The Company shall use the proceeds of the issuance

and sale of this Note solely in accordance with the provisions set forth therein and as required therein and in a certain Funding Agreement, dated as of the date hereof (as amended at any time, the "Funding Agreement"), by and among Elan Corporation, plc, an Irish public limited company and the parent corporation of EIS, Elan Pharma International Limited, EIS and the Company, and as described in Section 6 below. Capitalized terms used but not otherwise defined herein shall, unless otherwise indicated, have the meanings given such terms in the Securities Purchase Agreement.

SECTION 2. DISBURSEMENTS.

(a) From and after the date hereof and until July 14, 2002, disbursements shall be made by the Holder to the Company hereunder in minimum tranches of U.S.$500,000 (except in the event that an amount less than U.S.$500,000 shall be remaining and available for funding hereunder, in which case such lesser amount may be funded hereunder); provided, that the Company shall have, prior to each such disbursement, delivered a written request therefor to the Holder in the form attached hereto as Exhibit A (the "Disbursement Notice"), together with an Officer's Certificate confirming that as of such date no Event of Default exists hereunder; the Holder shall, subject to the terms and conditions hereof, fund the applicable amount within 10 business days of the receipt of the Disbursement Notice, subject to the receipt by the Holder of any required approvals under the Mergers and Takeovers (Control) Acts 1978-1996 and the terms of the development plan to be mutually agreed upon by the Company and EIS. A "business day" is any day that commercial banks are open for the transaction of business in the City of New York.

(b) The Holder shall not be required to (i) disburse more than the maximum principal amount hereunder, excluding accruals of interest, of U.S.$12,015,000 or (ii) make more than five disbursements to the Company within any 12 month period.

(c) Each disbursement shall accrue interest at the rate set forth in Section 1 from the date of each such disbursement through the date of payment.

SECTION 3. PAYMENTS AND COVENANTS.

(a) Unless earlier converted in accordance with the terms of Section 4 below, or prepaid in accordance with the terms hereof, the entire outstanding principal amount of this Note, together with any accrued and unpaid interest thereon, shall be due and payable on the Maturity Date.

(b) Accrued interest hereon shall not be paid in cash, but shall be capitalized and added to the principal amount outstanding hereunder on each Compounding Date and will be convertible into Common Stock pursuant to Section 4.

(c) This Note may be prepaid by the Company at its option, in whole or in part,

(i) in cash, upon not less than 30 days' prior written notice to EIS; or

(ii) in shares of the Company's Common Stock, par value $.001 per share (the "Common Stock"), at any time, at a price equal to 95% of the average of the closing prices

of the Common Stock for the 60 trading days ending two business days prior to the date of repayment; provided that no more than 50% of any prepayment amount shall be payable by the Company in the Company's Common Stock.

SECTION 4. CONVERSION.

(a) Conversion Right.

(i) From and after the Original Issue Date and until this Note is repaid in full, the Holder shall have the right from time to time, in its sole discretion, to convert all or any portion of the outstanding principal amount and accrued and unpaid interest then-outstanding hereunder, on a per tranche basis (each, a "Conversion Right"), into such number of shares of Common Stock that shall be obtained by dividing the sum of the outstanding principal amount of such tranche and all accrued and unpaid interest thereon by a per share price calculated as 140% of the average of the closing price of the Common Stock for the 60 trading days ending two business days prior to the date of disbursement of such tranche (each, a "Conversion Price").

(ii) The Holder shall be entitled to exercise a Conversion Right upon at least five days' prior written notice to the Company, such notice to be in the form attached hereto as Exhibit B. Within 10 days of the conversion date specified in such notice, the Company shall cause its transfer agent to issue stock certificates to EIS representing the aggregate number of shares of Common Stock due to EIS as a result of such conversion.

(b) Reclassification, Etc. In case of (i) any reclassification, reorganization, change or conversion of securities of the class issuable upon conversion of the outstanding principal amount and accrued and unpaid interest then-outstanding hereunder (other than a change in par value, or from par value to no par value), or (ii) any consolidation of the Company with or into another entity (other than a merger or consolidation with another entity in which the Company is the surviving entity and that does not result in any reclassification or change of the class of securities issuable upon the conversion of the outstanding principal amount and accrued and unpaid interest then-outstanding hereunder), or (iii) any sale of all or substantially all the assets of the Company (excluding the transactions contemplated by the Transaction Documents), then the Company, or such successor or purchasing entity, as the case may be, shall duly execute and deliver to the Holder a new Note or a supplement hereto (in form and substance reasonably satisfactory to the Holder of this Note), so that the Holder shall have the right to receive, at a total purchase price not to exceed the outstanding principal amount and accrued and unpaid interest then-outstanding hereunder, and in lieu of the shares of Common Stock theretofore issuable upon the conversion of such outstanding principal amount and accrued and unpaid interest then-outstanding hereunder, the kind and amount of shares of stock and other securities, money and property receivable upon such reclassification, reorganization, change, merger, consolidation or conversion by a holder of the number of shares of Common Stock then issuable under this Note. Such new Note shall provide for adjustments that shall be as nearly equivalent as may be practicable to the adjustments provided for in this Section 4. The provisions of this Section 4(b) shall similarly attach to successive reclassifications, reorganizations, changes, mergers, consolidations, transfers or conversions.

(c) No Impairment. The Company will not, by amendment of its Certificate of Incorporation or by-laws or through any reorganization, recapitalization, transfer of assets, consolidation, merger, dissolution, issue or sale of securities or any other voluntary action, avoid or seek to avoid the observance or performance of any of the terms to be observed or performed hereunder by the Company, but will at all times in good faith assist in the carrying out of all the provisions of this Section 4 and in the taking of all such action as may be necessary or appropriate in order to protect the rights of EIS against impairment. This provision shall not restrict the Company from otherwise amending and/or restating its Certificate of Incorporation in accordance with Delaware General Corporation Law.

(d) Notice of Adjustments. Whenever the consideration issuable upon a conversion hereunder shall be changed pursuant to this Section 4, the Company shall prepare a certificate setting forth, in reasonable detail, the event requiring the change and the kind and amount of shares of stock and other securities, money and property subsequently issuable upon a conversion hereof. Such certificate shall be signed by the Company's chief financial officer and shall be delivered to EIS.

(e) No Fractional Shares; Rounding. No fractional shares of Common Stock will be issued in connection with any exercise hereunder, but in lieu of such fractional shares the Company shall make a cash payment therefor based on the applicable Conversion Price. All calculations under this Section 4 shall be made to the nearest cent or to the nearest one-hundredth of a share, as the case may be.

SECTION 5. EXCHANGE RIGHT.

(a) In the event that EIS shall exercise the EIS Exchange Right, EIS shall, at its option, (i) cause to be paid to the Company, within 30 days of such exercise, an amount equal to 30.097% of the aggregate amount (but not including any accrued and unpaid interest thereon) of the Development Funding (as such term is defined in the Funding Agreement) through the date of such exercise provided by each of the parties to HepaSense, in accordance with the terms of the Funding Agreement, from and after the date hereof and until the date of such exercise, and/or (ii) offset against the amount then outstanding and payable under this Note an amount equal to 30.097% of the total amount (but not including any accrued and unpaid interest in respect of any debt, including the Note thereon) of Development Funding provided by each of the parties to HepaSense, in accordance with the terms of the Funding Agreement, from and after the date hereof and until the date of the exercise of the Exchange Right, against the principal amount outstanding hereunder, if any, or (iii) effect a combination of the provisions described in clauses (i) and (ii) above, if applicable.

(b)In no event shall the amount determined in accordance with subsection (a) above exceed the aggregate principal amount issued hereunder and accrued interest thereon.

SECTION 6. USE OF PROCEEDS.

The Company shall use the proceeds of this Note solely for developmental funding of HepaSense; provided, that the Board of Directors of HepaSense shall have determined that such

developmental funding is necessary (which approval shall in all events include the consent of at least one director designated by the Company that is an employee of the Company and at least one director designated by EIS) and that the parties thereto are in continuing agreement as to the Business Plan. Accordingly, total disbursements hereunder shall not in any event exceed the amount of Development Funding funded by the Company to HepaSense pursuant to the Funding Agreement.

SECTION 7. EVENTS OF DEFAULT.

The occurrence of any of the following events shall constitute an event of default (an "Event of Default"):

(a) a default in the payment of the principal amount of this Note, when and as the same shall become due and payable;

(b) a default in the payment of any accrued and unpaid interest on this Note, when and as the same shall become due and payable;

(c) a material breach by the Company of its obligations under any of the Transaction Documents, which breach remains uncured 30 days after written notice thereof by EIS; provided, however, that (x) if the Company has proposed a course of action to rectify the breach and is acting in good faith to rectify same but has not cured the breach by the 30th day, such period shall be extended by such period as is reasonably necessary to permit the breach to be rectified and (y) if such default involves a good faith dispute regarding the amount of any required payment, provided any undisputed amount is paid, such default shall be stayed and the remainder may be withheld for a reasonable period during which a good faith resolution of the amount owed is being pursued;

(d) a distress, execution, sequestration or other process is levied or enforced upon the Company or sued out against a material part of its property which is not discharged or challenged within 30 days;

(e) the Company is unable to pay its debts in the normal course of business;

(f) the Company ceases wholly or substantially to carry on its business, otherwise than for the purpose of a reconstruction or amalgamation, without the prior written consent of the EIS (such consent not to be unreasonably withheld);

(g) the appointment of a liquidator, receiver, administrator, examiner, trustee or similar officer of the Company or over all or substantially all of its assets under the law; or

(h) any other termination of the JDOA.

SECTION 8. REMEDIES IN THE EVENT OF DEFAULT.

(a) In the case of any Event of Default by the Company, the Holder, may in its sole discretion, demand that the aggregate amount of funds advanced to the Company under this Note and outstanding hereunder and accrued and unpaid interest thereon shall, in addition to all other rights and remedies of the Holder hereunder and under applicable law, be and become immediately due and payable upon written notice delivered by the Holder to the Company. Notwithstanding the preceding sentence, the rights of the Holder as set forth in Sections 4 and 5 hereunder shall survive any such acceleration and payment. If the Holder shall accelerate this Note after the occurrence of any Event of Default set forth in Section 7(a), 7(b) or 7(c) hereof and be paid and, prior to the earlier of (i) second anniversary of the date of such acceleration and (ii) the Maturity Date, the Holder elects to exercise the Conversion Right, the Holder shall reimburse to the Company an amount in respect of the shares of Common Stock issued under such Conversion Right equal to the principal amount of this Note attributable thereto as calculated in accordance with Section 4 above.

(b) The Company hereby waives demand and presentment for payment, notice of nonpayment, protest and notice of protest, diligence, filing suit, and all other notice and promises to pay the Holder its costs of collection of all amounts due hereunder, including reasonable attorneys' fees.

(c) In the case of any Event of Default under this Note by the Company this Note shall continue to bear interest after such default at the interest rate otherwise in effect hereunder plus 3% per annum (but in any event not in excess of the maximum rate of interest permitted by applicable law).

SECTION 9. VOTING RIGHTS.

This Note shall not entitle the holder hereof to any voting rights or other rights as a stockholder of the Company prior to its conversion.

SECTION 10. SENIORITY.

(a) The Holder acknowledges and agrees that the obligations evidenced hereby are subordinate in right to payment in full of interest and principal relating to the Company's $40,000,000 aggregate principal amount of 14% Senior Subordinated Discount Notes due November 2007 (the "Discount Notes") and therefore the obligations evidenced hereby are "Subordinated Indebtedness" as defined in that certain Purchase Agreement, dated October 24, 1997, between the Company and the purchasers listed on Schedule I thereto (the "Purchase Agreement"); it being understood that in the event there is any event of default in respect of the Purchase Agreement, the Company shall not pay to the Holder hereof in cash any amounts due hereunder until such event of default is cured or waived pursuant to the terms of such indenture.

(b) The Company shall not incur any indebtedness for money borrowed which shall rank senior to this Note without the prior written consent of the Holder; provided, however, that the Company may incur additional indebtedness which ranks pari passu with the obligations evidenced hereby.

SECTION 11. MISCELLANEOUS.

(a) EIS may assign this Note to its affiliates and subsidiaries, as well as any special purpose financing or similar vehicle entity established by EIS or its affiliates. Upon any such assignment, EIS shall promptly provide the Company with Notice in reasonable detail of such assignment and assignee (provided, that the failure to provide such notice shall not affect the rights of EIS hereunder). This Note and all of the provisions hereof shall be binding upon and inure to the benefit of the parties hereto and their respective successors and permitted assigns; provided, however, that EIS and the Company shall remain liable for their respective obligations hereunder after any such assignment.

(b) All notices, demands and requests of any kind to be delivered to any party in connection with this Agreement shall be in writing and shall be deemed to have been duly given if personally delivered or if sent by nationally-recognized overnight courier or by registered or certified mail, return receipt requested and postage prepaid, or by facsimile transmission, addressed as follows:

(i) if to the Company:

Isis Pharmaceuticals, Inc.
2292 Faraday Avenue
Carlsbad, CA 92008
Attn: B. Lynne Parshall
Tel.: 760-603-2460
Fax: 760-931-9639

with a copy to:

Cooley Godward LLP
4365 Executive Drive
San Diego, CA 92121
Attention: Julie Robinson, Esq.
Tel: 619-550-6000
Fax: 619-453-3555

(ii) if to EIS, to:

Elan International Services, Ltd.
102 St. James Court
Flatts, Smiths Parish
Bermuda SL04
Attention: President
Tel: 441-292-9169
Fax: 441-292-2224

with a copy to:

Brock Silverstein LLC
800 Third Avenue
New York, New York 10022
Attention: Scott Rosenblatt, Esq.
Tel: 212-371-2000
Fax: 212-371-5500

Each party, by written notice given to the other in accordance with this Section 11(b) may change the address to which notices, other communication or documents are to be sent to such party. All notices, other communications or documents shall be deemed to have been duly given when received. Any such notice or communication shall be deemed to have been effectively received, (a) in the case of personal delivery, on the date of such delivery, (b) in the case of nationally-recognized overnight courier, on the second business day after the date when sent, (c) in the case of mailing, on the fifth business day following that day on which the piece of mail containing such communication is posted, and (d) in the case of facsimile transmission, on the date of transmission.

(c) This Note may not be modified or amended, or any of the provisions hereof waived, except by written agreement of the Company and EIS.

(d) This Note shall be governed by and construed in accordance with the laws of the State of New York, without giving effect to principles thereof relating to conflicts of laws, except that all issues concerning the relative rights of the Company and its stockholders shall be governed by the Delaware General Corporation Law, without giving effect to the principles thereof relating to conflicts of laws.

(e) This Note may be executed in any number of counterparts, and each such counterpart hereof shall be deemed to be an original instrument, but all such counterparts together shall constitute one note. The Note may be signed and delivered to the other party by a facsimile transmission; such transmission shall be deemed a valid signature; provided that any signature delivered by facsimile transmission shall be replaced by an original signature within five days.

(f) Each of the parties shall be responsible for its own costs and expenses incurred in connection with the transactions contemplated hereby.

[Signature page follows]

IN WITNESS WHEREOF, the Company and EIS have executed this Note on the date first above written.

ISIS PHARMACEUTICALS, INC.

By:_____
B. Lynne Parshall
Executive Vice President

ELAN INTERNATIONAL SERVICES, LTD.

By:_____
Kevin Insley
President

EXHIBIT A

NOTICE OF REQUEST FOR DISBURSEMENT

Date:

To: Elan International Services, Ltd.

From: Isis Pharmaceuticals, Inc.

Re: Disbursement Request

Pursuant to the terms of the Convertible Promissory Note (the "Note") issued by Isis Pharmaceuticals, Inc. (the "Company") to Elan International Services, Ltd. ("EIS"), dated January 14, 2000, the Company hereby notifies EIS of its request for a disbursement thereunder in the amount of $_____. Please provide funding in the requested amount to the Company in accordance with the following wire instructions

[

]

Sincerely,

ISIS PHARMACEUTICALS, INC.

By: _____
Name:
Title:

EXHIBIT B

NOTICE OF ELECTION TO EXERCISE A CONVERSION RIGHT

Date:

To: Isis Pharmaceuticals, Inc.

From: Elan International Services, Ltd.

Re: Exercise of a Conversion Right

- ---

Pursuant to the terms of the Convertible Promissory Note (the "Note") issued by Isis Pharmaceuticals, Inc. (the "Company") to Elan International Services, Ltd. ("EIS"), dated January 14, 2000, specifically Section 4 thereof, EIS hereby notifies the Company of its intention to exercise a right of conversion.

Pursuant to Section 4 of the Note, EIS hereby elects to convert [$_____]* in aggregate principal amount and all accrued and unpaid interest thereon for shares of the Company's Common Stock, par value $.001 per share, effective [_____, ____]

We have instructed our attorneys to contact the Company to discuss the timing and documentation of the conversion.

Sincerely,

ELAN INTERNATIONAL SERVICES, LTD.

By: _____
Name:
Title:

- ---
* Amount must represent one or more tranches drawn down by the Company under the Note.

EXHIBIT 10.4

Exhibit F to Securities Purchase Agreement

THIS WARRANT AND THE SHARES OF COMMON STOCK ISSUABLE UPON EXERCISE HEREOF HAVE NOT BEEN REGISTERED UNDER THE SECURITIES ACT OF 1933, AS AMENDED, AND MAY NOT UNDER ANY CIRCUMSTANCES BE SOLD, TRANSFERRED OR OTHERWISE DISPOSED OF WITHOUT AN EFFECTIVE REGISTRATION STATEMENT FOR SUCH SECURITIES UNDER THE SECURITIES ACT OF 1933, AS AMENDED, AND ANY APPLICABLE STATE SECURITIES LAWS OR AN OPINION OF COUNSEL SATISFACTORY TO THE COMPANY THAT REGISTRATION IS NOT REQUIRED UNDER SUCH ACT OR APPLICABLE STATE SECURITIES LAWS.

THE TRANSFER OF THE SECURITIES REPRESENTED BY THIS CERTIFICATE IS ALSO SUBJECT TO THE RESTRICTIONS CONTAINED IN THAT CERTAIN SECURITIES PURCHASE AGREEMENT, DATED JANUARY 14, 2000, BY AND BETWEEN ISIS PHARMACEUTICALS, INC. AND ELAN INTERNATIONAL SERVICES, LTD.

[_____], 2000

ISIS PHARMACEUTICALS, INC.

WARRANT TO PURCHASE SHARES
OF COMMON STOCK

THIS CERTIFIES THAT for value received, Elan International Services, Ltd., a Bermuda exempted limited liability company ("EIS"), or its permitted transferees and successors as provided herein (each, a "Holder"), is entitled to subscribe for and purchase the Determined Number (as defined below) of shares (the "Shares") of the fully paid and nonassessable common stock, par value $.001 per share (the "Common Stock"), of Isis Pharmaceuticals, Inc., a Delaware corporation (the "Company"), with offices located at 2292 Faraday Avenue, Carlsbad, CA 92008, at the price per share equal to 200% of the price per share paid by EIS to purchase shares of Common Stock on the First Subsequent Purchase Date (such price, and such other prices that shall result from time to time, from the adjustments specified in Section 4, the "Warrant Price"), subject to the provisions and upon the terms and conditions hereinafter set forth. "Determined Number" shall mean 5% of the aggregate number of shares of Common Stock purchased by EIS, or its successors or permitted assigns, on the First Subsequent Purchase Date, pursuant to Section 1(b)(ii) of the Securities Purchase Agreement, dated as of January 14, 2000, by and between the Company and EIS (the "Securities Purchase Agreement"). Capitalized terms used but not otherwise defined herein shall, unless otherwise indicated, have the meanings given such terms in the Securities Purchase Agreement.

1. Term. The purchase right represented by this Warrant is exercisable, in whole or in part, at any time, and from time to time, from and after the date hereof and until 5:00 p.m. Eastern Standard Time on [_____], 2005 (the fifth anniversary of the First Subsequent Purchase Date). To the extent not exercised at 5:00 p.m. Eastern Standard Time on [_____], 2005, (the fifth anniversary of the First Subsequent Purchase Date) this Warrant shall completely and automatically terminate and expire, and thereafter it shall be of no force or effect.

2. Method of Exercise; Payment; Issuance of New Warrant.

(a) The purchase right represented by this Warrant may be exercised by the Holder, in whole or in part and from time to time, by the surrender of this Warrant (with the notice of exercise form attached hereto as Annex A duly executed) at the principal office of the Company and by the payment to the Company of an amount, in cash or other immediately available funds, equal to the then-applicable Warrant Price per Share multiplied by the number of Shares then being purchased or pursuant to the cashless exercise procedure described below.

(b) In lieu of delivering cash or other immediately available funds, the Holder may instruct the Company in writing to deduct from the number of Shares that would otherwise be issued upon such exercise, a number of shares of Common Stock equal to the quotient obtained from dividing (x) the product obtained by multiplying (A) the number of Shares for which the Warrant is being exercised and (B) the Warrant Price then in effect by (y) a price equal to the average of the closing price of the Common Stock for the 60 trading days ending two business days prior to the date of exercise.

(c) The persons or entities in whose name(s) any certificate(s) representing Shares shall be issuable upon exercise of this Warrant shall be deemed to have become the holder(s) of record of, and shall be treated for all purposes as the record holder(s) of, the Shares represented thereby (and such Shares shall be deemed to have been issued) immediately prior to the close of business on the date or dates upon which this Warrant is properly exercised and full payment for the Shares acquired pursuant to such exercise is made. Upon any exercise of the rights represented by this Warrant, certificates for the Shares purchased shall be delivered to the Holder hereof as soon as possible and in any event within 15 days of receipt of such notice and payment, and unless this Warrant has been fully exercised or expired, a new Warrant representing the portion of Shares, if any, with respect to which this Warrant shall not then have been exercised shall also be issued to the Holder hereof as soon as possible and in any event within such 15-day period.

3. Stock Fully Paid, Reservation of Shares. All Shares that may be issued upon the exercise of this Warrant shall, upon issuance, be duly and validly authorized and issued, fully paid and nonassessable, and will not be subject to any liens or charges imposed on the Company or issued in violation of any preemptive or similar rights. During the period within which this Warrant may be exercised, the Company will at all times have authorized and reserved for the purpose of the issue upon the exercise of the purchase rights evidenced by this Warrant a sufficient number of shares of its Common Stock to provide for the exercise of the rights represented by this Warrant.

4. Adjustment of Warrant Price and Number of Shares. The number and kind of securities purchasable upon the exercise of this Warrant and the Warrant Price shall be subject to adjustment from time to time upon the occurrence of certain events, as follows:

(a) Reclassification, Etc. In case of (i) any reclassification, reorganization, change or conversion of securities of the class issuable upon exercise of this Warrant (other than a change in par value, or from par value to no par value), or (ii) any consolidation of the Company with or into another entity (other than a merger or consolidation with another entity in which the Company is the surviving entity and that does not result in any reclassification or change of outstanding securities issuable upon exercise of this Warrant), or (iii) any sale of all or substantially all the assets of the Company, then, in any event, (x) the Company, or such successor or purchasing entity, as the case may be, shall duly execute and deliver to the Holder of this Warrant a new Warrant or a supplement hereto (in form and substance reasonably satisfactory to the Holder of this Warrant), and (y) the Holder shall have the right to receive, at a total purchase price not to exceed that payable upon the exercise of the unexercised portion of this Warrant, and in lieu of the shares of Common Stock theretofore issuable upon the exercise of this Warrant, the kind and amount of shares of stock and other securities, receivable upon such reclassification, reorganization, change or conversion by a holder of the number of shares of Common Stock then purchasable under this Warrant. Such new Warrant shall provide for adjustments that shall be as nearly equivalent as may be practicable to the adjustments provided for in this Section 4. The provisions of this Section 4(a) shall similarly attach to successive reclassifications, reorganizations, changes, and conversions.

(b) Subdivision or Combination of Shares. If the Company at any time during which this Warrant remains outstanding and unexpired shall subdivide or combine its Common Stock, (i) in the case of a subdivision, the Warrant Price shall be proportionately decreased and the number of Shares purchasable hereunder shall be proportionately increased, and (ii) in the case of a combination, the Warrant Price shall be proportionately increased and the number of Shares purchasable hereunder shall be proportionately decreased.

(c) No Impairment. The Company will not, by amendment of its Certificate of Incorporation or by-laws or through any reorganization, recapitalization, transfer of assets, consolidation, merger, dissolution, issue or sale of securities or any other voluntary action, avoid or seek to avoid the observance or performance of any of the terms to be observed or performed hereunder by the Company, but will at all times in good faith assist in the carrying out of all the provisions of this Section 4 and in the taking of all such action as may be necessary or appropriate in order to protect the rights of the Holder against impairment.

(d) Notice of Adjustments. Whenever the Warrant Price or the number of Shares purchasable hereunder shall be adjusted pursuant to this Section 4, the Company shall prepare a certificate setting forth, in reasonable detail, the event requiring the adjustment, the amount of the adjustment, the method by which such adjustment was calculated. Such certificate shall be signed by the Company's chief financial officer and shall be delivered to the Holder.

(e) Fractional Shares. No fractional shares of Common Stock will be issued in connection with any exercise hereunder, but in lieu of such fractional shares the Company

shall make a cash payment therefor based on the average of the closing price of the Common Stock for the 60 trading days ending two business days prior to date of exercise.

(f) Cumulative Adjustments. No adjustment in the Warrant Price or the number of Shares purchasable hereunder shall be required under this Section 4 until cumulative adjustments result in a concomitant change of 1% or more of the Warrant Price or in the number of shares of Common Stock purchasable upon exercise of this Warrant as in effect prior to the last such adjustment; provided, however, that any adjustments that by reason of this Section 4 are not required to be made shall be carried forward and taken into account in any subsequent adjustment. All calculations under this Section 4 shall be made to the nearest cent or to the nearest one-hundredth of a share, as the case may be.

5. Compliance with Securities Act; Disposition of Warrant or Shares of Common Stock.

(a) The Holder, by acceptance hereof, agrees that this Warrant and the Shares to be issued upon exercise hereof and, without limiting the foregoing, agrees that this Warrant and the Shares to be issued upon exercise hereof are being acquired for investment and that such Holder will not offer, sell or otherwise dispose of this Warrant or any Shares to be issued upon exercise hereof except under circumstances which will not result in a violation of applicable securities laws. Upon exercise of this Warrant, unless the Shares being acquired are registered under the Securities Act of 1933, as amended (the "Act"), or an exemption from the registration requirements of such Act is available, the Holder shall confirm in writing, by executing an instrument in form reasonably satisfactory to the Company, that the Shares so purchased are being acquired for investment and not with a view toward distribution or resale. This Warrant and all Shares issued upon exercise of this Warrant (unless registered under the Securities Act) shall be stamped or imprinted with legends in substantially the following forms:

> THE SECURITIES REPRESENTED HEREBY HAVE NOT BEEN REGISTERED UNDER THE SECURITIES ACT OF 1933, AS AMENDED, AND MAY NOT UNDER ANY CIRCUMSTANCES BE SOLD, TRANSFERRED OR OTHERWISE DISPOSED OF WITHOUT AN EFFECTIVE REGISTRATION STATEMENT FOR SUCH SECURITIES UNDER THE SECURITIES ACT OF 1933, AS AMENDED, AND ANY APPLICABLE STATE SECURITIES LAWS OR AN OPINION OF COUNSEL SATISFACTORY TO THE COMPANY THAT REGISTRATION IS NOT REQUIRED UNDER SUCH ACT OR APPLICABLE STATE SECURITIES LAWS.
>
> THE TRANSFER OF THE SECURITIES REPRESENTED BY THIS CERTIFICATE IS ALSO SUBJECT TO THE RESTRICTIONS CONTAINED IN THAT CERTAIN SECURITIES PURCHASE AGREEMENT, DATED JANUARY 14, 2000, BY AND BETWEEN ISIS

PHARMACEUTICALS, INC. AND ELAN INTERNATIONAL SERVICES, LTD.

(b) (i) This Warrant may be transferred or assigned, in whole or in part, by EIS to its affiliates and/or subsidiaries, as well as any special purpose financing or similar vehicle established by EIS or its affiliates; provided, that the transferor shall continue to be liable and obligated for its obligations hereunder. Subject to the foregoing, this Warrant and all of the provisions hereof shall be binding upon and inure to the benefit of the parties hereto and their respective successors and permitted assigns. Other than as set forth above, this Warrant may not be transferred or assigned by either party without the prior written consent of the other; provided, however, that no consent shall be required in connection with any transfer or assignment by a party pursuant to a sale of all or substantially all of the business of such party to which the Transaction Documents relate, whether by merger, sale of stock, sale of assets or otherwise.

(ii) With respect to any offer, sale or other disposition of this Warrant or any Shares acquired pursuant to the exercise of this Warrant prior to registration of such Shares, the Holder shall give written notice to the Company prior thereto, describing briefly the manner thereof, together with a written opinion of such Holder's counsel, if requested by the Company, to the effect that such offer, sale or other disposition may be effected without registration or qualification (under the Securities Act as then in effect or any other applicable federal or state securities law then in effect) of this Warrant or such Shares and indicating whether or not under the Securities Act certificates for this Warrant or such Shares to be sold or otherwise disposed of require any restrictive legend as to applicable restrictions on transferability in order to ensure compliance with the Securities Act. Promptly upon receiving such written notice and reasonably satisfactory opinion, if so requested, the Company, as promptly as practicable, shall notify such Holder that such Holder may sell or otherwise dispose of this Warrant or such Shares, all in accordance with the terms of the notice delivered to the Company. Each certificate representing this Warrant or the Shares thus transferred shall bear a legend as to the applicable restrictions on transferability in order to insure compliance with the Securities Act, unless in the aforesaid opinion of counsel for the Holder such legend is not required in order to insure compliance with the Securities Act. The Company may issue stop transfer instructions to its transfer agent in connection with such restrictions.

(iii) The shares of Common Stock underlying this Warrant are entitled to the benefit of certain registration rights as set forth in a Registration Rights Agreement dated as of the date hereof between the Company and the initial Holder named herein.

6. No Rights as Stockholders. No Holder, as such, shall be entitled to vote or receive dividends or be deemed the holder of Shares or any other securities of the Company which may at any time be issuable upon the exercise hereof for any purpose, nor shall anything contained herein be construed to confer upon the Holder, as such, any right to vote for the election of directors or upon any matter submitted to stockholders at any meeting thereof, or to receive notice of meetings, or to receive dividends or subscription rights or otherwise until this

Warrant is exercised and the Shares purchasable upon the exercise hereof shall have become deliverable, as provided herein.

7. Representations and Warranties. The Company represents and warrants to the Holder as follows:

(a) The Company has all requisite corporate power and authority to authorize and execute this Warrant and the certificates evidencing the Shares and to perform all obligations and undertakings under this Warrant and the certificates evidencing the Shares;

(b) This Warrant has been duly authorized and executed by the Company and is a valid and binding obligation of the Company enforceable in accordance with its terms; except that enforcement may be limited by (i) applicable bankruptcy, insolvency, reorganization, arrangement, moratorium or other similar laws affecting creditors' rights, and (ii) general equity principles and limitations on the availability of equitable relief, including specific performance.

(c) The Shares have been duly authorized and reserved for issuance by the Company and, when issued in accordance with the terms hereof, will be validly issued, fully paid and nonassessable; and

(d) The execution and delivery of this Warrant are not, and the issuance of the Shares upon exercise of this Warrant in accordance with the terms hereof will not be, inconsistent with the Company's Certificate of Incorporation or bylaws, as amended, and do not and will not constitute a default under, any indenture, mortgage, material contract or other material instrument to which the Company is a party or by which it is bound.

8. Miscellaneous.

(a) This Warrant may not be modified or amended, or any provisions hereof waived, except by written agreement of the Company and the Holder.

(b) Any notice, request or other document required or permitted to be given or delivered to the Holder or the Company shall (i) be in writing, (ii) be delivered personally or sent by mail or overnight courier to the intended recipient to Holder at its address as shown on the books of the Company, or to the Company at the address indicated therefor on the signature page of this Warrant, and (iii) be effective on receipt if delivered personally, two business days after dispatch if mailed, and one business day after dispatch if sent by overnight courier service.

(c) The Company covenants to the Holder that upon receipt of evidence reasonably satisfactory to the Company of the loss, theft, destruction or mutilation of this Warrant and, in the case of any such loss, theft or destruction, upon receipt of a bond or indemnity reasonably satisfactory to the Company, or in the case of any such mutilation upon surrender and cancellation of such Warrant, the Company will prepare and deliver a new Warrant, of like tenor, in lieu of the lost, stolen, destroyed or mutilated Warrant.

(d) The descriptive headings of the several sections and paragraphs of this Warrant are inserted for convenience only and do not constitute a part of this Warrant.

(e) This Warrant shall be governed by and construed in accordance with the laws of the State of New York without giving effect to the principles thereof relating to conflicts of laws, except that all issues concerning the relative rights of the Company and its stockholders shall be governed by the Delaware General Corporation Law, without giving effect to the principles thereof relating to conflicts of laws.

(f) This Warrant may be executed in any number of counterparts, and each such counterpart hereof shall be deemed to be an original instrument, but all such counterparts together shall constitute one Warrant. This Warrant may be signed and delivered to the other party by a facsimile transmission; such transmission shall be deemed a valid signature; provided that any signature delivered by facsimile transmission shall be replaced by an original signature within five days.

(g) Each of the parties shall be responsible for its own costs and expenses incurred in connection with the transactions contemplated hereby.

[Signature page follows]

IN WITNESS WHEREOF, Isis Pharmaceuticals, Inc. has caused this Warrant to be executed and delivered by its duly authorized corporate officers on the date first above written.

ISIS PHARMACEUTICALS, INC.

By:_____
B. Lynne Parshall
Executive Vice President

Attest:

By:_____
Name:
Title:

Agreed and accepted by:

ELAN INTERNATIONAL SERVICES, LTD.

By:_____
Kevin Insley
President

ANNEX A

NOTICE OF EXERCISE

To: Isis Pharmaceuticals, Inc.

1. The undersigned hereby elects to purchase _____ shares of Common Stock of Isis Pharmaceuticals, Inc. pursuant to the terms of the attached Warrant, and

[ ] (a) tenders herewith full payment of the purchase price of such shares, in cash or other immediately available funds.

[ ] (b) instructs and agrees that pursuant to paragraph 2(b) of the attached Warrant, _____ shares of Common Stock be withheld in payment therefor.

2. Please issue a certificate or certificates representing said shares in the name of the undersigned or in such other name or names as are specified below:

_____(Name)

_____(Address)

3. The undersigned represents that the aforesaid shares are being acquired for the account of the undersigned for investment and not with a view to, or for resale in connection with, the distribution thereof and that the undersigned has no present intention of distributing or reselling such shares and otherwise confirms the investment representations made in Section 5 of the Warrant with regard to the shares of Common Stock being acquired.

Signature:_____

Name:_____

Address:_____

Social Security or taxpayer identification number:

_____

EXHIBIT 10.5

ISIS PHARMACEUTICALS, INC.
REGISTRATION RIGHTS AGREEMENT

THIS REGISTRATION RIGHTS AGREEMENT (the "Agreement") is made as of January 14, 2000 by and between ISIS PHARMACEUTICALS, INC., a Delaware corporation (the "Company"), and ELAN INTERNATIONAL SERVICES, LTD., a Bermuda exempted limited liability company ("EIS").

R E C I T A L S:

A. Pursuant to a Securities Purchase Agreement, dated as of the date hereof by and between the Company and EIS (the "Purchase Agreement"), EIS has acquired, or may acquire in the future, (i) certain shares of common stock, par value $.001 per share, of the Company (the "Common Stock"), (ii) certain shares of Series B Convertible Exchangeable Preferred Stock, par value $.001 per share, of the Company (the "Series B Preferred Stock"), (iii) a convertible promissory note (the "Note"), which Series B Preferred Stock and Note are convertible into shares of Common Stock, and (iv) warrants to be issued pursuant to the Purchase Agreement (the "Warrants", together with the Series B Preferred Stock and the Note, the "Securities") exercisable for shares of Common Stock.

B. The execution of the Purchase Agreement has occurred on the date hereof and it is a condition to the closing of the transactions contemplated thereby that the parties execute and deliver this Agreement.

C. The parties desire to set forth herein their agreement as to the terms and subject to the conditions set forth herein related to the granting of certain registration rights to the Holders (as defined below) relating to the Common Stock held by such Holders and the Common Stock underlying the Securities.

A G R E E M E N T:

The parties hereto agree as follows:

1. Certain Definitions. As used in this Agreement, the following terms shall have the following respective meanings:

"Commission" shall mean the U.S. Securities and Exchange Commission.

"Exchange Act" shall mean the Securities Exchange Act of 1934, as amended, and the rules and regulations of the Commission thereunder, all as the same shall be in effect from time to time.

"Holders" or "Holders of Registrable Securities" shall mean EIS and any Person who shall have acquired Registrable Securities from EIS as permitted herein, either individually

or jointly, as the case may be, in a transaction pursuant to which registration rights are transferred pursuant to Section 11 hereof.

"Person" shall mean an individual, a partnership, a company, an association, a joint stock company, a trust, a joint venture, an unincorporated organization and a governmental or quasi-governmental entity, or any department, agency or political subdivision thereof.

"Registrable Securities" means (i) any shares of Common Stock purchased pursuant to the Purchase Agreement, any shares of Common Stock issued or issuable upon conversion of shares of Series B Preferred Stock (or issued as dividends thereon) or the Note, and any shares of Common Stock issued or issuable upon exercise of any Warrant, and (ii) any Common Stock issued or issuable in respect of the securities referred to in clause (i) above upon any stock split, stock dividend, recapitalization or similar event; excluding in all cases, however, any Registrable Securities sold by a Person in a transaction (including a transaction pursuant to a registration statement under this Agreement and a transaction pursuant to Rule 144 promulgated under the Securities Act) in which registration rights are not transferred pursuant to Section 11 hereof.

The terms "register," "registered" and "registration" refer to a registration effected by preparing and filing a registration statement in compliance with the Securities Act, and the declaration or order of the effectiveness of such registration statement.

"Registration Expenses" shall mean all expenses, other than Selling Expenses, incurred by the Company in complying with Sections 2, 3 or 4 hereof, including without limitation, all registration, qualification and filing fees, exchange listing fees, printing expenses, escrow fees, fees and disbursements of counsel for the Company, blue sky fees and expenses, the expense of any special audits incident to or required by any such registration and the reasonable fees and disbursements, not to exceed $10,000, of one counsel for the Holders, such counsel to be selected by Holders holding a majority of the Registrable Securities included in such registration.

"Securities Act" shall mean the Securities Act of 1933, as amended, and the rules and regulations of the Commission thereunder, all as the same shall be in effect from time to time.

"Selling Expenses" shall mean all underwriting discounts, selling commissions and stock transfer taxes applicable to the securities registered by the Holders and the costs of any accountants, attorneys or other experts retained by the Holders, except as expressly included in Registration Expenses.

2. Demand Registration.

(a) Requests for Registration. From and after the date hereof until the date of filing of the Shelf Registration Statement (as defined herein), any Holder or Holders who collectively hold Registrable Securities representing at least 50% of the Registrable Securities then outstanding shall have the right at any time from time to time, to request one registration

under the Securities Act of a minimum of 500,000 shares of Common Stock (as adjusted for any combinations, consolidations, stock distributions, stock dividends or other recapitalizations with respect to such shares) on Form S-1, S-2 or S-3 (if available) or any similar registration statement (a "Demand Registration"), such form to be selected by the Company as appropriate. The request for the Demand Registration shall specify the approximate number of Registrable Securities requested to be registered. Within 20 days after receipt of any such request, the Company will give written notice of such requested registration to all other Holders of Registrable Securities. The Company shall include such other Holders' Registrable Securities in such offering if they have responded affirmatively within 20 days after the receipt of the Company's notice. The Holders in aggregate will be entitled to request only one Demand Registration hereunder. A registration will not count as the permitted Demand Registration until it has become effective (unless such Demand Registration has not become effective due solely to the fault of the Holders requesting such registration, including a request by such Holders that such registration be withdrawn). The Company shall pay all Registration Expenses in connection with any Demand Registration whether or not such Demand Registration has become effective and the Holders requesting registration shall pay all Selling Expenses in connection therewith.

(b) Priority on Demand Registration. If a Demand Registration is an underwritten offering and the managing underwriters advise the Company in writing that in their opinion the number of Registrable Securities requested to be included in such offering exceeds the number of Registrable Securities which can be sold in such offering without adversely affecting the marketability of the offering, the Company will include in such registration such number of Registrable Securities allocated pro rata among the Holders thereof based upon the number of Registrable Securities owned by each such Holder. Other than the securities issued by the Company to Reliance Insurance Company, no securities other than Registrable Securities hereunder shall be included in such Demand Registration without the prior written consent of Holders who collectively hold Registrable Securities representing at least 50% of the Registrable Securities then outstanding.

(c) Restrictions on Demand Registration. The Company may postpone the filing or the effectiveness of a registration statement for a Demand Registration one time in any 12 month period for up to 90 days if the Company determines in good faith that such Demand Registration would reasonably be expected to have a material adverse effect on any proposal or plan by the Company or would require disclosure of any information that the board of directors of the Company determines in good faith the disclosure of which would be detrimental to the Company; provided, however, that in such event, the Holders initially requesting such Demand Registration will be entitled to withdraw such request and, if such request is withdrawn, such Demand Registration will not count as the permitted Demand Registration hereunder and the Company will pay any Registration Expenses in connection with such registration.

(d) Selection of Underwriters. The Holders will have the right to select the investment banker(s) and manager(s) to administer an offering pursuant to the Demand Registration, subject to the Company's prior written approval, which will not be unreasonably withheld or delayed.

(e) Other Registration Rights. Except as provided in this Agreement, so long as any Holder owns any Registrable Securities, the Company will not grant to any Persons the right to request the Company to register any equity securities of the Company, or any securities convertible or exchangeable into or exercisable for such securities, which conflicts with the rights granted to the Holders hereunder, without the prior written consent of the Holders of at least 50% of the Registrable Securities.

3. Shelf Registration Statement.

(a) The Company will cause, by June 30, 2002 (the "S-3 Filing Date"), to be prepared and filed, and will use commercially reasonable efforts to have declared effective with the Commission within 60 days after filing, a Registration Statement on Form S-3 (or such other form of registration statement that the Company shall determine and that is reasonably satisfactory to the Holders) for an offering to be made on a continuous basis pursuant to Rule 415 (or any similar rule that may be adopted by the Commission) under the Securities Act covering the Registrable Securities (the "Shelf Registration Statement" and such registration, the "Shelf Registration"); provided, however, that if the Company shall furnish to the Holders a certificate signed by any executive officer of the Company stating that in the good faith judgment of the Board of Directors of the Company it would be seriously detrimental to the Company to file the Shelf Registration Statement at such time and it is therefore essential to defer the filing of the Shelf Registration Statement, the Company shall have the right to defer such filing one time in any 12 month period for a reasonable period, not to exceed 60 days; provided further that, if the Completion Date (as defined in the Securities Purchase Agreement) is later than June 30, 2002, the S-3 Filing Date shall be 90 days after the Completion Date with respect to the Shares of Common Stock purchased on the Completion Date and the shares of Common Stock issuable upon exercise of the Warrant granted to any Holder on the Completion Date. The Shelf Registration Statement may be terminated (and the Company shall have no obligation to update the Shelf Registration Statement and may suspend sales thereunder) at such time as all Registrable Securities can be sold by their Holders within a three-month period without compliance with the registration requirements of the Securities Act pursuant to Rule 144 (including Rule 144(k)) promulgated thereunder (the "Termination Date"). The Holders shall furnish to the Company such information regarding themselves, the Registrable Securities held by them, and the intended method of distribution of such securities as shall be required to effect the Shelf Registration Statement. In that connection, each Holder shall be required to represent that all such information which is given is both complete and accurate in all material respects.

(b) So long as the Shelf Registration Statement is effective, the Company will furnish to the Purchaser as soon as practicable after available (but in the case of the Company's Annual Report to Stockholders, within 120 days after the end of each fiscal year of the Company), (i) one copy of (A) its Annual Report to Stockholders (which Annual Report shall contain financial statements audited in accordance with generally accepted auditing standards certified by a national firm of certified public accountants), (B) if not included in substance in the Annual Report to Stockholders, its Annual Report on Form 10-K, (C) if not included in substance in its Quarterly Reports to Stockholders, its quarterly reports on Form 10-Q during such fiscal year, and (D) a full copy of the particular Registration Statement covering the Registrable Securities (the foregoing, in each case, excluding exhibits), (ii) upon the reasonable

request of any Holder, all exhibits excluded by the parenthetical in clause (i) of this paragraph, in the form generally available to the public, and (c) upon the reasonable request of any Holder, an adequate number of copies of the prospectuses and supplements to supply to any other party requiring such prospectuses.

4. Piggyback Registrations. (a) Right to Piggyback. At any time that the Company shall propose to register Common Stock under the Securities Act (other than in a registration on Form S-3 relating to sales of securities to participants in a Company dividend reinvestment plan, S-4 or S-8 or any successor form or in connection with an acquisition or exchange offer or an offering of securities solely to the existing shareholders or employees of the Company), the Company shall give prompt written notice to all Holders of Registrable Securities of its intention to effect such a registration and, subject to Section 4(b) and the other terms of this Agreement, shall include in such registration all Registrable Securities that are permitted under applicable securities laws to be included in such registration and with respect to which the Company has received written requests for inclusion therein by the Holders within 20 days after the receipt of the Company's notice (each, a "Piggyback Registration"; together with a Demand Registration and the Shelf Registration, a "Registration").

(b) Priority on Piggyback Registrations. If a Piggyback Registration is an underwritten registration on behalf of the Company, and the managing underwriters advise the Company in writing that in their opinion the number of securities requested to be included in such registration exceeds the number that can be sold in such offering without adversely affecting the marketability of the offering, the Company shall include in such registration, only as may be permitted in the reasonable business judgment of the managing underwriters for such registration:

(i) first, up to that number of securities the Company proposes to sell;

(ii) second, up to that number of Registrable Securities requested to be included in such registration by the Holders and that number of securities requested to be included in such registration by any other Person, pro rata among the Holders of such Registrable Securities and such other Persons, on the basis of the number of Registrable Securities and other securities of the Company requested to be included by each such Holder and other Persons; and

(iii) third, up to that number of other securities requested to be included in such registration.

The Holders of any Registrable Securities included in such a registration shall execute an underwriting agreement and customary accompanying documents in form and substance satisfactory to the managing underwriters.

(c) Right to Terminate Registration. If, at any time after giving written notice of its intention to register any of its securities as set forth in Section 4(a) and prior to the effective date of the registration statement filed in connection with such registration, the Company shall determine for any reason not to register such securities, the Company may, at its

election, give written notice of such determination to each Holder of Registrable Securities and thereupon be relieved of its obligation to register any Registrable Securities in connection with such registration (but not from its obligation to pay the Registration Expenses in connection therewith as provided herein).

(d) Selection of Underwriters. The Company shall have the right to select the investment banker(s) and manager(s) to administer an offering pursuant to a Piggyback Registration.

5. Expenses of Registration. Except as otherwise provided herein, all Registration Expenses incurred in connection with all registrations pursuant to Sections 2, 3 and 4 shall be borne by the Company and all Selling Expenses relating to securities registered on behalf of the Holders of Registrable Securities shall be borne by such Holders.

6. Holdback Agreements.

(a) The Company agrees, unless the underwriters managing the registered public offering otherwise agree, (i) not to effect any public sale or distribution of its equity securities, or any securities convertible into or exchangeable or exercisable for such securities, for its own account during the seven days prior to and during the 90-day period beginning on the effective date of any underwritten Demand Registration (except (A) as part of such underwritten registration, (B) pursuant to registration statements on Form S-4 or Form S-8 or any successor form, (C) pursuant to a registration statement then in effect or (D) as required under any existing contractual obligation of the Company), and (ii) to cause its officers and directors and to use reasonable efforts to cause each holder of at least 5% (on a fully-diluted basis) of its outstanding Common Stock, or any securities convertible into or exchangeable or exercisable for Common Stock, purchased from the Company at any time after the date of this Agreement (other than in a registered public offering) to agree not to effect any public sale or distribution (including sales pursuant to Rule 144) of any such securities during such periods (except as part of such underwritten registration, if otherwise permitted).

(b) Each Holder agrees, if requested by the managing underwriter or underwriters in an underwritten offering of securities of the Company, not to effect any offer, sale, distribution or transfer, including a sale pursuant to Rule 144 (or any similar provision then effect) under the Securities Act (except as part of such underwritten registration), during the seven-day period prior to, and during the 180-day period (or such shorter period as may be agreed to in writing by the Company and the Holders of at least 50% of the Registrable Securities) following the effective date of such Registration Statement to the extent timely notified in writing by the managing underwriter or underwriters.

7. Registration Procedures. Whenever the Company is under the obligation to register Registrable Securities hereunder, the Company will use all reasonable efforts to effect the Registration and the sale of such Registrable Securities, and pursuant thereto the Company will as expeditiously as possible:

(a) subject to Section 2(c) and 3(a) hereof, prepare and file with the Commission a registration statement on any form for which the Company qualifies with respect

to such Registrable Securities and use all reasonable efforts to cause such registration statement to become effective (provided that before filing a registration statement or prospectus or any amendments or supplements thereto, the Company will (i) furnish to the counsel selected by the Holders copies of all such documents proposed to be filed, which documents will be subject to the prompt review of such counsel, and (ii) notify each Holder of Registrable Securities covered by such registration of any stop order issued or threatened in writing by the Commission);

(b) subject to Section 2(c), 3(b) and 7(e) hereof, prepare and file with the Commission such amendments and supplements to such registration statement and the prospectus used in connection therewith as may be necessary to keep such registration statement effective for, in the case of a Demand Registration, a period equal to the shorter of (i) six months and (ii) the time by which all securities covered by such registration statement have been sold, and in the case of the Shelf Registration Statement, a period equal to the shorter of (x) one year and (y) the date upon which the Termination Date occurs, and comply with the provisions of the Securities Act with respect to the disposition of all securities covered by such registration statement during such period in accordance with the intended methods of disposition by the sellers thereof set forth in such registration statement;

(c) furnish to each seller of Registrable Securities such number of copies of such registration statement, each amendment and supplement thereto, the prospectus included in such registration statement (including each preliminary prospectus) and such other documents as such seller may reasonably request in order to facilitate the disposition of the Registrable Securities owned by such seller;

(d) use all reasonable efforts to register or qualify such Registrable Securities under the securities or blue sky laws of such jurisdictions as any seller reasonably requests and do any and all other acts and things which may be reasonably necessary or advisable to enable such seller to consummate the disposition in such jurisdictions of the Registrable Securities owned by such seller (provided that the Company will not be required to (i) qualify generally to do business in any jurisdiction where it would not otherwise be required to qualify but for this Section 7(d), or (ii) subject itself to taxation in any jurisdiction;

(e) notify each seller of such Registrable Securities, at any time when a prospectus relating thereto is required to be delivered under the Securities Act, of the occurrence of any event as a result of which the prospectus included in such registration statement contains an untrue statement of a material fact or omits any material fact necessary to make the statements therein in light of the circumstances under which they were made were not misleading, and, at the request of any such seller, the Company will prepare a supplement or amendment to such prospectus so that, as thereafter delivered to the purchasers of such Registrable Securities, such prospectus will not contain an untrue statement of a material fact or omit to state any material fact necessary to make the statements therein in light of the circumstances under which they were made not misleading; provided, however, that the Company shall not be required to amend the registration statement or supplement the Prospectus for a period of up to six months if the board of directors of the Company determines in good faith that to do so would reasonably be expected to have a material adverse effect on any proposal or plan by the Company to engage in any financing, acquisition or disposition of assets (other than in the ordinary course of business)

or any merger, consolidation, tender offer or similar transaction or would require the disclosure of any information that the board of directors of the Company determines in good faith the disclosure of which would be detrimental to the Company, it being understood that the period for which the Company is obligated to keep the Registration Statement effective shall be extended for a number of days equal to the number of days the Company delays amendments or supplements pursuant to this provision. Upon receipt of any notice pursuant to this Section 7(e), the Holders shall suspend all offers and sales of securities of the Company and all use of any prospectus until advised by the Company that offers and sales may resume, and shall keep confidential the fact and content of any notice given by the Company pursuant to this Section 7(e);

(f) cause all such Registrable Securities to be listed on each securities exchange on which similar securities issued by the Company are then listed;

(g) provide a transfer agent and registrar for all such Registrable Securities not later than the effective date of such registration statement;

(h) enter into such customary agreements (including underwriting agreements in customary form) and take all such other actions as the Holders of a majority of the Registrable Securities being sold or the underwriters, if any, reasonably request in order to expedite or facilitate the disposition of such Registrable Securities;

(i) at reasonable times and as reasonably requested make available for inspection by a representative of the Holders of Registrable Securities included in the registration statement, any underwriter participating in any disposition pursuant to such registration statement and any attorney, accountant or other agent retained by any such seller or underwriter, all pertinent financial and other records, pertinent corporate documents and properties of the Company, and use commercially reasonable efforts to cause the Company's officers, directors, employees and independent accountants to supply all information reasonably requested by any such seller, underwriter, attorney, accountant or agent in connection with such registration statement;

(j) otherwise use its reasonable efforts to comply with all applicable rules and regulations of the Commission, and make available to its security holders, as soon as reasonably practicable, an earnings statement covering the period of at least 12 months beginning with the first day of the Company's first full calendar quarter after the effective date of the registration statement, which earnings statement shall satisfy the provisions of Section 12(a) of the Securities Act and Rule 158 thereunder;

(k) in the event of the issuance of any stop order suspending the effectiveness of a registration statement, or of any order suspending or preventing the use of any related prospectus or suspending the qualification of any Common Stock included in such registration statement for sale in any jurisdiction, use all reasonable efforts promptly to obtain the withdrawal of such order; and

(l) if the registration is an underwritten offering, use all reasonable efforts to obtain a so-called "cold comfort" letter from the Company's independent public accountants in customary form and covering such matters of the type customarily covered by cold comfort letters.

8. Obligations of Holders. Whenever the Holders of Registrable Securities sell any Registrable Securities pursuant to a Registration, such Holders shall be obligated to comply with the applicable provisions of the Securities Act, including the prospectus delivery requirements thereunder, and any applicable state securities or blue sky laws.

9. Indemnification. (a) In connection with any registration statement for any Registration in which a Holder of Registrable Securities is participating, the Company agrees to indemnify, to the fullest extent permitted by applicable law, each such Holder of Registrable Securities, its officers and directors and each Person who controls such Holder (within the meaning of the Securities Act) against all losses, claims, damages, liabilities, reasonable and documented expenses or any amounts paid in settlement of any litigation, investigation or proceeding commenced or threatened to which each such indemnified party may become subject under the Securities Act including, without limitation, reasonable attorneys fees and disbursements (collectively, "Claims") insofar as such Claim arose out of (i) any untrue or alleged untrue statement of material fact contained, on the effective date thereof, in any such registration statement, prospectus or preliminary prospectus or any amendment thereof or supplement thereto or (ii) any omission or alleged omission to state therein a material fact required to be stated therein or necessary to make the statements therein not misleading, except insofar as the same are caused by or contained in any information furnished in writing to the Company by such Holder expressly for use therein or by such Holder's failure to deliver a copy of the registration statement or prospectus or any amendments or supplements thereto after the Company has furnished such Holder with a sufficient number of copies of the same. In connection with an underwritten offering, the Company will indemnify the underwriters, their officers and directors and each Person who controls the underwriters (within the meaning of the Securities Act) to the same extent as provided above with respect to the indemnification of the Holders of Registrable Securities.

(b) In connection with any registration statements for any Registration in which a Holder of Registrable Securities is participating, each such Holder will furnish to the Company in writing such customary information as the Company reasonably requests for use in connection with any such registration statement or prospectus (the "Seller's Information") and, to the fullest extent permitted by applicable law, will indemnify the Company, its directors and officers and each Person who controls the Company (within the meaning of the Securities Act) against any and all Claims to which each such indemnified party may become subject under the Securities Act insofar as such Claim arose out of (i) any untrue or alleged untrue statement of material fact contained, on the effective date thereof, in any such registration statement, prospectus or preliminary prospectus or any amendment thereof or supplement thereto or (ii) any omission or alleged omission to state therein a material fact required to be stated therein or necessary to make the statements therein not misleading; provided that with respect to a Claim arising pursuant to clause (i) or (ii) above, the material misstatement or omission is contained in such Seller's Information; provided, further, that the obligation to indemnify will be individual to

each Holder and will be limited to the amount of proceeds received by such Holder from the sale of Registrable Securities pursuant to such registration statement.

(c) Any Person entitled to indemnification hereunder will (i) give prompt written notice to the indemnifying party of any claim with respect to which it seeks indemnification (but the failure to provide such notice shall not release the indemnifying party of its obligation under paragraphs (a) and (b), unless and then only to the extent that, the indemnifying party has been prejudiced by such failure to provide such notice) and (ii) unless in such indemnified party's reasonable judgment a conflict of interest between such indemnified and indemnifying parties may exist with respect to such claim, permit such indemnifying party to assume the defense of such claim with counsel reasonably satisfactory to the indemnified party. An indemnifying party who is not entitled to, or elects not to, assume the defense of a claim will not be obligated to pay the fees and expenses of more than one counsel for all parties indemnified by such indemnifying party with respect to such claim, unless in the reasonable judgment of any indemnified party a conflict of interest may exist between such indemnified party and any other of such indemnified parties with respect to such claim.

(d) The indemnifying party shall not be liable to indemnify an indemnified party for any settlement, or consent to judgment of any such action effected without the indemnifying party's written consent (but such consent will not be unreasonably withheld). Furthermore, the indemnifying party shall not, except with the prior written approval of each indemnified party, consent to entry of any judgment or enter into any settlement which does not include as an unconditional term thereof the giving by the claimant or plaintiff to each indemnified party of a release from all liability in respect of such claim or litigation without any payment or consideration provided by each such indemnified party.

(e) If the indemnification provided for in this Section 9 is unavailable to an indemnified party under clauses (a) and (b) above in respect of any losses, claims, damages or liabilities referred to therein, then each indemnifying party, in lieu of indemnifying such indemnified party, shall contribute to the amount paid or payable by such indemnified party as a result of such losses, claims, damages or liabilities in such proportion as is appropriate to reflect not only the relative benefits received by the Company (if any), the underwriters, the sellers of Registrable Securities and any other sellers participating in the registration statement from the sale of shares pursuant to the registered offering of securities for which indemnity is sought but also the relative fault of the Company, the underwriters, the sellers of Registrable Securities and any other sellers participating in the registration statement in connection with the statement or omission which resulted in such losses, claims, damages or liabilities, as well as any other relevant equitable considerations. The relative benefits received by the Company (if any), the underwriters, the sellers of Registrable Securities and any other sellers participating in the registration statement shall be deemed to be based on the relative relationship of the total net proceeds from the offering (before deducting expenses) to the Company (if any), the total underwriting commissions and fees from the offering (before deducting expenses) to the underwriters and the total net proceeds from the offering (before deducting expenses) to the sellers of Registrable Securities and any other sellers participating in the registration statement. The relative fault of the Company, the underwriters, the sellers of Registrable Securities and any other sellers participating in the registration statement shall be determined by reference to,

among other things, whether the untrue or alleged untrue statement of a material fact or the omission or alleged omission to state a material fact relates to information supplied by the Company or by the sellers of Registrable Securities and the parties' relative intent, knowledge, access to information and opportunity to correct or prevent such statement or omission.

(f) The indemnification provided for under this Agreement will remain in full force and effect regardless of any investigation made by or on behalf of the indemnified party or any officer, director or controlling person of such indemnified party and will survive the transfer of the Registrable Securities.

10. Participation in Underwritten Registrations. No Holder may participate in any registration hereunder which is underwritten unless such Holder (a) agrees to sell such Holder's securities on the basis provided in any underwriting arrangements approved by the Holder or Holders entitled hereunder to approve such arrangements, (b) as expeditiously as possible notifies the Company of the occurrence of any event as a result of which any prospectus contains an untrue statement of material fact or omits to state a material fact required to be stated therein or necessary to make the statements therein not misleading and (c) completes and executes all questionnaires, powers of attorney, indemnities, underwriting agreements and other documents reasonably required under the terms of such underwriting arrangements.

11. Transfer of Registration Rights. The rights granted to any Holder under this Agreement may be assigned to any permitted transferee of Registrable Securities, in connection with any transfer or assignment of Registrable Securities by a Holder; provided, however, that: (a) such transfer is otherwise effected in accordance with applicable securities laws, (b) if not already a party hereto, the assignee or transferee agrees in writing prior to such transfer to be bound by the provisions of this Agreement applicable to the transferor, (c) such transferee shall own, after giving effect to such transfer, Registrable Securities representing at least 200,000 shares of Common Stock (as adjusted for any combinations, consolidations, stock distributions, stock dividends or other recapitalizations with respect to such shares), and (d) EIS shall act as agent and representative for such Holder for the giving and receiving of notices hereunder.

12. Information by Holder. Each Holder shall furnish to the Company such written information regarding such Holder and any distribution proposed by such Holder as the Company may reasonably request in writing and as shall be reasonably required in connection with any registration, qualification or compliance referred to in this Agreement and shall promptly notify the Company of any changes or updates in such information.

13. Exchange Act Compliance. The Company shall comply with all of the reporting requirements of the Exchange Act then applicable to it and shall comply with all other public information reporting requirements of the Commission which are conditions to the availability of Rule 144 for the sale of the Registrable Securities. The Company shall cooperate with each Holder in supplying such information as may be necessary for such Holder to complete and file any information reporting forms presently or hereafter required by the Commission as a condition to the availability of Rule 144.

14. Termination of Registration Rights. All registration rights granted under this Agreement shall terminate and be of no further force and effect, as to any particular Holder, at such time as all Registrable Securities held by such Holder can be sold within a three-month period without compliance with the registration requirements of the Securities Act pursuant to Rule 144 (including Rule 144(k)) promulgated thereunder.

15. Miscellaneous.

(a) No Inconsistent Agreements. The Company will not hereafter enter into any agreement with respect to its securities which is inconsistent with or violates the rights granted to the Holders of Registrable Securities in this Agreement without the prior written consent of a majority in interest of such Registrable Securities.

(b) Remedies. Any Person having rights under any provision of this Agreement will be entitled to enforce such rights specifically to recover damages caused by reason of any breach of any provision of this Agreement and to exercise all other rights granted by law. The parties hereto agree and acknowledge that money damages may not be an adequate remedy for any breach of the provisions of this Agreement and that any party may in its sole discretion apply to any court of law or equity of competent jurisdiction (without posting any bond or other security) for specific performance and for other injunctive relief in order to enforce or prevent violation of the provisions of this Agreement; provided, however, that in no event shall any Holder have the right to enjoin, delay or interfere with any offering of securities by the Company.

(c) Amendments and Waivers. Except as otherwise provided herein, the provisions of this Agreement may be amended or waived only with the prior written consent of the Company and Holders of at least 50% of the Registrable Securities; provided, however, that without the prior written consent of all the Holders, no such amendment or waiver shall reduce the foregoing percentage required to amend or waive any provision of this Agreement.

(d) Successors and Assigns. All covenants and agreements in this Agreement by or on behalf of any of the parties hereto will bind and inure to the benefit of the respective successors and assigns of the parties hereto, and shall inure to the benefit and be enforceable by each Holder of Registrable Securities from time to time. In addition, whether or not any express assignment has been made, the provisions of this Agreement which are for the benefit of Holders of Registrable Securities are also for the benefit of, and enforceable by, any permitted transferee of Registrable Securities in accordance with Section 11 hereof.

(e) Severability. Whenever possible, each provision of this Agreement will be interpreted in such manner as to be effective and valid under applicable law, but if any provision of this Agreement is held to be prohibited by or invalid under applicable law, such provision will be ineffective only to the extent of such prohibition or invalidity, without invalidating the remainder of this Agreement.

(f) Counterparts. This Agreement may be executed simultaneously in two or more counterparts, any one of which need not contain the signatures of more than one party, but all such counterparts taken together will constitute one and the same Agreement.

(g) Descriptive Headings. The descriptive headings of this Agreement are inserted for convenience only and do not constitute a part of this Agreement.

(h) Governing Law. All questions concerning the construction, validity and interpretation of this Agreement will be governed by the laws of the State of New York without regard to principles of conflicts of laws, except that all issues concerning the relative rights of the Company and its stockholders shall be governed by the Delaware General Corporation Law, without giving effect to the principles thereof relating to conflicts of laws.

(i) Notices. All notices, demands and requests of any kind to be delivered to any party in connection with this Agreement shall be in writing and shall be deemed to have been duly given if personally delivered or if sent by nationally-recognized overnight courier or by registered or certified airmail, return receipt requested and postage prepaid or by facsimile transmission (with receipt confirmed by telephone), addressed as follows:

(i) if to the Company, to:

Isis Pharmaceuticals, Inc.
2292 Faraday Avenue
Carlsbad, CA 92008
Facsimile: (760) 931-9639
telephone confirmation required at (760) 603-2460
Attention: B. Lynne Parshall

with a copy to:

Cooley Godward LLP
4365 Executive Drive
San Diego, CA 92121
Facsimile: (619) 453-3555
telephone confirmation required at (619) 550-6000
Attention: Julie Robinson, Esq.

(ii) if to EIS, to:

Elan International Services, Ltd.
Flatts, Smiths Parish
Bermuda, FL 04
Facsimile: (441) 292-2224
telephone confirmation required at (441) 292-9169
Attention: President

with a copy to:

Brock Silverstein LLC
800 Third Avenue, 21st Floor
New York, New York 10022
Facsimile: (212) 371-5500
telephone confirmation required at (212) 371-2000
Attention: Scott Rosenblatt, Esq.

(j) Entire Agreement. This Agreement constitutes the full and entire understanding and agreement between the parties with regard to the subject matter hereof.

[Signature page follows]

IN WITNESS WHEREOF, the parties have executed this Registration Rights Agreement as of the date first written above.

ISIS PHARMACEUTICALS, INC.

By: _____
Name:B. Lynne Parshall
Title: Executive Vice President

ELAN INTERNATIONAL SERVICES, LTD.

By: _____
Name:Kevin Insley
Title: President

EXHIBIT 10.6

HEPASENSE LTD.
REGISTRATION RIGHTS AGREEMENT

THIS REGISTRATION RIGHTS AGREEMENT (the "Agreement") is made as of January 14, 2000, by and among HEPASENSE LTD., a Bermuda exempted limited liability company (the "Company"), ISIS PHARMACEUTICALS, INC., a Delaware corporation ("Isis"), and ELAN INTERNATIONAL SERVICES, LTD., a Bermuda exempted limited liability company ("EIS").

R E C I T A L S:

A. Pursuant to a Subscription, Joint Development and Operating Agreement, dated as of the date hereof, by and among the Company, Isis, ELAN CORPORATION, PLC, an Irish public limited company, ELAN PHARMA INTERNATIONAL LIMITED, a company incorporated under the laws of Ireland ("EPIL"), and EIS (the "JDOA"), Isis has acquired certain common shares, par value $1.00 per share (the "Common Shares"), of the Company, and certain non-voting convertible preferred shares, par value $1.00 per share (the "Preferred Shares"; together with Common Shares, the "Securities"), of the Company and EIS has acquired certain Preferred Shares, which Preferred Shares are convertible into Common Shares.

B. The execution of the JDOA has occurred on the date hereof and it is a condition to the closing of the transactions contemplated thereby that the parties execute and deliver this Agreement.

C. The parties desire to set forth herein their agreement as to the terms and conditions related to the granting of certain registration rights to the Holders (as defined below) relating to the Common Shares held by such Holders and the Common Shares underlying the Securities.

A G R E E M E N T:

The parties hereto agree as follows:

1. Certain Definitions. As used in this Agreement, the following terms shall have the following respective meanings:

"Commission" shall mean the U.S. Securities and Exchange Commission.

"Exchange Act" shall mean the Securities Exchange Act of 1934, as amended, and the rules and regulations of the Commission thereunder, all as the same shall be in effect from time to time.

"Holders" or "Holders of Registrable Securities" shall mean Isis, EIS and any Person who shall have acquired Registrable Securities from either Isis or EIS as permitted herein, either individually or jointly, as the case may be, in a transaction pursuant to which registration rights are transferred pursuant to Section 10 hereof.

"Person" shall mean an individual, a partnership, a company, an association, a joint stock company, a trust, a joint venture, an unincorporated organization and a governmental or quasi-governmental entity, or any department, agency or political subdivision thereof.

"Registrable Securities" means (i) any Common Shares subscribed for pursuant to the JDOA (ii) any Common Shares issuable upon conversion of the Preferred Shares and (iii) any Common Shares issued or issuable in respect of the securities referred to in clause (i) and (ii) above upon any stock split, stock dividend, recapitalization or similar event; excluding in all cases, however, any Registrable Securities sold by a Person in a transaction (including a transaction pursuant to a registration statement under this Agreement and a transaction pursuant to Rule 144 promulgated under the Securities Act) in which registration rights are not transferred pursuant to Section 10 hereof.

The terms "register," "registered" and "registration" refer to a registration effected by preparing and filing a registration statement in compliance with the Securities Act, and the declaration or order of the effectiveness of such registration statement.

"Registration Expenses" shall mean all expenses, other than Selling Expenses, incurred by the Company in complying with Sections 2 or 3 hereof, including without limitation, all registration, qualification and filing fees, exchange listing fees, printing expenses, escrow fees, fees and disbursements of counsel for the Company, blue sky fees and expenses, the expense of any special audits including without limitation reconciliation to US GAAP incident to or required by any such registration and the reasonable fees and disbursements, not to exceed $10,000, of one counsel for the Holders, such counsel to be selected by Holders holding a majority of the Registrable Securities included in such registration.

"Securities Act" shall mean the Securities Act of 1933, as amended, and the rules and regulations of the Commission thereunder, all as the same shall be in effect from time to time.

"Selling Expenses" shall mean all underwriting discounts, selling commissions and stock transfer taxes applicable to the securities registered by the Holders and the costs and fees of any accountants, attorneys or other experts retained by any Holder or the Holders.

2. Demand Registrations.

(a) Requests for Registration. From and after the occurrence of the initial public offering of the Company's Common Shares under the Securities Act, any Holder or Holders who collectively hold Registrable Securities representing at least 33% of the Registrable Securities then outstanding shall have the right at any time from time to time, to request three registrations under the Securities Act of all or part of their Registrable Securities on Form F-1, F-2 or F-3 (or other analogous forms applicable to foreign private issuers such as the Corporation if available) or any similar registration statement (each, a "Demand Registration"), such form to be selected by the Company as appropriate. The request for the Demand Registration shall specify the approximate number of Registrable Securities requested to be registered, which must have a

minimum expected aggregate offering price to the public of at least $1,000,000. Within 20 days after receipt of any such request, the Company will give written notice of such requested registration to all other Holders of Registrable Securities. The Company shall include such other Holders' Registrable Securities in such offering if they have responded affirmatively within 20 days after the receipt of the Company's notice. Each of EIS and Isis shall be permitted at least one Demand Registration; provided, however, that the Holders in aggregate will be entitled to request only one Demand Registration hereunder within any 12-month period. A registration will not count as a permitted Demand Registration until it has become effective (unless such Demand Registration has not become effective due solely to the fault of the Holders requesting such registration, including a request by such Holders that such registration be withdrawn). The Company shall pay all Registration Expenses in connection with any Demand Registration whether or not such Demand Registration has become effective.

(b) Priority on Demand Registrations. If a Demand Registration is an underwritten offering and the managing underwriters advise the Company in writing that in their opinion the number of Registrable Securities and, if permitted hereunder, other securities requested to be included in such offering, exceeds the number of Registrable Securities and other securities, if any, which can be sold in such offering without adversely affecting the marketability of the offering, the Company will include in such registration:

(i) first, the Registrable Securities requested to be included in such registration by the Holders (or, if necessary, such Registrable Securities pro rata among the Holders thereof based upon the number of Registrable Securities owned by each such Holder) together with any securities held by third parties holding a similar, previously granted right to be included in such registration; and

(ii) thereafter, other securities requested to be included in such registration, as determined by the Company.

(c) Restrictions on Demand Registration. The Company may postpone for up to 90 days in any 12-month period, the filing or the effectiveness of a registration statement for a Demand Registration if the Company determines in good faith that such Demand Registration would reasonably be expected to have a material adverse effect on any proposal or plan by the Company to engage in any financing, acquisition or disposition of assets (other than in the ordinary course of business) or any merger, consolidation, tender offer or similar transaction or would require disclosure of any information that the board of directors of the Company determines in good faith the disclosure of which would be detrimental to the Company; provided, that in such event, the Holders initially requesting such Demand Registration will be entitled to withdraw such request and, if such request is withdrawn, such Demand Registration will not count as a permitted Demand Registration hereunder and the Company will pay any Registration Expenses in connection with such registration.

(d) Selection of Underwriters. The Holders will have the right to select the investment banker(s) and manager(s) to administer an offering pursuant to the Demand Registration, subject to the Company's prior written approval, which will not be unreasonably withheld or delayed.

(e) Other Registration Rights. Except as provided in this Agreement, so long as any Holder owns any Registrable Securities, the Company will not grant to any Persons the right to request the Company to register any equity securities of the Company, or any securities convertible or exchangeable into or exercisable for such securities, pari passu with or which conflicts with the rights granted to the Holders hereunder, without the prior written consent of the Holders of at least 50% of the Registrable Securities; provided, however, that the Company may grant rights to other Persons to demand and piggyback registrations so long as the Holders of Registrable Securities are entitled to participate in any such registrations with such Persons pro rata on the basis of the number of shares owned by each such Holder.

3. Piggyback Registrations.

(a) Right to Piggyback. At any time the Company shall propose to register Common Shares under the Securities Act (other than in a registration statement on Form S-3 relating to sales of securities to participants in a Company dividend reinvestment plan, or Form S-4 or S-8 or any successor form or in connection with an acquisition or exchange offer or an offering of securities solely to the existing shareholders or employees of the Company) (each, a "Piggyback Registration", together with a Demand Registration, a "Registration"), the Company will give prompt written notice to all Holders of Registrable Securities of its intention to effect such a registration and, subject to Section 3(b) and the other terms of this Agreement, will include in such registration all Registrable Securities which are permitted under applicable securities laws to be included in the form of registration statement selected by the Company and with respect to which the Company has received written requests for inclusion therein within 20 days after the receipt of the Company's notice.

(b) Priority on Piggyback Registrations. If a Piggyback Registration is to be an underwritten offering, and the managing underwriters advise the Company in writing that in their opinion the number of securities requested to be included in such registration exceeds the number which can be sold in such offering without adversely affecting the marketability of the offering, the Company will include in such registration:

(i) first, the securities the Company proposes to sell;

(ii) the Registrable Securities requested to be included in such registration by the Holders and any securities requested to be included in such registration by any other Person having equal priority to registration with the Holders, pro rata among the Holders of such Registrable Securities and such other Persons, on the basis of the number of shares owned by each of such Holders; and

(iii) thereafter, other securities requested to be included in such registration.

The Holders of any Registrable Securities included in such an underwritten offering must execute an underwriting agreement, in customary form and in form and substance satisfactory to the managing underwriters.

(c) Right to Terminate Registration. If, at any time after giving written notice of its intention to register any of its securities as set forth in Section 3(a) and prior to the effective date of the registration statement filed in connection with such registration, the Company shall determine for any reason not to register such securities, the Company may, at its election, give written notice of such determination to each Holder of Registrable Securities and thereupon be relieved of its obligation to register any Registrable Securities in connection with such registration (but not from its obligation to pay the Registration Expenses in connection therewith as provided herein).

(d) Selection of Underwriters. The Company will have the right to select the investment banker(s) and manager(s) to administer an offering pursuant to a Piggyback Registration.

4. Expenses of Registration. Except as otherwise provided herein or as may otherwise be prohibited by applicable law, all Registration Expenses incurred in connection with Registrations pursuant to Sections 2 and 3 shall be borne by the Company and all Selling Expenses relating to securities registered on behalf of the Holders of Registrable Securities shall be borne by such Holders; provided that, and notwithstanding anything herein contained to the contrary, the Company shall not have any obligation pursuant to the provisions hereof unless and until the Company is able to satisfy (after taking into account such obligations) the requirements of Section 39A (2A) of the Bermuda Companies Act of 1981 (or any successor legislation).

5. Holdback Agreements.

(a) The Company agrees (i) not to effect any public sale or distribution of its equity securities, or any securities convertible into or exchangeable or exercisable for such securities, during the seven days prior to and during the 180-day period beginning on the effective date of any underwritten Demand Registration or any underwritten Piggyback Registration (except as part of such underwritten registration or pursuant to registration statements on Form S-4 or Form S-8 or any successor form), unless the underwriters managing the registered public offering otherwise agree, and (ii) to cause its officers and directors and to use reasonable efforts to cause each holder of at least 5% (on a fully-diluted basis) of its outstanding Common Shares, or any securities convertible into or exchangeable or exercisable for Common Shares, purchased from the Company at any time after the date of this Agreement (other than in a registered public offering) to agree not to effect any public sale or distribution (including sales pursuant to Rule 144) of any such securities during such periods (except as part of such underwritten registration, if otherwise permitted), unless the underwriters managing the registered public offering otherwise agree.

(b) Each Holder agrees, if requested by the managing underwriter or underwriters in an underwritten offering of securities of the Company, not to effect any offer, sale, distribution or transfer, including a sale pursuant to Rule 144 (or any similar provision then effect) under the Securities Act (except as part of such underwritten registration), during the seven-day period prior to, and during the 180-day period (or such shorter period as may be agreed to in writing by the Company and the Holders of at least 50% of the Registrable Securities) following the effective date of such Registration Statement to the extent timely notified in writing by the managing underwriter or underwriters; provided, that each of the Persons described in Section 5(a)(ii) shall also have agreed to such restriction on sale.

6. Registration Procedures. Whenever the Holders of Registrable Securities have requested that any Registrable Securities be registered pursuant to this Agreement, the Company will use all reasonable efforts to effect the registration and the sale of such Registrable Securities in accordance with the intended method of distribution thereof, and pursuant thereto the Company will as expeditiously as possible:

(a) subject to Section 2(c) hereof, prepare and file with the Commission a registration statement on any form for which the Company qualifies with respect to such Registrable Securities and use all reasonable efforts to cause such registration statement to become effective (provided that before filing a registration statement or prospectus or any amendments or supplements thereto, the Company will (i) furnish to the counsel selected by the Holders copies of all such documents proposed to be filed, which documents will be subject to the review of such counsel, and (ii) notify each Holder of Registrable Securities covered by such registration of any stop order issued or threatened by the Commission);

(b) subject to Section 2(c) hereof, prepare and file with the Commission such amendments and supplements to such registration statement and the prospectus used in connection therewith as may be necessary to keep such registration statement effective for a period equal to the shorter of (i) six months and (ii) the time by which all securities covered by such registration statement have been sold, and comply with the provisions of the Securities Act with respect to the disposition of all securities covered by such registration statement during such period in accordance with the intended methods of disposition by the sellers thereof set forth in such registration statement;

(c) furnish to each seller of Registrable Securities such number of copies of such registration statement, each amendment and supplement thereto, the prospectus included in such registration statement (including each preliminary prospectus) and such other documents as such seller may reasonably request in order to facilitate the disposition of the Registrable Securities owned by such seller;

(d) use all reasonable efforts to register or qualify such Registrable Securities under the securities or blue sky laws of such jurisdictions as any seller reasonably requests and do any and all other acts and things which may be reasonably necessary or advisable to enable such seller to consummate the disposition in such jurisdictions of the Registrable Securities owned by such seller (provided that the Company will not be required to (i) qualify generally to

do business in any jurisdiction where it would not otherwise be required to qualify but for this Section 6(d) or (ii) subject itself to taxation in any jurisdiction;

(e) notify each seller of such Registrable Securities, at any time when a prospectus relating thereto is required to be delivered under the Securities Act, of the occurrence of any event as a result of which the prospectus included in such registration statement contains an untrue statement of a material fact or omits any fact necessary to make the statements therein not misleading, and, at the request of any such seller, the Company will prepare a supplement or amendment to such prospectus so that, as thereafter delivered to the purchasers of such Registrable Securities, such prospectus will not contain an untrue statement of a material fact or omit to state any fact necessary to make the statements therein not misleading; provided, however, that the Company shall not be required to amend the registration statement or supplement the Prospectus for a period of up to six months if the board of directors of the Company determines in good faith that to do so would reasonably be expected to have a material adverse effect on any proposal or plan by the Company to engage in any financing, acquisition or disposition of assets (other than in the ordinary course of business) or any merger, consolidation, tender offer or similar transaction or would require the disclosure of any information that the board of directors of the Company determines in good faith the disclosure of which would be detrimental to the Company, it being understood that the period for which the Company is obligated to keep the Registration Statement effective shall be extended for a number of days equal to the number of days the Company delays amendments or supplements pursuant to this provision. Upon receipt of any notice pursuant to this Section 6(e), the Holders shall suspend all offers and sales of securities of the Company and all use of any prospectus until advised by the Company that offers and sales may resume, and shall keep confidential the fact and content of any notice given by the Company pursuant to this Section 6(e);

(f) cause all such Registrable Securities to be listed on each securities exchange on which similar securities issued by the Company are then listed;

(g) provide a transfer agent and registrar for all such Registrable Securities not later than the effective date of such registration statement;

(h) enter into such customary agreements (including underwriting agreements in customary form) and take all such other actions as the Holders of a majority of the Registrable Securities being sold or the underwriters, if any, reasonably request in order to expedite or facilitate the disposition of such Registrable Securities;

(i) make available for inspection by a representative of the Holders of Registrable Securities included in the registration statement, any underwriter participating in any disposition pursuant to such registration statement and any attorney, accountant or other agent retained by any such seller or underwriter, all pertinent financial and other records, pertinent corporate documents and properties of the Company, and cause the Company's officers, directors, employees and independent accountants to supply all information reasonably requested by any such seller, underwriter, attorney, accountant or agent in connection with such registration statement;

(j) otherwise use its reasonable efforts to comply with all applicable rules and regulations of the Commission, and make available to its security holders, as soon as reasonably practicable, an earnings statement covering the period of at least 12 months beginning with the first day of the Company's first full calendar quarter after the effective date of the registration statement, which earnings statement shall satisfy the provisions of Section 11(a) of the Securities Act and Rule 158 thereunder;

(k) in the event of the issuance of any stop order suspending the effectiveness of a registration statement, or of any order suspending or preventing the use of any related prospectus or suspending the qualification of any Common Shares included in such registration statement for sale in any jurisdiction, use all reasonable efforts promptly to obtain the withdrawal of such order; and

(l) if the registration is an underwritten offering, use all reasonable efforts to obtain a so-called "cold comfort" letter from the Company's independent public accountants in customary form and covering such matters of the type customarily covered by cold comfort letters.

7. Obligations of Holders. Whenever the Holders of Registrable Securities sell any Registrable Securities pursuant to a Registration, such Holders shall be obligated to comply with the applicable provisions of the Securities Act, including the prospectus delivery requirements thereunder, and any applicable state securities or blue sky laws.

8. Indemnification. (a) The Company agrees to indemnify, to the fullest extent permitted by applicable law, each Holder of Registrable Securities, its officers and directors and each Person who controls such Holder (within the meaning of the Securities Act) against all losses, claims, damages, liabilities, expenses or any amounts paid in settlement of any litigation, investigation or proceeding commenced or threatened, including, without limitation, attorneys fees and disbursements (collectively, "Claims") to which each such indemnified party may become subject under the Securities Act insofar as such Claim arose out of (i) any untrue or alleged untrue statement of material fact contained, on the effective date thereof, in any registration statement, prospectus or preliminary prospectus or any amendment thereof or supplement thereto or (ii) any omission or alleged omission to state therein a material fact required to be stated therein or necessary to make the statements therein not misleading, except insofar as the same are caused by or contained in any information furnished in writing to the Company by such Holder expressly for use therein or by such Holder's failure to deliver a copy of the registration statement or prospectus or any amendments or supplements thereto after the Company has furnished such Holder with a sufficient number of copies of the same. In connection with an underwritten offering, the Company will indemnify the underwriters, their officers and directors and each Person who controls the underwriters (within the meaning of the Securities Act) to the same extent as provided above with respect to the indemnification of the Holders of Registrable Securities.

(b) In connection with any registration statements in which a Holder of Registrable Securities is participating, each such Holder will furnish to the Company in writing such customary information as the Company reasonably requests for use in connection with any

such registration statement or prospectus (the "Seller's Information") and, to the fullest extent permitted by applicable law, will indemnify the Company, its directors and officers and each Person who controls the Company (within the meaning of the Securities Act) against any and all Claims to which each such indemnified party may become subject under the Securities Act insofar as such Claim arose out of (i) any untrue or alleged untrue statement of material fact contained, on the effective date thereof, in any registration statement, prospectus or preliminary prospectus or any amendment thereof or supplement thereto regarding Seller's Information or (ii) any omission or alleged omission to state therein a material fact required to be stated therein or necessary to make the statements therein regarding Seller's Information not misleading; provided that with respect to a Claim arising pursuant to clause (i) or (ii) above, the material misstatement or omission is contained in such Seller's Information; provided, further, that the obligation to indemnify will be individual to each Holder and will be limited to the amount of proceeds received by such Holder from the sale of Registrable Securities pursuant to such registration statement.

(c) Any Person entitled to indemnification hereunder will (i) give prompt written notice to the indemnifying party of any claim with respect to which it seeks indemnification (but the failure to provide such notice shall not release the indemnifying party of its obligation under paragraphs (a) and (b), unless and then only to the extent that, the indemnifying party has been prejudiced by such failure to provide such notice) and (ii) unless in such indemnified party's reasonable judgment a conflict of interest between such indemnified and indemnifying parties may exist with respect to such claim, permit such indemnifying party to assume the defense of such claim with counsel reasonably satisfactory to the indemnified party. An indemnifying party who is not entitled to, or elects not to, assume the defense of a claim will not be obligated to pay the fees and expenses of more than one counsel for all parties indemnified by such indemnifying party with respect to such claim, unless in the reasonable judgment of any indemnified party a conflict of interest may exist between such indemnified party and any other of such indemnified parties with respect to such claim.

(d) The indemnifying party shall not be liable to indemnify an indemnified party for any settlement, or consent to judgment of any such action effected without the indemnifying party's written consent (but such consent will not be unreasonably withheld). Furthermore, the indemnifying party shall not, except with the prior written approval of each indemnified party, consent to entry of any judgment or enter into any settlement which does not include as an unconditional term thereof the giving by the claimant or plaintiff to each indemnified party of a release from all liability in respect of such claim or litigation without any payment or consideration provided by each such indemnified party.

(e) If the indemnification provided for in this Section 8 is unavailable to an indemnified party under clauses (a) and (b) above in respect of any losses, claims, damages or liabilities referred to therein, then each indemnifying party, in lieu of indemnifying such indemnified party, shall contribute to the amount paid or payable by such indemnified party as a result of such losses, claims, damages or liabilities in such proportion as is appropriate to reflect not only the relative benefits received by the Company, the underwriters, the sellers of Registrable Securities and any other sellers participating in the registration statement from the sale of shares pursuant to the registered offering of securities for which indemnity is sought but

also the relative fault of the Company, the underwriters, the sellers of Registrable Securities and any other sellers participating in the registration statement in connection with the statement or omission which resulted in such losses, claims, damages or liabilities, as well as any other relevant equitable considerations. The relative benefits received by the Company, the underwriters, the sellers of Registrable Securities and any other sellers participating in the registration statement shall be deemed to be based on the relative relationship of the total net proceeds from the offering (before deducting expenses) to the Company, the total underwriting commissions and fees from the offering (before deducting expenses) to the underwriters and the total net proceeds from the offering (before deducting expenses) to the sellers of Registrable Securities and any other sellers participating in the registration statement. The relative fault of the Company, the underwriters, the sellers of Registrable Securities and any other sellers participating in the registration statement shall be determined by reference to, among other things, whether the untrue or alleged untrue statement of a material fact or the omission or alleged omission to state a material fact relates to information supplied by the Company or by the sellers of Registrable Securities and the parties' relative intent, knowledge, access to information and opportunity to correct or prevent such statement or omission.

(f) The indemnification provided for under this Agreement will remain in full force and effect regardless of any investigation made by or on behalf of the indemnified party or any officer, director or controlling person of such indemnified party and will survive the transfer of the Registrable Securities.

9. Participation in Underwritten Registrations. No Holder may participate in any registration hereunder which is underwritten unless such Holder (a) agrees to sell such Holder's securities on the basis provided in any underwriting arrangements approved by the Holder or Holders entitled hereunder to approve such arrangements, (b) as expeditiously as possible notifies the Company of the occurrence of any event as a result of which any prospectus contains an untrue statement of material fact or omits to state a material fact required to be stated therein or necessary to make the statements therein not misleading and (c) completes and executes all questionnaires, powers of attorney, indemnities, underwriting agreements and other documents reasonably required under the terms of such underwriting arrangements.

10. Transfer of Registration Rights. The rights granted to any Holder under this Agreement may be assigned to any permitted transferee of Registrable Securities, in connection with any transfer or assignment of Registrable Securities by a Holder; provided, however, that: (a) such transfer is otherwise effected in accordance with applicable securities laws, (b) if not already a party hereto, the assignee or transferee agrees in writing prior to such transfer to be bound by the provisions of this Agreement applicable to the transferor, (c) such transferee shall own Registrable Securities representing at least 3,000 Common Shares (as adjusted for any combinations, consolidations, stock distributions, stock dividends or other recapitalizations with respect to such shares), and (d) Isis or EIS, as applicable, shall act as agent and representative for such Holder for the giving and receiving of notices hereunder.

11. Information by Holder. Each Holder shall furnish to the Company such written information regarding such Holder and any distribution proposed by such Holder as the Company may reasonably request in writing and as shall be reasonably required in connection

with any registration, qualification or compliance referred to in this Agreement and shall promptly notify the Company of any changes in such information.

12. Exchange Act Compliance. The Company shall comply with all of the reporting requirements of the Exchange Act then applicable to it and shall comply with all other public information reporting requirements of the Commission which are conditions to the availability of Rule 144 for the sale of the Registrable Securities. The Company shall cooperate with each Holder in supplying such information as may be necessary for such Holder to complete and file any information reporting forms presently or hereafter required by the Commission as a condition to the availability of Rule 144.

13. Termination of Registration Rights. All registration rights granted under this Agreement shall terminate and be of no further force and effect, as to any particular Holder, at such time as all Registrable Securities held by such Holder can be sold within a three-month period without compliance with the registration requirements of the Securities Act pursuant to Rule 144 (including Rule 144(k)) promulgated thereunder or have been resold pursuant to a registration statement hereunder.

14. Miscellaneous.

(a) No Inconsistent Agreements. The Company will not hereafter enter into any agreement with respect to its securities which is inconsistent with or violates the rights granted to the Holders of Registrable Securities in this Agreement without the prior written consent of a majority in interest of such Registrable Securities.

(b) Remedies. Any Person having rights under any provision of this Agreement will be entitled to enforce such rights specifically to recover damages caused by reason of any breach of any provision of this Agreement and to exercise all other rights granted by law. The parties hereto agree and acknowledge that money damages may not be an adequate remedy for any breach of the provisions of this Agreement and that any party may in its sole discretion apply to any court of law or equity of competent jurisdiction (without posting any bond or other security) for specific performance and for other injunctive relief in order to enforce or prevent violation of the provisions of this Agreement; provided, however, that in no event shall any Holder have the right to enjoin, delay or interfere with any offering of securities by the Company.

(c) Amendments and Waivers. Except as otherwise provided herein, the provisions of this Agreement may be amended or waived only with the prior written consent of the Company and Holders of at least 50% of the Registrable Securities; provided, however, that without the prior written consent of all the Holders, no such amendment or waiver shall reduce the foregoing percentage required to amend or waive any provision of this Agreement.

(d) Successors and Assigns. All covenants and agreements in this Agreement by or on behalf of any of the parties hereto will bind and inure to the benefit of the respective successors and assigns of the parties hereto, and shall inure to the benefit and be enforceable by each Holder of Registrable Securities from time to time. In addition, whether or not any express

assignment has been made, the provisions of this Agreement which are for the benefit of Holders of Registrable Securities are also for the benefit of, and enforceable by, any permitted transferee of Registrable Securities, in accordance with Section 10 hereof.

(e) Severability. Whenever possible, each provision of this Agreement will be interpreted in such manner as to be effective and valid under applicable law, but if any provision of this Agreement is held to be prohibited by or invalid under applicable law, such provision will be ineffective only to the extent of such prohibition or invalidity, without invalidating the remainder of this Agreement.

(f) Counterparts. This Agreement may be executed simultaneously in two or more counterparts, any one of which need not contain the signatures of more than one party, but all such counterparts taken together will constitute one and the same Agreement.

(g) Descriptive Headings. The descriptive headings of this Agreement are inserted for convenience only and do not constitute a part of this Agreement.

(h) Governing Law. All questions concerning the construction, validity and interpretation of this Agreement will be governed by the laws of the State of New York without regard to principles of conflicts of laws.

(i) Notices. All notices, demands and requests of any kind to be delivered to any party in connection with this Agreement shall be in writing and shall be deemed to have been duly given if personally delivered or if sent by nationally-recognized overnight courier or by registered or certified airmail, return receipt requested and postage prepaid or by facsimile transmission (with receipt confirmed by telephone), addressed as follows:

(i) if to the Company, to:

HepaSense Ltd.
c/o Conyers Dill & Pearman
Clarendon House
Church Street, P.O. Box HM 666
Hamilton HM CX, Bermuda
Attention: David J. Doyle
Facsimile: (441) 292-4720

with a copy to each of Isis, EIS and their respective counsel at the addresses indicated below

(ii) if to Isis, to:

Isis Pharmaceuticals, Inc.
2292 Faraday Avenue
Carlsbad, CA 92008
Facsimile: (760) 931-9639
telephone confirmation required at (760) 603-2460
Attention: B. Lynne Parshall

with a copy to:

Cooley Godward LLP
4365 Executive Drive
San Diego, CA 92121
Facsimile: (619) 453-3555
telephone confirmation required at (619) 550-6000
Attention: Julie Robinson, Esq.

(iii) if to EIS, to:

Elan International Services, Ltd.
Flatts, Smiths Parish
Bermuda, FL 04
Facsimile: (441) 292-2224
telephone confirmation required at (441) 292-9169
Attention: President

with a copy to:

Brock Silverstein LLC
800 Third Avenue, 21st Floor
New York, New York 10022
Facsimile: (212) 371-5500
telephone confirmation required at (212) 371-2000
Attention: Scott Rosenblatt, Esq.

(j) Entire Agreement. This Agreement constitutes the full and entire understanding and agreement between the parties with regard to the subject matter hereof.

[Signature page follows]

IN WITNESS WHEREOF, the parties have executed this Registration Rights Agreement as of the date first written above.

HEPASENSE LTD.

By: _____
Name:
Title:

ISIS PHARMACEUTICALS, INC.

By: _____
Name: B. Lynne Parshall
Title: Executive Vice President

ELAN INTERNATIONAL SERVICES, LTD.

By: _____
Name: Kevin Insley
Title: President

EXHIBIT 10.7

TEXT OMITTED AND FILED SEPARATELY
"CONFIDENTIAL TREATMENT REQUESTED
UNDER 17 C.F.R. SECTIONS 200.80(B)(4),
200.83 AND 240.24b-2."

LICENSE AGREEMENT

BETWEEN

ELAN CORPORATION, PLC
(ACTING THROUGH ITS DIVISION ELAN PHARMACEUTICAL TECHNOLOGIES)

AND

ELAN PHARMA INTERNATIONAL LIMITED

AND

HEPASENSE LTD.

JANUARY 14, 2000

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THIS AGREEMENT made this 14th January 2000

BETWEEN:

(1) ELAN CORPORATION, PLC, a public limited company incorporated under the laws of Ireland, acting through its division ELAN PHARMACEUTICAL TECHNOLOGIES and having its registered office at Lincoln House, Lincoln Place, Dublin 2, Ireland and ELAN PHARMA INTERNATIONAL LIMITED, a private limited company and having its registered office at WIL House, Shannon Business Park, Shannon, County Clare, Ireland;

(2) HEPASENSE LTD., a private limited company incorporated under the laws of Bermuda and having its registered office at 102 St. James Court, Clarendon House, Church St., Hamilton, Bermuda; and

(3) ISIS PHARMACEUTICALS, INC., a corporation duly incorporated and validly existing under the laws of the state of Delaware and having its principal place of business at 2292 Faraday Avenue, Carlsbad, California 92008, United States of America.

RECITALS:

A. Simultaneously herewith, Isis, Elan, EIS, and HepaSense (capitalized terms used herein are defined below) are entering into the JDOA for the purpose of recording the terms and conditions of the joint venture and of regulating their relationship with each other and certain aspects of the affairs of, and their dealings with HepaSense.

B. HepaSense desires to enter into this Agreement with Elan so as to permit HepaSense to utilize the Elan Intellectual Property in making, having made, importing, using, offering for sale and selling the Products in the Field in the Territory.

C. Simultaneously herewith HepaSense and Isis are entering into the Isis License Agreement relating to HepaSense's use of the Isis Intellectual Property.

1 DEFINITIONS

1.1 In this Agreement unless the context otherwise requires:

"ADDITIONAL OLIGONUCLEOTIDES" shall mean another Oligonucleotide from the Isis portfolio of Oligonucleotides nominated by Isis and accepted by Elan to be incorporated within or packaged with the System for commercialization. For the avoidance of doubt, the Parties acknowledge that any Additional Oligonucleotide shall be at least at the same stage of development as the Designated Oligonucleotide, i.e., shall be ready for clinical testing;

"ADDITIONAL PRODUCTS" shall mean the pharmaceutical formulation incorporating an

Additional Oligonucleotide and incorporated within or packaged with the System.

"AFFILIATE" shall mean any corporation or entity controlling, controlled or under the common control of Elan or Isis, as the case may be. For the purpose of this definition, "control" shall mean direct or indirect ownership of fifty percent (50%) or more of the stock or shares entitled to vote for the election of directors. HepaSense is not an Affiliate of Elan or EIS.

"AGREEMENT" shall mean this license agreement (which expression shall be deemed to include the Recitals and Schedules hereto).

"BUSINESS PLAN" shall have the meaning, as such term is defined in the JDOA.

"COMPETITIVE CHANGE OF CONTROL EVENT" shall mean that a Primary Technological Competitor of Elan acquires directly or indirectly voting stock or equivalent securities in Isis or HepaSense representing [*] percent or more of the stock which carries entitlement to vote, or a Primary Technological Competitor of Elan acquires by all or substantially all of the business of Isis or HepaSense to which the Definitive Documents relate, whether by merger, sale of stock, sale of assets or otherwise;

"CONFIDENTIAL INFORMATION" shall have the meaning, as such term is defined in Clause 9.

"DEFINITIVE DOCUMENTS" shall mean the definitive agreements relating to the transaction including finance, stock purchase, research and license agreements.

"DESIGNATED OLIGONUCLEOTIDE" shall mean Isis 14803.

"EFFECTIVE DATE" shall mean the date of this Agreement.

"ELAN" shall mean Elan, plc and EPIL, and their respective successors and permitted assigns.

"ELAN, PLC" shall mean Elan Corporation, plc, a public limited company incorporated under the laws of Ireland acting through its division Elan Pharmaceutical Technologies.

"EIS" shall mean Elan International Services, Ltd., a private limited company incorporated under the laws of Bermuda and having its registered office at St James Court, Flatts, Smiths, FL04 Bermuda.

"ELAN IMPROVEMENTS" shall mean any enhancement or improvement relating to the System, developed (i) by Elan whether or not pursuant to the Project, (ii) by HepaSense or Isis or by a third party (under contract with HepaSense) pursuant to the Project, and/or (iii) jointly by any combination of Elan, Isis or HepaSense pursuant to the Project, except as limited by agreements with third parties.

Subject to third party agreements, Elan Improvements shall constitute part of Elan

Intellectual Property and be included in the license of the Elan Intellectual Property pursuant to Clause 2.1 solely for the purposes set forth therein; provided, however, that an enhancement or improvement relating to the System which modifies the System in a manner for delivery of a drug other than delivery of factory pre-programmed continuous amounts of the drug shall remain the property of Elan but shall not be included in the license of the Elan Intellectual Property pursuant to Clause 2.1. If the inclusion of a Elan Improvement in the license of Elan Intellectual Property is restricted or limited by a third party agreement, Elan shall use reasonable commercial efforts to minimize any such restriction or limitation.

For the avoidance of doubt, any enhancement or improvement relating to both the System and the Isis Know-How or Isis Patents developed by any of the parties individually or jointly pursuant to the Project or by a third party (under contract with HepaSense) pursuant to the Project shall, except as limited by agreements with third parties, be deemed to be HepaSense Intellectual Property.

"ELAN INTELLECTUAL PROPERTY" shall mean the Elan Know-How, the Elan Patents and the Elan Improvements. For the avoidance of doubt, Elan Intellectual Property shall exclude inventions, patents and know-how owned, licensed or controlled by Targon Corporation, Axogen Limited and Neuralab Limited and by all Affiliates or subsidiaries (present or future) of Elan, plc. within the division of Elan, plc carrying on business as Elan Pharmaceuticals which incorporates, inter alia, EPIL (to the extent that EPIL is the owner of patents, know-how or other intellectual property or technology invented and/or developed within the division of Elan, plc carrying on business as Elan Pharmaceuticals), Athena Neurosciences, Inc., Elan Pharmaceuticals, Inc., Elan Diagnostics, Carnrick Laboratories, and Elan Europe Limited.

"ELAN KNOW-HOW" shall mean any and all rights owned, licensed or controlled by Elan to any scientific, pharmaceutical or technical information, data, discovery, invention (whether patentable or not), technique, process, procedure, system, formulation or design relating to the System that is not generally known to the public.

"ELAN LICENSE" shall have the meaning set forth in Clause 2.1 hereof.

"ELAN PATENTS" shall mean any and all patents and patent applications as set forth in Schedule 1, and all rights therein, and including all extensions, continuations, continuations-in-part, divisionals, patents-of-additions, re-examinations, re-issues, supplementary protection certificates and foreign counterparts thereto owned by or licensed to Elan containing claims relating to the System.

"EPIL" shall mean Elan Pharma International Limited, a private limited company incorporated under the laws of Ireland, that is wholly owned by Elan, plc.

"FIELD" shall mean the administration of the Designated Oligonucleotide by all routes of administration. Upon nomination by Isis and acceptance by Elan of an Additional Oligonucleotide, the parties shall amend the definition of the Field to include the administration of the Additional Oligonucleotide by such means of administration as agreed to by the parties.

Notwithstanding the foregoing, the Parties acknowledge and agree that, pursuant to existing agreement among Elan, Isis and Orasense Ltd, both Isis and Elan and their Affiliates may be subject to certain restrictions concerning the development and commercialization of products comprised upon the oral administration of any Oligonucleotide.

"FINANCIAL YEAR" shall mean each year commencing on 1 January (or in the case of the first Financial Year, the Effective Date) and expiring on 31 December of each year.

"HCV" shall mean the hepatitis C virus.

"HEPASENSE INTELLECTUAL PROPERTY" shall mean HepaSense Patents and HepaSense Know How. In addition to the foregoing, any enhancement or improvement relating to both the System and the Isis Know-How or Isis Patents developed by any of the Parties individually or jointly pursuant to the Project or by a third party (under contract with HepaSense) pursuant to the Project shall, except as limited by agreements with third parties, be deemed to be HepaSense Intellectual Property.

"HEPASENSE KNOW-HOW" shall mean any and all rights owned, licensed or controlled by HepaSense to any scientific, pharmaceutical or technical information, data, discovery, invention (whether patentable or not), technique, process, procedure, system, formulation or design that is not generally known to the public arising out of the conduct of the Project by any person that does not constitute Elan Improvements or Isis Improvements.

"HEPASENSE PATENTS" shall mean any and all patents and patent applications arising out of the conduct of the Project by any person that does not constitute Elan Improvements or Isis Improvements and all rights therein, and including all extensions, continuations, continuations-in-part, divisionals, patents-of-additions, re-examinations, re-issues, supplementary protection certificates and foreign counterparts thereto owned or licensed to HepaSense.

"IN MARKET" shall mean the sale of the Product and Additional Products in the Territory by HepaSense or its Affiliates, or where applicable by a permitted sub-licensee, to an unaffiliated third party, such as (i) the end-user consumer of the Product (ii) a wholesaler, managed care organization, hospital or pharmacy or other third party who effects the final commercial sale to the end-user consumer of the Product, and shall exclude the transfer pricing of the Product(s) by Elan to an Affiliate

or a sub-licensee.

"ISIS" shall mean Isis Pharmaceuticals, Inc. and its Affiliates, excluding HepaSense.

"ISIS INTELLECTUAL PROPERTY" shall mean the Isis Know-How, the Isis Patents and the Isis Improvements, as such terms are defined in the Isis License Agreement.

"ISIS LICENSE" shall mean have the meaning set forth in Clause 2.1 of the Isis License Agreement.

"ISIS LICENSE AGREEMENT" shall mean that certain license agreement, of even date herewith, entered into between Isis and HepaSense.

"ISIS PATENTS" shall have the meaning as such term is defined in the Isis License Agreement.

"ISIS IMPROVEMENTS" shall have the meaning as such term is defined in the Isis License Agreement.

"ISIS 14803" shall mean the Oligonucleotide described in Exhibit A to the Isis License Agreement.

"JDOA" shall mean that certain joint development and operating agreement, of even date herewith, by and between Elan, Isis, EIS and HepaSense.

"LICENSED TECHNOLOGIES" shall mean the Elan Intellectual Property and the Isis Intellectual Property.

"LICENSES" shall mean the Elan License and the Isis License.

"NET SALES" shall mean that sum determined by deducting the following deductions from the aggregate gross In Market sales proceeds billed for the Products by HepaSense or, its Affiliate or a permitted sub-licensee, as the case may be:

(i) transportation charges or allowances, if any, included in such price;

(ii) trade, quantity or cash discounts, broker's or agent's commissions, if any, allowed or paid;

(iii) credits or allowances, if any, given or made on account of price adjustments, returns, promotional discounts, rebates and any and all federal, state or local government rebates whether in existence now or enacted at any time during the term of the Licenses;

(iv) any tax, excise or governmental charge upon or measured by the sale, transportation, delivery or use of the Products; and

(v) reasonable samples, materials for clinical studies and reasonable

compassionate programs.

Net Sales shall also include the amount or fair market value of all other consideration received by HepaSense or its Affiliates or sublicensees in respect of Products and Additional Products, whether such consideration is payment in kind, exchange or another form. If a Product or Additional Product is provided to an third party by HepaSense or its Affiliates or sublicensees without charge or provision of invoice and used by such third party, then HepaSense or its Affiliates or sublicensees shall be treated as having sold such Product or Additional Product to such third party for an amount equal to the fair market value of such Product. Sales between or among HepaSense and its respective Affiliates or authorized licensees shall be excluded from the computation of Net Sales. A "sale" of a Product or Additional Product is deemed to occur upon the earlier of invoicing, shipment or transfer of title in the Product or the Additional Product to an third party. For avoidance of doubt, Net Sales shall include royalties received by HepaSense or its Affiliates from any third party in respect of Products and Additional Products.

"OLIGONUCLEOTIDE" shall mean any single stranded, [*] oligonucleotide including those [*] used as a human therapeutic and/or prophylactic compound containing between [*] nucleotides and/or nucleosides including oligonucleotide analogs which may include [*]. For purposes of this agreement, Oligonucleotide shall specifically exclude oligonucleotides used in gene therapy except [*] an oligonucleotide, oligonucleotides used as [*] or oligonucleotides used as adjuvants. Oligonucleotide shall also specifically exclude polymers in which the linkages are amide based, such as peptides and proteins and shall also exclude [*].

"ORAL" shall mean administration by way of the mouth for the purpose of topical or systemic delivery by way of the alimentary canal.

"PARTY" shall mean Elan or HepaSense, as the case may be, and "PARTIES" shall mean Elan and HepaSense.

"PRIMARY TECHNOLOGICAL COMPETITOR OF ELAN" shall mean those entities listed on Schedule 2A hereto.

"PRODUCT" shall mean the pharmaceutical formulation incorporating the Designated Oligonucleotide for [*] within the Field, including, without limitation, the incorporation of the Designated Oligonucleotide within or packaged with the System.

"PROJECT" shall mean all activities as undertaken by Elan, Isis and HepaSense in order to develop the Products

"SUBSTITUTE OLIGONUCLEOTIDE" shall have the meaning set forth in Clause 2.2 hereof;

"SYSTEM" shall mean an ambulatory drug delivery system for direct attachment to the body of a patient having a flexible diaphragm drug reservoir, which is capable of delivering factory pre-programmed continuous amounts of drug upon activation as disclosed and described in the Elan Patents set forth in Schedule 1 attached hereto.

"TECHNOLOGICAL COMPETITOR OF ELAN" shall mean a company, corporation or person listed in Schedule 2B and successors thereof or any additional broad-based technological competitor of Elan added to such Schedule from time to time upon mutual agreement of the Parties.

"TERM" shall have the meaning set forth in Clause 8.

"TERRITORY" shall mean all the countries of the world.

"UNITED STATES DOLLAR" and "US$" shall mean the lawful currency for the time being of the United States of America.

1.2 In this Agreement:

1.2.1 The singular includes the plural and vice versa, and the masculine includes the feminine and vice versa and the neuter includes the masculine and the feminine.

1.2.2 Any reference to a Clause or Schedule shall, unless otherwise specifically provided, be to a Clause or Schedule of this Agreement.

1.2.3 The headings of this Agreement are for ease of reference only and shall not affect its construction or interpretation.

2 ELAN LICENSE TO HEPASENSE

2.1 Elan hereby grants to HepaSense for the Term an exclusive license (including the limited right to grant sublicenses under Clause 10 of the JDOA) (the "Elan License") to the Elan Intellectual Property to make, have made, import, use, offer for sale and sell the Product in the Field in the Territory, subject to any contractual obligations that Elan has as of the Effective Date, including but not limited to the Development License and Supply Agreement dated 26 July 1999 between EPIL and Merck Corporation and the License Agreement dated as of April 20, 1999 between Orasense Ltd, and Elan Pharmaceutical Technologies, and the Manufacturing Agreement dated June 11, 1999 among Elan Corporation plc, EPIL and MiniMed. Upon nomination by Isis and acceptance by Elan of an Additional Oligonucleotide, the Parties shall negotiate in good faith how the Additional Product based upon such Additional Oligonucleotide should be developed and commercialized, whether a license should be granted to Isis or HepaSense or otherwise, (i) the terms of a grant of a new license of Elan Intellectual Property for use with the Additional Oligonucleotide or (ii) the

terms for amendment of the Elan License to include the license of the Elan Intellectual Property to make, have made, import, use, offer for sale and sell Additional Products based upon the Additional Oligonucleotide in the Field in the Territory, subject to any contractual obligations that Elan has as of the date of such agreement.

2.2 Elan hereby confirms that no financial or compensation obligations are in effect on the date hereof between Elan and an unaffiliated third party relating to the System for use in the Field.

To the extent royalty or other compensation obligations payable to third parties with respect to the Elan Intellectual Property would be triggered by use of such Elan Intellectual Property in connection with the Project, Elan shall inform HepaSense and Isis of such royalty or compensation obligations. If HepaSense and Isis agree to utilize such Elan Intellectual Property in connection with the Project, HepaSense will be responsible for the payment of such royalty or other compensation obligations relating thereto.

2.3 Isis shall be a third party beneficiary under this Agreement and shall have the right to cause HepaSense to enforce HepaSense's rights under this Agreement against Elan.

2.4 Notwithstanding anything contained in this Agreement to the contrary, Elan shall have the right outside the Field and subject to the non-competition provisions of Clause 4 to exploit and grant licenses and sublicenses of the Elan Intellectual Property.

For the avoidance of doubt, HepaSense shall have no right to use the Elan Intellectual Property outside the Field.

2.5 Except as provided in Clause 10 in the JDOA, HepaSense shall not be permitted to assign, license or sublicense any of its rights under the Elan Intellectual Property and/or the HepaSense Intellectual Property without the prior written consent of Elan.

2.6 Any agreement between HepaSense and any permitted third party for the development or exploitation of the Elan Intellectual Property shall require such third party to maintain the confidentiality of all information concerning the Elan Intellectual Property and shall provide that any Elan Improvements shall belong to Elan and shall permit an assignment of rights by HepaSense to Elan in accordance with the terms of this Agreement.

Insofar as the obligations owed by HepaSense to Elan are concerned, HepaSense shall remain responsible for all acts and omissions of any permitted sub-licensee, including Isis, as if they were acts and omissions by HepaSense.

3 INTELLECTUAL PROPERTY

3.1 OWNERSHIP OF INTELLECTUAL PROPERTY:

3.1.1 HepaSense shall own the HepaSense Intellectual Property.

3.1.2 Elan shall own the Elan Intellectual Property.

4 NON-COMPETITION/AFTER ACQUIRED TECHNOLOGY

4.1 Subject to Clause 4.2 hereof and Clause 14 of the JDOA, Elan, alone or in conjunction with a third party, shall not, for a period of [*] years from the Effective Date, develop or commercialize the Designated Oligonucleotide or any other Oligonucleotide designated towards the treatment of HCV, subject to (a) the Development, License and Supply Agreement dated 26 July 1999 between EPIL and Merck Corporation, (b) the Subscription, Joint Development and Operating Agreement, dated July 21, 1999, between Elan, plc, EIS, Targeted Genetics Corporation and Targeted Genetics HepaSense, Ltd. and (c) the License Agreement, dated as of July 20, 1999, between Targeted Genetics HepaSense, Ltd. and Elan, plc.

Notwithstanding anything to the contrary contained herein, the provisions of Clause 4.1 shall only act as a restriction upon Affiliates and subsidiaries of Elan, plc. carrying on business as Elan Pharmaceutical Technologies and, except for the development and commercialization of any Oligonucleotide designated towards the treatment of HCV administered by the System during such [*] year period, shall not act as a restriction upon, nor in any way affect, Targon Corporation, Axogen Limited, Neuralab Limited, Affiliates and subsidiaries (present or future) within the division of Elan, plc carrying on business as Elan Pharmaceuticals which incorporates, inter alia, EPIL (to the extent that EPIL is the owner of patents, know-how or other intellectual property or technology invented and/or developed within the division of Elan, plc carrying on business as Elan Pharmaceuticals), Athena Neurosciences, Inc., Elan Pharmaceuticals, Inc., Elan Diagnostics, Carnrick Laboratories, and Elan Europe Limited.

4.2 If, after the Effective Date, Elan obtains or licenses from a third party know-how or patent rights relating to the System in the Field, or acquires or merges with a third party entity that has know-how or patent rights relating to the System in the Field, Elan shall offer to license such know-how and patent rights to HepaSense (subject to existing contractual obligations), on commercially reasonable terms on an arm's length basis for a reasonable period under the prevailing circumstances.

If HepaSense determines that HepaSense should not acquire such license, Elan shall be free to fully exploit such know-how and patent rights with the Elan Intellectual Property then licensed to HepaSense, whether inside or outside the Field, and to grant to third parties licenses and sublicenses with respect thereto.

5 FINANCIAL PROVISIONS

*CONFIDENTIAL TREATMENT REQUESTED

5.1 LICENSE FEE:

In consideration of the license by Elan to HepaSense of the Elan Patents under Clause 2, HepaSense shall pay to Elan a non-refundable license fee of US [*] (the "LICENSE FEE"), the receipt of which is hereby acknowledged by Elan.

The License Fee shall not be subject to future performance obligations of Elan to HepaSense or Isis and shall not be applicable against future services provided by Elan to HepaSense or Isis. The license fee terms as set out in Clause 5.1 of this Agreement are independent and distinct from the other terms of this Agreement.

5.2 MILESTONE AND ROYALTY PAYMENTS RELATING TO PRODUCTS: All net proceeds derived by HepaSense from the Product shall be allocated as additional royalties in proportion to [*], as more particularly set forth below.

(a) Milestone Payments - If any third party shall make milestone payments (e.g., for NDA filing, approvals, etc.) to HepaSense, HepaSense shall pay to Elan and Isis an additional royalty in the amount of such milestone payments [*].

(b) Royalties payable to Elan and Isis Upon sales of the Product - Elan and Isis shall receive royalties based on In-market Net Sales of the Product aggregating [*] for sales directly by HepaSense or its sublicensees or such other royalty as the Parties may negotiate.

5.3 MILESTONE AND ROYALTY PAYMENTS RELATING TO ADDITIONAL PRODUCTS: All net proceeds derived by HepaSense from Additional Products shall be allocated as additional royalties [*], as more particularly set forth below. Elan, Isis and HepaSense shall negotiate separate royalty payments for Elan (including, without limitation, participation by HepaSense and Elan in milestone payments made by independent third parties to Isis) for any Additional Products at commercially reasonable rates on arms length terms between unrelated parties; provided, however, that HepaSense or Isis, as the case may be, shall not be obligated for the payment of an additional one-time access license fee.

5.4 Payment of royalties pursuant to Clause 5.3 shall be made quarterly in arrears during each Financial Year within 50 days after the expiry of the calendar quarter. The method of payment shall be by wire transfer to an account specified by Elan. Each payment made to Elan shall be accompanied by a true accounting of all Products sold by HepaSense's permitted sublicensees, if any, during such quarter.

Such accounting shall show, on a country-by-country and Product-by-Product basis, Net Sales (and the calculation thereof) and each calculation of royalties with respect

thereto, including the calculation of all adjustments and currency conversions.

Any royalties, license fees or other payments due under this Agreement to Elan shall be apportioned in accordance with a formula agreed between Elan, plc and EPIL.

5.5 HepaSense shall maintain and keep clear, detailed, complete, accurate and separate records for a period of 3 years:

5.5.1 to enable any royalties on Net Sales that shall have accrued hereunder to be determined; and

5.5.2 to enable any deductions made in the Net Sales calculation to be determined.

5.6 All payments due hereunder shall be made in United States Dollars. Payments due on Net Sales of any Product for each calendar quarter made in a currency other than United States Dollars shall first be calculated in the foreign currency and then converted to United States Dollars on the basis of the exchange rate in effect on the last working day for such quarter for the purchase of United States Dollars with such foreign currency quoted in the Wall Street Journal (or comparable publication if not quoted in the Wall Street Journal) with respect to the currency of the country of origin of such payment, determined by averaging the rates so quoted on each business day of such quarter.

5.7 If, at any time, legal restrictions in the Territory prevent the prompt payment when due of royalties or any portion thereof, the Parties shall meet to discuss suitable and reasonable alternative methods of paying Elan the amount of such royalties. In the event that HepaSense is prevented from making any payment under this Agreement by virtue of the statutes, laws, codes or government regulations of the country from which the payment is to be made, then such payments may be paid by depositing them in the currency in which they accrue to Elan's account in a bank acceptable to Elan in the country the currency of which is involved or as otherwise agreed by the Parties.

5.8 Elan and HepaSense agree to co-operate in all respects necessary to take advantage of any double taxation agreements or similar agreements as may, from time to time, be available.

5.9 Any taxes payable by Elan on any payment made to Elan pursuant to this Agreement shall be for the account of Elan. If so required by applicable law, any payment made pursuant to this Agreement shall be made by HepaSense after deduction of the appropriate withholding tax, in which event the Parties shall co-operate to obtain the appropriate tax clearance as soon as is practicable. On receipt of such clearance, HepaSense shall forthwith arrange payment to Elan of the amount so withheld.

6 RIGHT OF INSPECTION AND AUDIT

6.1 Once during each Financial Year, or more often not to exceed quarterly as reasonably requested by Elan, HepaSense shall permit Elan or its duly authorised representatives,

upon reasonable notice and at any reasonable time during normal business hours, to have access to inspect and audit the accounts and records of HepaSense and any other book, record, voucher, receipt or invoice relating to the calculation of the royalty payments on Net Sales submitted to Elan.

Any such inspection of HepaSense's records shall be at the expense of Elan, except that if any such inspection reveals a deficiency in the amount of the royalty actually paid to Elan hereunder in any Financial Year quarter of 5% or more of the amount of any royalty actually due to Elan hereunder, then the expense of such inspection shall be borne solely by HepaSense. Any amount of deficiency shall be paid promptly to Elan by HepaSense.

If such inspection reveals a surplus in the amount of royalties actually paid to Elan by HepaSense, Elan shall reimburse HepaSense the surplus within 15 days after determination.

6.2 In the event of any unresolved dispute regarding any alleged deficiency or overpayment of royalty payments hereunder, the matter will be referred to an independent firm of chartered accountants chosen by agreement of Isis and Elan for a resolution of such dispute. Any decision by the said firm of chartered accountants shall be binding on the Parties.

7 REPRESENTATIONS AND WARRANTIES

7.1 Elan represents and warrants to HepaSense and Isis as of the Effective Date that, except as set forth on Schedule 3 hereto:

7.1.1 Elan has the right to grant the Elan License;

7.1.2 there are no agreements between Elan and any third party that conflict with the Elan License;

7.1.3 the patents and patent applications included in the Elan Patents are free and clear of encumbrances and liens;

7.1.4 to the best of Elan's knowledge, there are no proceedings pending or threatened against Elan in connection with the Elan Intellectual Property in relation to the Field; and

7.1.5 the Elan Intellectual Property constitutes all intellectual property owned or licensed by Elan that is reasonably applicable to the Project as it relates to the System.

7.2 In addition to any other indemnities provided for herein, Elan shall indemnify and hold harmless HepaSense and its Affiliates and their respective employees, agents, officers and directors from and against any claims, losses, liabilities or damages

(including reasonable attorney's fees and expenses) incurred or sustained by HepaSense arising out of or in connection with any:

7.2.1 breach of any representation, covenant, warranty or obligation by Elan hereunder; or

7.2.2 act or omission on the part of Elan or any of its respective employees, agents, officers and directors in the performance of this Agreement.

7.3 In addition to any other indemnities provided for herein, HepaSense shall indemnify and hold harmless Elan and its Affiliates and their respective employees, agents, officers and directors from and against any claims, losses, liabilities or damages (including reasonable attorney's fees and expenses) incurred or sustained by Elan arising out of or in connection with any:

7.3.1 breach of any representation, covenant, warranty or obligation by HepaSense hereunder; or

7.3.2 act or omission on the part of HepaSense or any of its agents or employees in the performance of this Agreement.

7.4 The Party seeking an indemnity shall:

7.4.1 fully and promptly notify the other Party of any claim or proceeding, or threatened claim or proceeding;

7.4.2 permit the indemnifying Party to take full care and control of such claim or proceeding;

7.4.3 co-operate in the investigation and defence of such claim or proceeding;

7.4.4 not compromise or otherwise settle any such claim or proceeding without the prior written consent of the other Party, which consent shall not be unreasonably withheld conditioned or delayed; and

7.4.5 take all reasonable steps to mitigate any loss or liability in respect of any such claim or proceeding.

7.5 EXCEPT AS SET FORTH IN THIS CLAUSE 7, ELAN IS GRANTING THE LICENSES HEREUNDER ON AN "AS IS" BASIS WITHOUT REPRESENTATION OR WARRANTY WHETHER EXPRESS OR IMPLIED INCLUDING WARRANTIES OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE, OR INFRINGEMENT OF THIRD PARTY RIGHTS, AND ALL SUCH WARRANTIES ARE EXPRESSLY DISCLAIMED.

7.6 NOTWITHSTANDING ANYTHING TO THE CONTRARY IN THIS AGREEMENT, ELAN AND HEPASENSE SHALL NOT BE LIABLE TO THE

OTHER BY REASON OF ANY REPRESENTATION OR WARRANTY, CONDITION OR OTHER TERM OR ANY DUTY OF COMMON LAW, OR UNDER THE EXPRESS TERMS OF THIS AGREEMENT, FOR ANY CONSEQUENTIAL, SPECIAL OR INCIDENTAL OR PUNITIVE LOSS OR DAMAGE (WHETHER FOR LOSS OF PROFITS OR OTHERWISE) AND WHETHER OCCASIONED BY THE NEGLIGENCE OF THE RESPECTIVE PARTIES, THEIR EMPLOYEES OR AGENTS OR OTHERWISE.

8. TERM AND TERMINATION

8.1 On a product by product basis, subject to the provisions of Clause 10 and 11, the term of the Licenses granted hereunder with respect to a Product and/or Additional Product in each country in the Territory (the "TERM") shall be the greater of:

8.1.1 [*] years from the date of the first commercial sale of the Product or Additional Products; or

8.1.2 the life of the patent rights utilized in the Product or Additional Products or upon which the Product or Additional Product is based.

8.2 If either Party commits a Relevant Event, the other Party shall have, in addition to all other legal and equitable rights and remedies hereunder, the right to terminate this Agreement upon 30 days' prior written notice to the defaulting Party.

8.3 For the purpose of this Clause 8, a "RELEVANT EVENT" is committed or suffered by a Party if:

8.3.1 it commits a material breach of its obligations under this Agreement or the JDOA and such breach (i) is not capable of being cured or (ii) is capable of being cured the breaching Party fails to remedy it within 60 days of being specifically required in writing to do so by the other Party; provided, that if the breaching Party has proposed a course of action to rectify the breach and is acting in good faith to rectify same but has not cured the breach by the 60th day, such period shall be extended by such period as is reasonably necessary to permit the breach to be rectified;

8.3.2 a distress, execution, sequestration or other process is levied or enforced upon or sued out against a material part of its property which is not discharged or challenged within 30 days;

8.3.3 it is unable to pay its debts in the normal course of business;

8.3.4 it ceases wholly or substantially to carry on its business, otherwise than for the purpose of a reconstruction or amalgamation, without the prior written consent of the other Party (such consent not to be unreasonably withheld);

8.3.5 the appointment of a liquidator, receiver, administrator, examiner, trustee or similar officer of such Party or over all or substantially all of its assets under the law of any applicable jurisdiction, including without limitation, the United States of America, Bermuda or Ireland;

8.3.6 an application or petition for bankruptcy, corporate re-organisation, composition, administration, examination, arrangement or any other procedure similar to any of the foregoing under the law of any applicable jurisdiction, including without limitation, the United States of America, Bermuda or Ireland, is filed, and is not discharged within 60 days, or a Party applies for or consents to the appointment of a receiver, administrator, examiner or similar officer of it or of all or a material part of its assets, rights or revenues or the assets and/or the business of a Party are for any reason seized, confiscated or condemned.

8.4 In the event that a Competitive Change of Control Event shall occur, at the sole option of Elan and upon written notice to Isis and HepaSense, the Elan License shall be immediately terminated. Upon written notice from Isis to Elan of a proposed Competitive Change of Control Event or the occurrence of a Competitive Change of Control Event, Elan shall have thirty (30) days from such notice to Isis to provide written notice to Isis as to whether it intends to terminate the Elan License. In the event Elan does not provide written notice to Isis during such thirty (30) day period of its intention to terminate the Elan License, such termination right shall be deemed waived with respect to such occurrence.

8.5 Upon expiration or termination of the Agreement:

8.5.1. any sums that were due from HepaSense to Elan on Net Sales in the Territory or in such particular country or countries in the Territory (as the case may be) prior to the expiration or termination of this Agreement as set forth herein shall be paid in full within 60 days after the expiration or termination of this Agreement for the Territory or for such particular country or countries in the Territory (as the case may be);

8.5.2 any provisions that expressly survive termination or expiration of this Agreement, including without limitation this Clause 8, shall remain in full force and effect;

8.5.3 all representations, warranties and indemnities shall insofar as are appropriate remain in full force and effect;

8.5.4 the rights of inspection and audit set out in Clause 6 shall continue in force for a period of one year; and

8.5.5 all rights and licenses granted pursuant to this Agreement and to the Elan Intellectual Property pursuant to the JDOA (including the rights of HepaSense pursuant to Clause 11 of the JDOA) shall cease for the Territory or for such particular country or countries in the Territory (as the case may be) and shall

revert to or be transferred to Elan, and HepaSense shall not thereafter use in the Territory or in such particular country or countries in the Territory (as the case may be) any rights covered by this Agreement;

8.5.6 subject to Clause 8.5.7 and to such license, if any, granted by HepaSense to Elan pursuant to the provisions of Clause 10 of the JDOA, all rights to HepaSense Intellectual Property shall be transferred to and jointly owned by Isis and Elan but may not be exploited by both Elan and Isis, unless otherwise agreed by the unanimous vote of the Management Committee, and may only be exploited by either Elan and Isis pursuant to written consent from the other Party.

In the event of a dispute arising pursuant to this Clause 8.5.6, Elan and Isis agree to negotiate in good faith on the course of action to be taken with respect to determining their respective entitlements pursuant to this Clause 8.5.6; and

8.5.7 the rights of permitted third party sub-licensees in and to the Elan Intellectual Property shall survive the termination of the license and sublicense agreements granting said intellectual property rights to HepaSense; and HepaSense, Elan and Isis shall in good faith agree upon the form most advantageous to Elan and Isis in which the rights of HepaSense under any such licenses and sublicenses are to be held (which form may include continuation of HepaSense solely as the holder of such licenses or assignment of such rights to a third party or parties, including an assignment to both Elan and Isis).

Any sublicense agreement between HepaSense and such permitted sublicensee shall permit an assignment of rights by HepaSense and shall contain appropriate confidentiality provisions.

9 CONFIDENTIAL INFORMATION

9.1 The Parties agree that it will be necessary, from time to time, to disclose to each other confidential and proprietary information, including without limitation, inventions, works of authorship, trade secrets, specifications, designs, data, know-how and other proprietary information relating to the Field, the Products, processes, services and business of the disclosing Party.

The foregoing shall be referred to collectively as "CONFIDENTIAL INFORMATION".

9.2 Any Confidential Information disclosed by one Party to another Party shall be used by the receiving Party exclusively for the purposes of fulfilling the receiving Party's obligations under this Agreement and the JDOA and for no other purpose.

9.3 Each Party shall disclose Confidential Information of the other Party only to those employees, representatives and agents requiring knowledge thereof in connection with fulfilling the Party's obligations under this Agreement. Each Party further agrees to inform all such employees, representatives and agents of the terms and provisions of

this Agreement and their duties hereunder and to obtain their agreement hereto as a condition of receiving Confidential Information. Each Party shall exercise the same standard of care as it would itself exercise in relation to its own confidential information (but in no event less than a reasonable standard of care) to protect and preserve the proprietary and confidential nature of the Confidential Information disclosed to it by the other Party. Each Party shall, upon request of the other Party, return all documents and any copies thereof containing Confidential Information belonging to, or disclosed by, such other Party.

9.4 Any breach of this Clause 9 by any person informed by one of the Parties is considered a breach by the Party itself.

9.5 Confidential Information shall not be deemed to include:

9.5.1 information that is in the public domain;

9.5.2 information which is made public through no breach of this Agreement;

9.5.3 information which is independently developed by a Party as evidenced by such Party's records;

9.5.4 information that becomes available to a Party on a non-confidential basis, whether directly or indirectly, from a source other than a Party, which source did not acquire this information on a confidential basis; or

9.5.5 information which the receiving Party is required to disclose pursuant to:

(i) a valid order of a court or other governmental body; or

(ii) any other requirement of law;

provided that if the receiving Party becomes legally required to disclose any Confidential Information, the receiving Party shall give the disclosing Party prompt notice of such fact so that the disclosing Party may obtain a protective order or other appropriate remedy concerning any such disclosure. The receiving Party shall fully co-operate with the disclosing Party in connection with the disclosing Party's efforts to obtain any such order or other remedy. If any such order or other remedy does not fully preclude disclosure, the receiving Party shall make such disclosure only to the extent that such disclosure is legally required.

9.6 The provisions relating to confidentiality in this Clause 9 shall remain in effect during the term of this Agreement, and for a period of 7 years following the expiration or earlier termination of this Agreement.

9.7 The Parties agree that the obligations of this Clause 9 are necessary and reasonable in order to protect the Parties' respective businesses, and each Party agrees that monetary damages would be inadequate to compensate a Party for any breach by the

other Party of its covenants and agreements set forth herein.

Accordingly, the Parties agree that any such violation or threatened violation shall cause irreparable injury to a Party and that, in addition to any other remedies that may be available, in law and equity or otherwise, each Party shall be entitled to obtain injunctive relief against the threatened breach of the provisions of this Clause 9, or a continuation of any such breach by the other Party, specific performance and other equitable relief to redress such breach together with its damages and reasonable counsel fees and expenses to enforce its rights hereunder, without the necessity of proving actual or express damages.

9.8 For the avoidance of doubt, all Confidential Information of HepaSense received by Elan hereunder shall not be disclosed by Elan to its Affiliates and/or subsidiaries (present or future) within the division of Elan Pharmaceuticals Corporation, plc. carrying on business as Elan Pharmaceuticals (which incorporates, inter alia, Athena Neurosciences, Inc., Elan Pharmaceuticals, Inc., Elan Diagnostics, Carnrick Laboratories, and Elan Europe Limited) and Targon Corporation.

10 GOVERNING LAW AND DISPUTE RESOLUTION

10.1 This Agreement shall be governed by and construed in accordance with the laws of the State of New York without regard to principles relating to conflicts of laws.

10.2 The Parties will attempt in good faith to resolve any dispute arising out of or relating to this Agreement promptly by negotiation between executives of the Parties. In the event that such negotiations do not result in a mutually acceptable resolution, the Parties agree to consider other dispute resolution mechanisms including mediation.

10.3 Any dispute under this Agreement which is not settled by mutual consent under Clause 10.2 will be subject to resolution in accordance with Clauses 19 and 24.8 of the JDOA, which is incorporated by reference and shall for such purposes survive termination of the JDOA.

11 IMPOSSIBILITY OF PERFORMANCE - FORCE MAJEURE

Neither Elan nor HepaSense shall be liable for delay in the performance of any of its obligations hereunder if such delay results from causes beyond its reasonable control, including, without limitation, acts of God, fires, strikes, acts of war, intervention of a government authority, but any such delay or failure shall be remedied by such Party as soon as practicable.

12 ASSIGNMENT

This Agreement may not be assigned by either Party without the prior written consent of the other, save that either Party may assign this Agreement to its Affiliates or subsidiaries without such prior written consent [and that Elan may assign this Agreement to any off-balance sheet special purpose entity established by Elan or EIS without such prior written consent;] provided that such assignment does not have any

adverse tax consequences on the other Party.

13 NOTICES

13.1 Any notice to be given under this Agreement shall be sent in writing in English by registered airmail or telefaxed to the following addresses:

If to HepaSense at:

102 St. James Court
Clarendon House
Church St.
Hamilton, Bermuda
Attention: Secretary
Telephone: 441-295-1422
Fax: 441-292-4720

with a copy to Elan, plc and EPIL at:

Elan Corporation, plc
Elan Pharma International Limited
c/o Elan International Services, Ltd.
102 St. James Court
Flatts,
Smiths FL04
Bermuda
Attention: Secretary
Telephone: 441 292 9169
Fax: 441 292 2224

with a copy to:

Isis Pharmaceuticals, Inc.
2292 Faraday Avenue
Carlsbad, California 92008
Attention: B. Lynne Parshall, Esq.
Telephone: (760) 603-2460
Telefax: (760) 931-9639

If to Isis at:

Isis Pharmaceuticals, Inc.
2292 Faraday Avenue
Carlsbad, California 92008
Attention: B. Lynne Parshall, Esq.
Telephone: (760) 603-2460
Telefax: (760) 931-9639

If to Elan, plc and/or EPIL at:

Elan Corporation, plc
Elan Pharma International Limited
C/o Elan International Services, Ltd.
102 St. James Court
Flatts,
Smiths FL04
Bermuda
Attention: Secretary
Telephone: 441 292 9169
Fax: 441 292 2224

or to such other address(es) and telefax numbers as may from time to time be notified by either Party to the other hereunder.

13.2 Any notice sent by mail shall be deemed to have been delivered within seven 7 working days after dispatch and any notice sent by telex or telefax shall be deemed to have been delivered within twenty 24 hours of the time of the dispatch. Notice of change of address shall be effective upon receipt.

14 MISCELLANEOUS

14.1 WAIVER:

No waiver of any right under this Agreement shall be deemed effective unless contained in a written document signed by the Party charged with such waiver, and no waiver of any breach or failure to perform shall be deemed to be a waiver of any other breach or failure to perform or of any other right arising under this Agreement.

14.2 SEVERABILITY:

If any provision in this Agreement is agreed by the Parties to be, or is deemed to be, or becomes invalid, illegal, void or unenforceable under any law that is applicable hereto:

14.2.1 such provision will be deemed amended to conform to applicable laws so as to be valid and enforceable; or

14.2.2 if it cannot be so amended without materially altering the intention of the Parties, it will be deleted, with effect from the date of such agreement or such earlier date as the Parties may agree, and the validity, legality and enforceability of the remaining provisions of this Agreement shall not be impaired or affected in any way.

14.3 FURTHER ASSURANCES:

At the request of any of the Parties, the other Party or Parties shall (and shall use reasonable efforts to procure that any other necessary parties shall) execute and perform all such documents, acts and things as may reasonably be required subsequent to the signing of this Agreement for assuring to or vesting in the requesting Party the full benefit of the terms hereof.

14.4 SUCCESSORS:

This Agreement shall be binding upon and enure to the benefit of the Parties hereto, their successors and permitted assigns.

14.5 NO EFFECT ON OTHER AGREEMENTS/CONFLICT:

No provision of this Agreement shall be construed so as to negate, modify or affect in any way the provisions of any other agreement between the Parties unless specifically referred to, and solely to the extent provided herein.

In the event of a conflict between the provisions of this Agreement and the provisions of the JDOA, the terms of the JDOA shall prevail unless this Agreement specifically provides otherwise.

14.6 AMENDMENTS:

No amendment, modification or addition hereto shall be effective or binding on any Party unless set forth in writing and executed by a duly authorised representative of each Party.

14.7 COUNTERPARTS:

This Agreement may be executed in any number of counterparts, each of which when so executed shall be deemed to be an original and all of which when taken together shall constitute this Agreement.

14.8 GOOD FAITH:

Each Party undertakes to do all things reasonably within its power which are necessary or desirable to give effect to the spirit and intent of this Agreement.

14.9 NO RELIANCE:

Each Party hereby acknowledges that in entering into this Agreement it has not relied on any representation or warranty save as expressly set out herein or in any document referred to herein.

14.10 RELATIONSHIP OF THE PARTIES:

Nothing contained in this Agreement is intended or is to be construed to constitute

Elan and HepaSense as partners, or Elan as an employee of HepaSense, or HepaSense as an employee of Elan.

Neither Party hereto shall have any express or implied right or authority to assume or create any obligations on behalf of or in the name of the other Party or to bind the other Party to any contract, agreement or undertaking with any third party.

IN WITNESS WHEREOF the Parties hereto have executed this Agreement.

SIGNED BY:
---
for and on behalf of
ELAN CORPORATION, PLC ACTING
THROUGH ITS DIVISION ELAN
PHARMACEUTICAL TECHNOLOGIES

SIGNED BY:
---
for and on behalf of
ELAN PHARMA INTERNATIONAL LIMITED

SIGNED BY:

For and on behalf of
HEPASENSE LTD.

AGREED TO AND ACCEPTED BY

SIGNED BY:

For and on behalf of ISIS PHARMACEUTICAL, INC.

SCHEDULE 1

ELAN PATENTS

CONTINUOUS SYSTEM

FILE NUMBER	BRIEF DESCRIPTION	COUNTRY	STATUS
EMT 13	Original System	Australia	Granted (693136)
		Canada	Pending
		EP	Pending
		Israel	Granted (111685)
		Japan	Pending
		New Zealand	Granted (276485)
		Taiwan	Granted (079227)
		United States	2 Granted (5,527,288; 5,848,991); 1 Pending
		South Africa	Granted (94/9185)
EMT 19	Medipad-Vial on board, needle on the periphery	Australia	Pending
		Canada	Pending
		EP	Pending
		Ireland	Granted (77523)
		Japan	Pending
		Mexico	Pending
		New Zealand	Pending
		Norway	Pending
		Taiwan	Pending
		United States	Granted (5,814,020)
		South Korea	Pending
		South Africa	Granted (96/7502)
EMT 24	Delivery Needle	Australia	Pending
		Canada	Canada
		EP	Pending
		Ireland	Granted (80772)
		Israel	Pending
		Japan	Pending
		New Zealand	Pending
		South Africa	Granted (97/5065)
		South Korea	Pending
		Taiwan	Issued (096579)
		United States	Pending
EMT 29	Improved Medipad & Filling System (pressure adjustmt. valve, 3-position needle)	PCT	Pending
		Argentina	Pending
		Ireland	Pending
		Taiwan	Pending
		United States	Pending
EMT 33	Improved Method of Packaging a Drug	PCT	Pending

	Delivery Kit	Ireland	Pending
		South Africa	Issued (98/5188)
		Taiwan	Pending
		United States	Pending
EMT 36	Improved Adhesive System for a Medical Device	PCT	Pending
		Taiwan	Pending
		United States	Pending
EMT41DES	Design of Medipad Housing (3ml)	United States	Granted (D404482)
EMT 45	Liquid Drug Container	United States	Pending

All countries are initially designated when filing in the European Patent Office or the Patent Cooperation Treaty, and are then selected during the regional or national phase.

SCHEDULE 2A
PRIMARY TECHNOLOGICAL COMPETITORS OF ELAN(1)

[*]

SCHEDULE 2B
TECHNOLOGICAL COMPETITORS OF ELAN(1)

[*]

- ----------

1. Including any and all divisions or subsidiaries of the above.

*CONFIDENTIAL TREATMENT REQUESTED

SCHEDULE 3

ELAN EXCEPTIONS AND DISCLOSURES

[* .]

*CONFIDENTIAL TREATMENT REQUESTED

EXHIBIT 10.8

TEXT OMITTED AND FILED SEPARATELY
"CONFIDENTIAL TREATMENT REQUESTED
UNDER 17 C.F.R. SECTIONS 200.80(B)(4),
200.83 AND 240.24B-2."

LICENSE AGREEMENT

BETWEEN

ISIS PHARMACEUTICALS, INC.

AND

HEPASENSE LTD.

JANUARY 14, 2000

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14 MISCELLANEOUS

THIS AGREEMENT made this 14th day of January 2000

BETWEEN:

(1) ISIS PHARMACEUTICALS, INC., a corporation duly incorporated and validly existing under the laws of the state of Delaware and having its principal place of business at 2292 Faraday Avenue, Carlsbad, California 92008, United States of America; and

(2) HEPASENSE LTD., a private limited company incorporated under the laws of Bermuda and having its registered office at 102 St. James Court, Clarendon House Church St. Hamilton, Bermuda; and

(3) ELAN CORPORATION, PLC, a public limited company incorporated under the laws of Ireland, acting through its division ELAN PHARMACEUTICAL TECHNOLOGIES and having its registered office at Lincoln House, Lincoln Place, Dublin 2, Ireland and ELAN PHARMA INTERNATIONAL LIMITED, a private limited company and having its registered office at WIL House, Shannon Business Park, Shannon, County Clare, Ireland;

RECITALS:

A. Simultaneously herewith, Isis, Elan, EIS, and HepaSense (capitalized terms used herein are defined below) are entering into the JDOA for the purpose of recording the terms and conditions of the joint venture and of regulating their relationship with each other and certain aspects of the affairs of, and their dealings with HepaSense.

B. HepaSense desires to enter into this Agreement with Isis so as to permit HepaSense to utilize the Isis Intellectual Property in making, having made, importing, using, offering for sale and selling the Products in the Field in the Territory.

C. Simultaneously herewith HepaSense and Elan are entering into the Elan License Agreement relating to HepaSense's use of the Elan Intellectual Property.

1 DEFINITIONS

1.1 In this Agreement unless the context otherwise requires:

"ADDITIONAL OLIGONUCLEOTIDES" shall mean another Oligonucleotide from the Isis portfolio of Oligonucleotides nominated by Isis and accepted by Elan to be incorporated within or packaged with the System for commercialization. For the avoidance of doubt, the Parties acknowledge that any Additional Oligonucleotide shall be at least at the same stage of development as the Designated Oligonucleotide, i.e., shall be ready for clinical testing.

"ADDITIONAL PRODUCTS" shall mean the pharmaceutical formulation incorporating an Additional Oligonucleotide and incorporated within or packaged with the System.

"AFFILIATE" shall mean any corporation or entity controlling, controlled or under the common control of Elan or Isis, as the case may be. For the purpose of this definition, "control" shall mean direct or indirect ownership of fifty percent (50%) or more of the stock or shares entitled to vote for the election of directors. HepaSense is not an Affiliate of Elan or EIS.

"AGREEMENT" shall mean this license agreement (which expression shall be deemed to include the Recitals and Schedules hereto).

"BUSINESS PLAN" shall have the meaning, as such term is defined in the JDOA.

"CONFIDENTIAL INFORMATION" shall have the meaning, as such term is defined in Clause 9.

"DEFINITIVE DOCUMENTS" shall mean the definitive agreements relating to the transaction including finance, stock purchase, research and license agreements.

"DESIGNATED OLIGONUCLEOTIDE" shall mean Isis 14803.

"EFFECTIVE DATE" shall mean the date of this Agreement.

"ELAN" shall mean Elan, plc and EPIL, and their respective successors and permitted assigns.

"ELAN, PLC" shall mean Elan Corporation, plc, a public limited company incorporated under the laws of Ireland acting through its division Elan Pharmaceutical Technologies.

"EIS" shall mean Elan International Services, Ltd., a private limited company incorporated under the laws of Bermuda and having its registered office at St James Court, Flatts, Smiths, FL04 Bermuda.

"ELAN IMPROVEMENTS" shall have the meaning as such term is defined in the Elan License Agreement.

"ELAN INTELLECTUAL PROPERTY" shall mean the Elan Know-How, the Elan Patents and the Elan Improvements. For the avoidance of doubt, Elan Intellectual Property shall exclude inventions, patents and know-how owned, licensed or controlled by Targon Corporation, Axogen Limited and Neuralab Limited and by all Affiliates or subsidiaries (present or future) of Elan, plc. within the division of Elan, plc carrying on business as Elan Pharmaceuticals which incorporates, inter alia, EPIL (to the extent that EPIL is the owner of patents, know-how or other intellectual property or technology invented and/or developed within the division of Elan, plc carrying on business as Elan Pharmaceuticals), Athena Neurosciences, Inc., Elan Pharmaceuticals, Inc., Elan Diagnostics, Carnrick Laboratories, and Elan Europe Limited.

"ELAN KNOW-HOW" shall have the meaning as such term is defined in the Elan

License Agreement.

"ELAN LICENSE" shall have the meaning set forth in Clause 2.1 of the Elan License Agreement.

"ELAN LICENSE AGREEMENT" shall mean that certain license agreement, of even date herewith, entered into between Elan and HepaSense.

"ELAN PATENTS" shall have the meaning as such term is defined in the Elan License Agreement.

"EPIL" shall mean Elan Pharma International Limited, a private limited company incorporated under the laws of Ireland, that is wholly owned by Elan, plc.

"EXISTING ISIS LICENSE AGREEMENTS" shall mean the following agreements: (a) Amended License Agreement, between Public Health Service and Gen-Probe, Incorporated, as amended by the Second License Agreement between Public Health Service and Gen-Probe, Incorporated, (b) the Settlement Agreement among Public Health Service, Gen-Probe, Incorporated and Genta Incorporated and (c) Asset Purchase Agreement, effective as of December 19, 1997 between Gen-Probe, Incorporated and Isis.

Notwithstanding anything contained herein to the contrary, nothing contained in this License Agreement shall be deemed to constitute an admission by Isis that any of the Isis Intellectual Property is subject to or governed by any of the Existing Isis License Agreements.

"FIELD" shall mean the administration of the Designated Oligonucleotide by all routes of administration. Upon nomination by Isis and acceptance by Elan of an Additional Oligonucleotide, the parties shall amend the definition of the Field to include the administration of the Additional Oligonucleotide by such means of administration as agreed to by the parties.

Notwithstanding the foregoing, the Parties acknowledge and agree that, pursuant to existing agreement among Elan, Isis and Orasense Ltd, both Isis and Elan and their Affiliates may be subject to certain restrictions concerning the development and commercialization of products comprised upon the oral administration of any Oligonucleotide.

"FINANCIAL YEAR" shall mean each year commencing on 1 January (or in the case of the first Financial Year, the Effective Date) and expiring on 31 December of each year.

"HCV" shall mean the hepatitis C virus.

"HEPASENSE INTELLECTUAL PROPERTY" shall mean HepaSense Patents and HepaSense Know How. In addition to the foregoing, any enhancement or improvement relating to both the System and the Isis Know-How or Isis Patents developed by any of the

Parties individually or jointly pursuant to the Project or by a third party (under contract with HepaSense) pursuant to the Project shall, except as limited by agreements with third parties, be deemed to be HepaSense Intellectual Property.

"HEPASENSE KNOW-HOW" shall mean any and all rights owned, licensed or controlled by HepaSense to any scientific, pharmaceutical or technical information, data, discovery, invention (whether patentable or not), technique, process, procedure, system, formulation or design that is not generally known to the public arising out of the conduct of the Project by any person that does not constitute Elan Improvements or Isis Improvements.

"HEPASENSE PATENTS" shall mean any and all patents and patent applications arising out of the conduct of the Project by any person that does not constitute Elan Improvements or Isis Improvements and all rights therein, and including all extensions, continuations, continuations-in-part, divisionals, patents-of-additions, re-examinations, re-issues, supplementary protection certificates and foreign counterparts thereto owned or licensed to HepaSense.

"IN MARKET" shall mean the sale of the Product and Additional Products in the Territory by HepaSense or its Affiliates, or where applicable by a permitted sub-licensee, to an unaffiliated third party, such as (i) the end-user consumer of the Product (ii) a wholesaler, managed care organization, hospital or pharmacy or other third party who effects the final commercial sale to the end-user consumer of the Product, and shall exclude the transfer pricing of the Product(s) by Elan to an Affiliate or a sub-licensee.

"ISIS" shall mean Isis Pharmaceuticals, Inc. and its Affiliates, excluding HepaSense.

"ISIS IMPROVEMENTS" shall mean improvements to the Isis Patents and/or the Isis Know-How developed (i) by Isis whether or not pursuant to the Project, (ii) by HepaSense or Elan or by a third party (under contract with HepaSense) pursuant to the Project, and/or (iii) jointly by any combination of Isis, Elan or HepaSense pursuant to the Project, except as limited by agreements with third parties.

Subject to third party agreements, Isis Improvements shall constitute part of Isis Intellectual Property and be included in the license of the Isis Intellectual Property pursuant to Clause 2.1 solely for the purposes set forth therein. If the inclusion of a Isis Improvement in the license of Isis Intellectual Property is restricted or limited by a third party agreement, Isis shall use reasonable commercial efforts to minimize any such restriction or limitation.

"ISIS INTELLECTUAL PROPERTY" shall mean the Isis Know-How, the Isis Patents and the Isis Improvements, as such terms are defined in the Isis License Agreement.

"ISIS KNOW-HOW" shall mean any and all rights owned, licensed or controlled by Isis to any scientific, pharmaceutical or technical information, data, discovery, invention (whether patentable or not), technique, process, procedure, system, formulation or design relating to the Designated Oligonucleotide that is not generally known to the

public.

"ISIS LICENSE" shall mean have the meaning set forth in Clause 2.1 hereof.

"ISIS PATENTS" shall mean any and all patents and patent applications as set forth in Schedule 1, and all rights therein, and including all extensions, continuations, continuations-in-part, divisionals, patents-of-additions, re-examinations, re-issues, supplementary protection certificates and foreign counterparts thereto owned by or licensed to Isis containing claims relating to the Designated Oligonucleotide. Upon nomination and approval of an Additional Oligonucleotide, Schedule 1 shall be amended to include any and all patents and patent applications and all rights therein, and including all extensions, continuations, continuations-in-part, divisionals, patents-of-additions, re-examinations, re-issues, supplementary protection certificates and foreign counterparts thereto owned by or licensed to Isis containing claims relating to the Additional Oligonucleotide.

"ISIS IMPROVEMENTS" shall have the meaning as such term is defined in the Isis License Agreement.

"ISIS 14803" shall mean the Oligonucleotide described in Exhibit A hereto.

"JDOA" shall mean that certain joint development and operating agreement, of even date herewith, by and between Elan, Isis, EIS and HepaSense.

"LICENSED TECHNOLOGIES" shall mean the Elan Intellectual Property and the Isis Intellectual Property.

"LICENSES" shall mean the Elan License and the Isis License.

"NET SALES" shall mean that sum determined by deducting the following deductions from the aggregate gross In Market sales proceeds billed for the Products by HepaSense or, its Affiliate or a permitted sub-licensee, as the case may be:

(i) transportation charges or allowances, if any, included in such price;

(ii) trade, quantity or cash discounts, broker's or agent's commissions, if any, allowed or paid;

(iii) credits or allowances, if any, given or made on account of price adjustments, returns, promotional discounts, rebates and any and all federal, state or local government rebates whether in existence now or enacted at any time during the term of the Licenses;

(iv) any tax, excise or governmental charge upon or measured by the sale, transportation, delivery or use of the Products; and

(v) reasonable samples, materials for clinical studies and reasonable compassionate programs

Net Sales shall also include the amount or fair market value of all other consideration received by HepaSense or its Affiliates or sublicensees in respect of Products and Additional Products, whether such consideration is payment in kind, exchange or another form. If a Product or Additional Product is provided to an third party by HepaSense or its Affiliates or sublicensees without charge or provision of invoice and used by such third party, then HepaSense or its Affiliates or sublicensees shall be treated as having sold such Product or Additional Product to such third party for an amount equal to the fair market value of such Product. Sales between or among HepaSense and its respective Affiliates or authorized licensees shall be excluded from the computation of Net Sales. A "sale" of a Product or Additional Product is deemed to occur upon the earlier of invoicing, shipment or transfer of title in the Product or the Additional Product to an third party. For avoidance of doubt, Net Sales shall include royalties received by HepaSense or its Affiliates from any third party in respect of Products and Additional Products.

"OLIGONUCLEOTIDE" shall mean any single stranded, [*] oligonucleotide including those [*] used as a human therapeutic and/or prophylactic compound containing between [*] nucleotides and/or nucleosides including oligonucleotide analogs which may include [*]. For purposes of this agreement, Oligonucleotide shall specifically exclude oligonucleotides used in gene therapy except [*] an oligonucleotide, oligonucleotides used as [*] or oligonucleotides used as adjuvants. Oligonucleotide shall also specifically exclude polymers in which the linkages are amide based, such as peptides and proteins and shall also exclude [*].

"ORAL" shall mean administration by way of the mouth for the purpose of topical or systemic delivery by way of the alimentary canal.

"PARTY" shall mean Isis or HepaSense, as the case may be, and "PARTIES" shall mean Isis and HepaSense.

"PRODUCT" shall mean the pharmaceutical formulation incorporating the Designated Oligonucleotide for [*] within the Field, including, without limitation, the incorporation of the Designated Oligonucleotide within or packaged with the System.

"PROJECT" shall mean all activities as undertaken by Elan, Isis and HepaSense in order to develop the Products.

"SUBSTITUTE OLIGONUCLEOTIDE" shall have the meaning set forth in Clause 2.2 hereof;

"SYSTEM" shall have the meaning as such term is defined in the Elan License Agreement.

"TECHNOLOGICAL COMPETITOR OF ISIS" shall mean a company, corporation or person listed in Schedule 2 and successors thereof or any additional broad-based technological competitor of Isis added to such Schedule from time to time upon mutual agreement of the Parties.

"TERM" shall have the meaning set forth in Clause 8.

"TERRITORY" shall mean all the countries of the world.

"UNITED STATES DOLLAR" and "US$" shall mean the lawful currency for the time being of the United States of America.

1.2 In this Agreement:

1.2.1 The singular includes the plural and vice versa, and the masculine includes the feminine and vice versa and the neuter includes the masculine and the feminine.

1.2.2 Any reference to a Clause or Schedule shall, unless otherwise specifically provided, be to a Clause or Schedule of this Agreement.

1.2.3 The headings of this Agreement are for ease of reference only and shall not affect its construction or interpretation.

2 ISIS LICENSE TO HEPASENSE

2.1 Isis hereby grants to Newco for the Term an exclusive license (including the limited right to grant sublicenses under Clause 10 of the JDOA) (the "ISIS License") to the Isis Intellectual Property to make, have made, import, use, offer for sale and sell the Product in the Field in the Territory, subject to any contractual obligations that Isis has as of the Effective Date. Upon nomination by Isis and acceptance by Elan of an Additional Oligonucleotide, the Parties shall negotiate in good faith how the Additional Product based upon such Additional Oligonucleotide should be developed and commercialized, whether a license should be granted to Isis or HepaSense or otherwise, (i) the terms of a grant of a new license of Isis Intellectual Property for use with the Additional Oligonucleotide or (ii) the terms for amendment of the Isis License to include the license of the Isis Intellectual Property to make, have made, import, use, offer for sale and sell Additional Products based upon the Additional Oligonucleotide in the Field in the Territory, subject to any contractual obligations that Isis has as of the date of such agreement.

2.2 Isis hereby confirms that no obligations are in effect on the date hereof between Isis and an unaffiliated third party relating to the Designated Oligonucleotide for use in the Field, other than the Existing Isis License Agreements.

Isis shall be responsible for payments related to the financial provisions and

obligations under the Existing Isis License Agreements (including amendments thereto), including, without limitation, any royalty or other compensation obligations.

2.3 Subject to the provisions of Clause 2.2, to the extent royalty or other compensation obligations are payable to third parties with respect to Isis Intellectual Property would be triggered by use of such Isis Intellectual Property in connection with the Project, Isis shall inform Elan of such royalty or compensation obligation. If HepaSense and Elan agree to utilize such Isis Intellectual Property in connection with the Project, HepaSense shall be responsible for the payment of such royalty or other compensation obligations relating thereto.

2.4 Elan shall have the right to cause HepaSense to enforce HepaSense's rights under this Agreement against Isis.

2.5 Notwithstanding anything contained in this Agreement to the contrary, Isis shall have the right outside the Field and subject to the non-competition provisions of Clause 4 to exploit and grant licenses and sublicenses of the Isis Intellectual Property.

For the avoidance of doubt, HepaSense shall have no right to use the Isis Intellectual Property outside the Field.

2.6 Except as provided in Clause 11 in the JDOA, HepaSense shall not be permitted to assign, license or sublicense any of its rights under the Isis Intellectual Property and/or the HepaSense Intellectual Property without the prior written consent of Isis.

2.7 Any agreement between HepaSense and any permitted third party for the development or exploitation of the Isis Intellectual Property shall require such third party to maintain the confidentiality of all information concerning the Isis Intellectual Property and shall provide that any Isis Improvements shall belong to Isis and shall permit an assignment of rights by HepaSense to Isis in accordance with the terms of this Agreement.

Insofar as the obligations owed by HepaSense to Isis are concerned, HepaSense shall remain responsible for all acts and omissions of any permitted sub-licensee, including Isis, as if they were acts and omissions by HepaSense.

3 INTELLECTUAL PROPERTY

3.1 OWNERSHIP OF INTELLECTUAL PROPERTY:

3.1.1 HepaSense shall own the HepaSense Intellectual Property.

3.1.2 Isis shall own the Isis Intellectual Property.

4 NON-COMPETITION/AFTER ACQUIRED TECHNOLOGY

4.1 Subject to Clause 4.2 hereof and Clause 13 of the JDOA, during the [*] year period commencing on the effective date, Isis, alone or in conjunction with a third party, shall not develop or commercialize (i) any Oligonucleotide for the treatment of HCV or (ii) the Designated Oligonucleotide for the treatment of HCV or any other indication.

4.2 If after the Effective Date Isis acquires know-how or patent rights from a third party relating to the Isis Intellectual Property, or if Isis acquires or merges with a third party entity that owns or has license rights to know-how or patent rights relating to the Isis Intellectual Property, then Isis shall offer to license such know-how and patent rights to HepaSense (subject to existing contractual obligations) solely for HepaSense to research, develop and otherwise engage in the commercialization of the Product solely for use in the Field on such terms as would be offered to an independent third party negotiating in good faith on an arms-length basis.

If HepaSense determines that HepaSense should not acquire such license, Isis shall be free to fully exploit such know-how and patent rights with the Isis Intellectual Property then licensed to HepaSense, whether inside or outside the Field, and to grant to third parties licenses and sublicenses with respect thereto.

5 FINANCIAL PROVISIONS

5.1 MILESTONE AND ROYALTY PAYMENTS RELATING TO PRODUCTS: All net proceeds derived by HepaSense from the Product shall be allocated as additional royalties in proportion to [*], as more particularly set forth below.

(a) Milestone Payments - If any third party shall make milestone payments (e.g., for NDA filing, approvals, etc.) to HepaSense, HepaSense shall pay to Elan and Isis an additional royalty in the amount of such milestone payments [*].

(b) Royalties payable to Elan and Isis Upon sales of the Product - Elan and Isis shall receive royalties based on In-market Net Sales of the Product aggregating [*] for sales directly by HepaSense or its sublicensees or such other royalty as the Parties may negotiate.

5.2 MILESTONE AND ROYALTY PAYMENTS RELATING TO ADDITIONAL PRODUCTS: All net proceeds derived by HepaSense from Additional Products shall be allocated as additional royalties [*], as more particularly set forth below. Elan, Isis and HepaSense shall negotiate separate royalty payments for Elan (including, without limitation, participation by HepaSense and Elan in milestone payments made by independent third parties to Isis) for any Additional Products at commercially reasonable rates on arms length terms between unrelated parties; provided, however, that HepaSense or Isis, as the case may be, shall not be obligated for the payment of

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an additional one-time access license fee.

5.3 Payment of royalties pursuant to Clause 5.3 shall be made quarterly in arrears during each Financial Year within 50 days after the expiry of the calendar quarter. The method of payment shall be by wire transfer to an account specified by Isis. Each payment made to Isis shall be accompanied by a true accounting of all Products sold by HepaSense's permitted sublicensees, if any, during such quarter.

Such accounting shall show, on a country-by-country and Product-by-Product basis, Net Sales (and the calculation thereof) and each calculation of royalties with respect thereto, including the calculation of all adjustments and currency conversions.

5.5 HepaSense shall maintain and keep clear, detailed, complete, accurate and separate records for a period of 3 years:

5.5.1 to enable any royalties on Net Sales that shall have accrued hereunder to be determined; and

5.5.2 to enable any deductions made in the Net Sales calculation to be determined.

5.6 All payments due hereunder shall be made in United States Dollars. Payments due on Net Sales of any Product for each calendar quarter made in a currency other than United States Dollars shall first be calculated in the foreign currency and then converted to United States Dollars on the basis of the exchange rate in effect on the last working day for such quarter for the purchase of United States Dollars with such foreign currency quoted in the Wall Street Journal (or comparable publication if not quoted in the Wall Street Journal) with respect to the currency of the country of origin of such payment, determined by averaging the rates so quoted on each business day of such quarter.

5.7 If, at any time, legal restrictions in the Territory prevent the prompt payment when due of royalties or any portion thereof, the Parties shall meet to discuss suitable and reasonable alternative methods of paying Isis the amount of such royalties. In the event that HepaSense is prevented from making any payment under this Agreement by virtue of the statutes, laws, codes or government regulations of the country from which the payment is to be made, then such payments may be paid by depositing them in the currency in which they accrue to Isis's account in a bank acceptable to Isis in the country the currency of which is involved or as otherwise agreed by the Parties.

5.8 Isis and HepaSense agree to co-operate in all respects necessary to take advantage of any double taxation agreements or similar agreements as may, from time to time, be available.

5.9 Any taxes payable by Isis on any payment made to Isis pursuant to this Agreement shall be for the account of Isis. If so required by applicable law, any payment made pursuant to this Agreement shall be made by HepaSense after deduction of the appropriate withholding tax, in which event the Parties shall co-operate to obtain the appropriate tax clearance as soon as is practicable. On receipt of such clearance,

HepaSense shall forthwith arrange payment to Isis of the amount so withheld.

6 RIGHT OF INSPECTION AND AUDIT

6.1 Once during each Financial Year, or more often not to exceed quarterly as reasonably requested by Isis, HepaSense shall permit Isis or its duly authorised representatives, upon reasonable notice and at any reasonable time during normal business hours, to have access to inspect and audit the accounts and records of HepaSense and any other book, record, voucher, receipt or invoice relating to the calculation of the royalty payments on Net Sales submitted to Isis.

Any such inspection of HepaSense's records shall be at the expense of Isis, except that if any such inspection reveals a deficiency in the amount of the royalty actually paid to Isis hereunder in any Financial Year quarter of 5% or more of the amount of any royalty actually due to Isis hereunder, then the expense of such inspection shall be borne solely by HepaSense. Any amount of deficiency shall be paid promptly to Isis by HepaSense.

If such inspection reveals a surplus in the amount of royalties actually paid to Isis by HepaSense, Elan shall reimburse HepaSense the surplus within 15 days after determination.

6.2 In the event of any unresolved dispute regarding any alleged deficiency or overpayment of royalty payments hereunder, the matter will be referred to an independent firm of chartered accountants chosen by agreement of Isis and Elan for a resolution of such dispute. Any decision by the said firm of chartered accountants shall be binding on the Parties.

7 REPRESENTATIONS AND WARRANTIES

7.1 Isis represents and warrants to HepaSense and Elan as of the Effective Date that:

7.1.1 Isis has the right to grant the Isis License;

7.1.2 there are no agreements between Isis and any third party that conflict with the Isis License;

7.1.3 the patents and patent applications included in the Isis Patents are free and clear of encumbrances and liens except for any license which would not preclude Isis from granting the licenses granted hereunder;

7.1.4 to the best of Isis's knowledge, there are no proceedings pending or threatened against Isis in connection with the Isis Intellectual Property in relation to the Field; and

7.1.5 the Isis Intellectual Property constitutes all intellectual property owned or licensed by Isis that is reasonably applicable to the Project as it relates to the Designated Oligonucleotide.

7.2 Isis shall not amend, modify, waive or terminate any of its rights under any Existing Isis License Agreement without the prior written consent of the Management Committee (by the unanimous vote of its members); provided, however, that such consent will be required only if such amendment, modification, waiver or termination would have an adverse effect, individually or in the aggregate, on the financial condition, prospects, results of operation, business, and/or assets (including, without limitation, the Licensed Technologies, and/or the HepaSense Intellectual Property) of HepaSense.

7.3 Isis agrees and represents and warrants to HepaSense and Elan as follows: (i) the Existing Isis License Agreements are valid and in full force and effect, (ii) there are no existing or claimed defaults by Isis, and to Isis's knowledge by any other party, under the Existing Isis License Agreements; and no event, act or omission has occurred which (with or without notice, lapse of time or the happening or occurrence of any other event) would result in a default under the Existing Isis License Agreements by Isis, or to Isis's knowledge by any other party, and (iii) Isis shall during the term of the Licenses, fully comply with all terms and conditions of the Existing Isis License Agreements; Isis will enforce its rights under the Existing Isis License Agreements, as they relate to the Designated Oligonucleotide; and Isis will not assign its rights under the Existing Isis License Agreements, as they relate the Designated Oligonucleotide. Isis will keep HepaSense and Elan fully informed with respect to Isis's arrangements under the Existing Isis License Agreements that relate to HepaSense and/or the transactions contemplated hereunder. Isis shall provide HepaSense and Elan with any written notices delivered by any party under the Existing Isis License Agreements, which written notices relate to or could affect HepaSense and/or the transactions contemplated hereunder.

7.4 In addition to any other indemnities provided for herein, Isis shall indemnify and hold harmless HepaSense and its Affiliates and their respective employees, agents, officers and directors from and against any claims, losses, liabilities or damages (including reasonable attorney's fees and expenses) incurred or sustained by HepaSense arising out of or in connection with any:

7.4.1 breach of any representation, covenant, warranty or obligation by Isis hereunder; or

7.4.2 act or omission on the part of Isis or any of its respective employees, agents, officers and directors in the performance of this Agreement.

7.5 In addition to any other indemnities provided for herein, HepaSense shall indemnify and hold harmless Isis and its Affiliates and their respective employees, agents, officers and directors from and against any claims, losses, liabilities or damages (including reasonable attorney's fees and expenses) incurred or sustained by Isis arising out of or in connection with any:

7.5.1 breach of any representation, covenant, warranty or obligation by HepaSense hereunder; or

7.5.2 act or omission on the part of HepaSense or any of its agents or employees in the performance of this Agreement.

7.6 The Party seeking an indemnity shall:

7.6.1 fully and promptly notify the other Party of any claim or proceeding, or threatened claim or proceeding;

7.6.2 permit the indemnifying Party to take full care and control of such claim or proceeding;

7.6.3 co-operate in the investigation and defence of such claim or proceeding;

7.6.4 not compromise or otherwise settle any such claim or proceeding without the prior written consent of the other Party, which consent shall not be unreasonably withheld conditioned or delayed; and

7.6.5 take all reasonable steps to mitigate any loss or liability in respect of any such claim or proceeding.

7.7 EXCEPT AS SET FORTH IN THIS CLAUSE 7, ISIS IS GRANTING THE LICENSES HEREUNDER ON AN "AS IS" BASIS WITHOUT REPRESENTATION OR WARRANTY WHETHER EXPRESS OR IMPLIED INCLUDING WARRANTIES OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE, OR INFRINGEMENT OF THIRD PARTY RIGHTS, AND ALL SUCH WARRANTIES ARE EXPRESSLY DISCLAIMED.

7.8 NOTWITHSTANDING ANYTHING TO THE CONTRARY IN THIS AGREEMENT, ISIS AND HEPASENSE SHALL NOT BE LIABLE TO THE OTHER BY REASON OF ANY REPRESENTATION OR WARRANTY, CONDITION OR OTHER TERM OR ANY DUTY OF COMMON LAW, OR UNDER THE EXPRESS TERMS OF THIS AGREEMENT, FOR ANY CONSEQUENTIAL, SPECIAL OR INCIDENTAL OR PUNITIVE LOSS OR DAMAGE (WHETHER FOR LOSS OF PROFITS OR OTHERWISE) AND WHETHER OCCASIONED BY THE NEGLIGENCE OF THE RESPECTIVE PARTIES, THEIR EMPLOYEES OR AGENTS OR OTHERWISE.

8. TERM AND TERMINATION

8.1 On a product by product basis, subject to the provisions of Clause 10 and 11, the term of the Licenses granted hereunder with respect to a Product and/or Additional Product in each country in the Territory (the "TERM") shall be the

greater of:

8.1.1 [*] years from the date of the first commercial sale of the Product or Additional Products; or

8.1.2 the life of the patent rights utilized in the Product or Additional Products or upon which the Product or Additional Product is based.

8.2 If either Party commits a Relevant Event, the other Party shall have, in addition to all other legal and equitable rights and remedies hereunder, the right to terminate this Agreement upon 30 days' prior written notice to the defaulting Party.

8.3 For the purpose of this Clause 8, a "RELEVANT EVENT" is committed or suffered by a Party if:

8.3.1 it commits a material breach of its obligations under this Agreement or the JDOA and such breach (i) is not capable of being cured or (ii) is capable of being cured the breaching Party fails to remedy it within 60 days of being specifically required in writing to do so by the other Party; provided, that if the breaching Party has proposed a course of action to rectify the breach and is acting in good faith to rectify same but has not cured the breach by the 60th day, such period shall be extended by such period as is reasonably necessary to permit the breach to be rectified;

8.3.2 a distress, execution, sequestration or other process is levied or enforced upon or sued out against a material part of its property which is not discharged or challenged within 30 days;

8.3.3 it is unable to pay its debts in the normal course of business;

8.3.4 it ceases wholly or substantially to carry on its business, otherwise than for the purpose of a reconstruction or amalgamation, without the prior written consent of the other Party (such consent not to be unreasonably withheld);

8.3.5 the appointment of a liquidator, receiver, administrator, examiner, trustee or similar officer of such Party or over all or substantially all of its assets under the law of any applicable jurisdiction, including without limitation, the United States of America or Bermuda; or

8.3.6 an application or petition for bankruptcy, corporate re-organisation, composition, administration, examination, arrangement or any other procedure similar to any of the foregoing under the law of any applicable jurisdiction, including without limitation, the United States of America, Bermuda or Ireland, is filed, and is not discharged within 60 days, or a Party applies for or consents to the appointment of a receiver, administrator, examiner or similar officer of it or of all or a material part of its assets, rights or revenues or the assets and/or the business of a Party are for any reason seized, confiscated or condemned.

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8.4 Upon expiration or termination of the Agreement:

8.4.1 any sums that were due from HepaSense to Isis on Net Sales in the Territory or in such particular country or countries in the Territory (as the case may be) prior to the expiration or termination of this Agreement as set forth herein shall be paid in full within 60 days after the expiration or termination of this Agreement for the Territory or for such particular country or countries in the Territory (as the case may be);

8.4.2 any provisions that expressly survive termination or expiration of this Agreement, including without limitation this Clause 8, shall remain in full force and effect;

8.4.3 all representations, warranties and indemnities shall insofar as are appropriate remain in full force and effect;

8.4.4 the rights of inspection and audit set out in Clause 6 shall continue in force for a period of one year; and

8.4.5 all rights and licenses granted pursuant to this Agreement and to the Isis Intellectual Property pursuant to the JDOA (including the rights of HepaSense pursuant to Clause 11 of the JDOA) shall cease for the Territory or for such particular country or countries in the Territory (as the case may be) and shall revert to or be transferred to Isis, and HepaSense shall not thereafter use in the Territory or in such particular country or countries in the Territory (as the case may be) any rights covered by this Agreement;

8.4.6 subject to Clause 8.4.7 and to such license, if any, granted by HepaSense to Isis pursuant to the provisions of Clause 10 of the JDOA, all rights to HepaSense Intellectual Property shall be transferred to and jointly owned by Isis and Elan but may not be exploited by both Elan and Isis, unless otherwise agreed by the unanimous vote of the Management Committee, and may only be exploited by either Elan and Isis pursuant to written consent from the other Party;

In the event of a dispute arising pursuant to this Clause 8.4.6, Elan and Isis agree to negotiate in good faith on the course of action to be taken with respect to determining their respective entitlements pursuant to this Clause 8.4.6.

8.4.7 the rights of permitted third party sub-licensees in and to the Isis Intellectual Property shall survive the termination of the license and sublicense agreements granting said intellectual property rights to HepaSense; and HepaSense, Elan and Isis shall in good faith agree upon the form most advantageous to Elan and Isis in which the rights of HepaSense under any such licenses and sublicenses are to be held (which form may include continuation of HepaSense solely as the holder of such licenses or assignment of such rights to a third party or parties, including an assignment to both Elan

and Isis).

Any sublicense agreement between HepaSense and such permitted sublicensee shall permit an assignment of rights by HepaSense and shall contain appropriate confidentiality provisions.

9 CONFIDENTIAL INFORMATION

9.1 The Parties agree that it will be necessary, from time to time, to disclose to each other confidential and proprietary information, including without limitation, inventions, works of authorship, trade secrets, specifications, designs, data, know-how and other proprietary information relating to the Field, the Products, processes, services and business of the disclosing Party.

The foregoing shall be referred to collectively as "CONFIDENTIAL INFORMATION".

9.2 Any Confidential Information disclosed by one Party to another Party shall be used by the receiving Party exclusively for the purposes of fulfilling the receiving Party's obligations under this Agreement and the JDOA and for no other purpose.

9.3 Each Party shall disclose Confidential Information of the other Party only to those employees, representatives and agents requiring knowledge thereof in connection with fulfilling the Party's obligations under this Agreement. Each Party further agrees to inform all such employees, representatives and agents of the terms and provisions of this Clause 9 and their duties hereunder and to obtain their agreement hereto as a condition of receiving Confidential Information. Each Party shall exercise the same standard of care as it would itself exercise in relation to its own confidential information (but in no event less than a reasonable standard of care) to protect and preserve the proprietary and confidential nature of the Confidential Information disclosed to it by the other Party. Each Party shall, upon request of the other Party, return all documents and any copies thereof containing Confidential Information belonging to, or disclosed by, such other Party.

9.4 Any breach of this Clause 9 by any person informed by one of the Parties is considered a breach by the Party itself.

9.5 Confidential Information shall not be deemed to include:

9.5.1 information that is in the public domain;

9.5.2 information which is made public through no breach of this Agreement;

9.5.3 information which is independently developed by a Party as evidenced by such Party's records;

9.5.4 information that becomes available to a Party on a non-confidential basis, whether directly or indirectly, from a source other than a Party, which source did not acquire this information on a confidential basis; or

9.5.5 information which the receiving Party is required to disclose pursuant to:

(i) a valid order of a court or other governmental body; or

(ii) any other requirement of law;

provided that if the receiving Party becomes legally required to disclose any Confidential Information, the receiving Party shall give the disclosing Party prompt notice of such fact so that the disclosing Party may obtain a protective order or other appropriate remedy concerning any such disclosure. The receiving Party shall fully co-operate with the disclosing Party in connection with the disclosing Party's efforts to obtain any such order or other remedy. If any such order or other remedy does not fully preclude disclosure, the receiving Party shall make such disclosure only to the extent that such disclosure is legally required.

9.6 The provisions relating to confidentiality in this Clause 9 shall remain in effect during the term of this Agreement, and for a period of 7 years following the expiration or earlier termination of this Agreement.

9.7 The Parties agree that the obligations of this Clause 9 are necessary and reasonable in order to protect the Parties' respective businesses, and each Party agrees that monetary damages would be inadequate to compensate a Party for any breach by the other Party of its covenants and agreements set forth herein.

Accordingly, the Parties agree that any such violation or threatened violation shall cause irreparable injury to a Party and that, in addition to any other remedies that may be available, in law and equity or otherwise, each Party shall be entitled to obtain injunctive relief against the threatened breach of the provisions of this Clause 9, or a continuation of any such breach by the other Party, specific performance and other equitable relief to redress such breach together with its damages and reasonable counsel fees and expenses to enforce its rights hereunder, without the necessity of proving actual or express damages.

10 GOVERNING LAW AND DISPUTE RESOLUTION

10.1 This Agreement shall be governed by and construed in accordance with the laws of the State of New York without regard to principles relating to conflicts of laws.

10.2 The Parties will attempt in good faith to resolve any dispute arising out of or relating to this Agreement promptly by negotiation between executives of the Parties. In the event that such negotiations do not result in a mutually acceptable resolution, the Parties agree to consider other dispute resolution mechanisms including mediation.

10.3 Any dispute under this Agreement which is not settled by mutual consent under Clause 10.2 will be subject to resolution in accordance with Clauses 19 and 24.8 of the JDOA, which are incorporated by reference and shall for such purposes survive

termination of the JDOA

11 IMPOSSIBILITY OF PERFORMANCE - FORCE MAJEURE

Neither Isis nor HepaSense shall be liable for delay in the performance of any of its obligations hereunder if such delay results from causes beyond its reasonable control, including, without limitation, acts of God, fires, strikes, acts of war, intervention of a government authority, but any such delay or failure shall be remedied by such Party as soon as practicable.

12 ASSIGNMENT

This Agreement may not be assigned by either Party without the prior written consent of the other, save that either Party may assign this Agreement to its Affiliates or subsidiaries without such prior written consent; provided that such assignment does not have any adverse tax consequences on the other Party.

13 NOTICES

13.1 Any notice to be given under this Agreement shall be sent in writing in English by registered airmail or telefaxed to the following addresses:

If to HepaSense at:

102 St. James Court
Clarendon House
Church St.
Hamilton, Bermuda
Attention: Secretary
Telephone: 441-295-1422
Fax: 441-292-4720

with a copy to Elan, plc and EPIL at:

Elan Corporation, plc
Elan Pharma International Limited
c/o Elan International Services, Ltd.
102 St. James Court
Flatts,
Smiths FL04
Bermuda
Attention: Secretary
Telephone: 441 292 9169
Fax: 441 292 2224

with a copy to:

Isis Pharmaceuticals, Inc.
2292 Faraday Avenue
Carlsbad, California 92008
Attention: B. Lynne Parshall, Esq.
Telephone: (760) 603-2460
Telefax: (760) 931-9639

If to Isis at:

Isis Pharmaceuticals, Inc.
2292 Faraday Avenue
Carlsbad, California 92008
Attention: B. Lynne Parshall, Esq.
Telephone: (760) 603-2460
Telefax: (760) 931-9639

If to Elan, plc and/or EPIL at:

Elan Corporation, plc
Elan Pharma International Limited
C/o Elan International Services, Ltd.
102 St. James Court
Flatts,
Smiths FL04
Bermuda
Attention: Secretary
Telephone: 441 292 9169
Fax: 441 292 2224

or to such other address(es) and telefax numbers as may from time to time be notified by either Party to the other hereunder.

13.2 Any notice sent by mail shall be deemed to have been delivered within seven 7 working days after dispatch and any notice sent by telex or telefax shall be deemed to have been delivered within twenty 24 hours of the time of the dispatch. Notice of change of address shall be effective upon receipt.

14 MISCELLANEOUS

14.1 WAIVER:

No waiver of any right under this Agreement shall be deemed effective unless contained in a written document signed by the Party charged with such waiver, and no waiver of any breach or failure to perform shall be deemed to be a waiver of any other breach or failure to perform or of any other right arising under this Agreement.

14.2 SEVERABILITY:

If any provision in this Agreement is agreed by the Parties to be, or is deemed to be, or becomes invalid, illegal, void or unenforceable under any law that is applicable hereto:

14.2.1 such provision will be deemed amended to conform to applicable laws so as to be valid and enforceable; or

14.2.2 if it cannot be so amended without materially altering the intention of the Parties, it will be deleted, with effect from the date of such agreement or such earlier date as the Parties may agree, and the validity, legality and enforceability of the remaining provisions of this Agreement shall not be impaired or affected in any way.

14.3 FURTHER ASSURANCES:

At the request of any of the Parties, the other Party or Parties shall (and shall use reasonable efforts to procure that any other necessary parties shall) execute and perform all such documents, acts and things as may reasonably be required subsequent to the signing of this Agreement for assuring to or vesting in the requesting Party the full benefit of the terms hereof.

14.4 SUCCESSORS:

This Agreement shall be binding upon and enure to the benefit of the Parties hereto, their successors and permitted assigns.

14.5 NO EFFECT ON OTHER AGREEMENTS/CONFLICT:

No provision of this Agreement shall be construed so as to negate, modify or affect in any way the provisions of any other agreement between the Parties unless specifically referred to, and solely to the extent provided herein.

In the event of a conflict between the provisions of this Agreement and the provisions of the JDOA, the terms of the JDOA shall prevail unless this Agreement specifically provides otherwise.

14.6 AMENDMENTS:

No amendment, modification or addition hereto shall be effective or binding on any Party unless set forth in writing and executed by a duly authorised representative of each Party.

14.7 COUNTERPARTS:

This Agreement may be executed in any number of counterparts, each of which when

so executed shall be deemed to be an original and all of which when taken together shall constitute this Agreement.

14.8 GOOD FAITH:

Each Party undertakes to do all things reasonably within its power which are necessary or desirable to give effect to the spirit and intent of this Agreement.

14.9 NO RELIANCE:

Each Party hereby acknowledges that in entering into this Agreement it has not relied on any representation or warranty save as expressly set out herein or in any document referred to herein.

14.10 RELATIONSHIP OF THE PARTIES:

Nothing contained in this Agreement is intended or is to be construed to constitute Isis and HepaSense as partners, or Isis as an employee of HepaSense, or HepaSense as an employee of Isis.

Neither Party hereto shall have any express or implied right or authority to assume or create any obligations on behalf of or in the name of the other Party or to bind the other Party to any contract, agreement or undertaking with any third party.

IN WITNESS WHEREOF the Parties hereto have executed this Agreement.

SIGNED BY:_____
For and on behalf of
ISIS PHARMACEUTICAL, INC.

SIGNED BY:_____
For and on behalf of
HEPASENSE LTD.

AGREED TO AND ACCEPTED BY

SIGNED BY:_____
for and on behalf of
ELAN CORPORATION, PLC ACTING
THROUGH ITS DIVISION ELAN
PHARMACEUTICAL TECHNOLOGIES

SIGNED BY: _____
for and on behalf of
ELAN PHARMA INTERNATIONAL LIMITED

EXHIBIT A

DESCRIPTION OF ISIS 14803

[*].

* CONFIDENTIAL TREATMENT REQUESTED

SCHEDULE 1

ISIS PATENTS

The following US patent applications are directed to antisense inhibition of Hepatitis C virus and have claims whose scope includes the ISIS 14803 compound, either broadly or specifically:

DOCKET NO.	APPL. NO.	FILE DATE	STATUS
DOC-0002	PCT/JP 93/01293		entered national phase
ISPH-0031	US 08/397,220		pending
ISPH-0136	US 08/452,841		pending
ISPH-0138	US 08/453,085		abandoned
ISPH-0145	US 08/650,093		pending
ISPH-0203	US 08/823,895		pending
ISPH-0245	US 08/988,321		pending
ISPH-0335	PCT/US 98/26040		international phase
ISIS Manufacturing US Patents Applications covering 14803:			
Isis-2710	09/032,972	2/26/98	Pending
Isis-2585	08/950,779	10/15/97	Notice of allowance
Isis-3294	09167,165	10/06/98	Pending
Isis-3380	09/288,679	4/09/99	Pending
Isis-3349	09/271,220	3/17/99	Pending

SCHEDULE 2

TECHNOLOGICAL COMPETITORS OF ISIS(1)

[*]

1. Including any and all divisions or subsidiaries

* CONFIDENTIAL TREATMENT REQUESTED

[ISIS PHARMACEUTICALS, INC. LOGO]

Record of Invention

Patent Group Use Only

Docket No. _____

[Illegible}_____

1. ROI TITLE: Folate Conjuated Novel Oligonucleotide Carriers

2. POTENTIAL INVENTORS: Mano Manoharan

Signature	Date
Signature	Date
Signature	Date
Signature	Date
Signature	Date
Signature	Date
Signature	Date
Signature	Date

3. COLLABORATION, SUPPORT:

Is there any corporate collaboration? [ ]

If so, who?

4. DISCLOSURE:

Due Date (if applicable): 01/26/2001

Reason for Due Date:

5. DATES OF INVENTION:

Conception, on or about (Date): 01/01/1999 By: M. Manoharan & B. Bh

First Written Record (Date): By:

Disclosure to Others (Date): 10/04/1999 By: W/N. Dean, S. Cooper

First Preparation Work begun (Date): By:

Indicate relevant Lab/Conception Notebook No. and Page No.

5. REVIEWED, READ, UNDERSTOOD, DISCUSSED WITH AND APPROVED BY:

Department Head:

Print Name	Signature	Date

Vice President of Research (appropriate department only): [ ] approved [ ] prior invention/filing [ ] trade secret

Print Name	Signature	Date

Member of Patent Group:

Print Name	Signature	Date

Printed on: 01/26/2000