18-05321-E

07/172018

U.S. Securities and Exchange Commission

Office of FOIA Services

100 F Street, NE Mail Stop 2745

Washington, DC 20549-5100


Dear FOIA Office:

Under the Freedom of Information Act (FOIA), please send a copy of the following:

Exhibit 10.10 to the form S-1/A by COTHERIX INC on 2004-04-19.

We authorize up to $61.00 in processing fees.

Thank You,

Auguste Norkeviciute

RoyaltyRange

Registered Office: 138 South Street,

Romford, RM1 1TE, United Kingdom

Telephone: +44 20 3734 7558

E-mail: auguste.norkeviciute@royaltyrange.com

Website: www.royaltyrange.com'

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
STATION PLACE
100 F STREET, NE
WASHINGTON, DC 20549-2465

Office of FOIA Services

August 22, 2018

Ms. Auguste Norkeviciute
RoyaltyRange Europe UAB
138 South Street
Romford, 1U RM1 1TE

RE: Freedom of Information Act (FOIA), 5 U.S.C. § 552
Request No. **18-05321-E**

Dear Ms. Norkeviciute:

This letter is in response to your request, dated and received in this office on July 17, 2018, for Exhibit 10.10 to the Form S-1/A filed by Cotherix, Inc. on April 19, 2004.

Your request is granted in full. The 58-page exhibit is enclosed with this letter. Because this exhibit was released in response to a previous FOIA request, no processing fees have been assessed.

If you have any questions, please contact me at Gbenoua@sec.gov or (202) 551-5327. You may also contact me at foiapa@sec.gov or (202) 551-7900. You also have the right to seek assistance from Jeffery Ovall as a FOIA Public Liaison or contact the Office of Government Information Services (OGIS) for dispute resolution services. OGIS can be reached at 1-877-684-6448 or Archives.gov or via e-mail at ogis@nara.gov.

Sincerely,

*Amy Gbenou*
Amy Gbenou
FOIA Research Specialist

Enclosure

Exhibit 10.10

# DEVELOPMENT AND LICENSE AGREEMENT

THIS AGREEMENT is made the 2nd day of October 2003 by and between Exhale Therapeutics, Inc., a U.S. corporation having its principal place of business at 1301 Shoreway Road, Suite 320, Belmont, California 94002, U.S.A. (hereinafter referred to as "Exhale") and Schering Aktiengesellschaft, a corporation organized and existing under the laws of Germany having its principal place of business at Muellerstraße 178, 13353 Berlin, Germany (hereinafter referred to as "Schering"). Schering and Exhale are sometimes referred to herein individually as a "Party" and collectively as the "Parties".

## WITNESSETH:

WHEREAS, Schering is engaged in the development of the Substance (hereinafter defined) in the Field (hereinafter defined) for the European Union and has been granted regulatory approval of the Substance in the Field by the European Commission;

WHEREAS, Exhale is interested in developing and commercializing the Substance in the Field for the U.S. and obtaining from Schering certain rights and licenses therefor, and Schering is willing to grant such rights and licenses to Exhale under the terms and conditions hereinafter set forth.

NOW, THEREFORE, in consideration of the foregoing recitals and the mutual covenants and agreements contained herein, the Parties hereto, intending to be legally bound, do hereby agree as follows:

## ARTICLE I

## DEFINITIONS

The following terms, when capitalized, shall have the following meanings (such meanings to be equally applicable to both the singular and plural forms of the terms defined), when used in this Agreement.

"Affiliate" means, with respect to a Party, any person, corporation, firm, joint venture, or other entity which, directly or indirectly, by itself or through one or more intermediaries, controls, is controlled by, or is under common control with such Party. As used in this definition, the term "control" means the possession of the power to direct or cause the direction of the management and policies of an entity, whether through the ownership of the outstanding voting securities or by contract or otherwise.

"Agreement" means this Development and License Agreement.

"ANDA" means a drug application filed with the FDA to obtain marketing approval for a generic product.

"Audit Disagreement" shall have the meaning set forth in Section 8.10(b).

"Best Efforts" means the highest level of endeavor which a prudent business person in the prescription pharmaceutical industry would reasonably expend to accomplish an important objective.

"Business Day" means a day which is not a Saturday, a Sunday or other day on which banks are required or authorized by law to be closed in New York, U.S., or in Berlin, Germany.

"CFR" means the US Code of Federal Regulations.

"Clinical Development" means the conduct of studies of the Product in humans in the Field to assess the dosing, safety and/or efficacy of the Product, including but not limited to Phase 1 Clinical Trials, Phase 2 Clinical Trials and Phase 3 Clinical Trials.

"Commercialization" and "Commercialize" shall refer to all activities undertaken relating to the use, pre-marketing, marketing, sale, import for sale and distribution of the Product.

"Commercialization Plan" shall mean the document attached hereto as Schedule 3.

"Commercially Reasonable Efforts" means the level of endeavor which a prudent business person in the prescription pharmaceutical industry would ordinarily expend to accomplish an important objective.

"Confidential Information" shall have the meaning set forth in Section 10.1.

"Control" or "Controlled" means the right to grant an exclusive license or sublicense of patent rights, know-how, information or other intangible rights as provided for herein without violating the terms of any agreement or other arrangement with any Third Party.

"Development" and "Develop" mean all activities relating to the Pre-clinical Development and Clinical Development of the Product in the Field.

"Development and Commercialization Committee" means the committee established by the parties pursuant to Section 5.1.

"Development Plan" shall mean the document attached hereto as

Schedule 2.

"DMF" shall mean the drug master file concerning Drug Substance and Drug Product in the Field.

"Domain Names" means any domain name identical or confusingly similar with the Trademarks owned or controlled by Schering and used by Exhale for the Commercialization of the Product in the Field in the Territory.

"Drug Approval Application" means an application for Regulatory Approval which is required before commercial sale or use of the Product as a drug in the Territory.

"Drug Product" shall mean the pharmaceutical product for inhaled use which includes, as an active ingredient, the Substance (hereinafter defined), and complies with the relevant Specifications (hereinafter defined).

"Drug Substance" shall mean Schering's proprietary compound Iloprost in acid form, and complies with the relevant Specifications (hereinafter defined).

"Effective Date" shall mean the date when the Agreement is executed by both Parties and Exhale has provided written proof to Schering that it has entered into an agreement with investors for at least USD 15 million of additional funding available for the Development and Commercialization of the Product in the Field in the Territory (as defined hereinafter).

"FDA" means the U.S. Food and Drug Administration, or any successor health regulatory authority.

"Field" means inhaled use of the Substance and/or Product in the indication "pulmonary hypertension" in humans.

"First Commercial Sale" means the date Exhale or an Affiliate or sublicensee of Exhale first sells commercially, pursuant to Regulatory Approval, the Product in the Territory.

"Health Regulatory Authority" means the FDA.

"IND" means an Investigational New Drug application filed with the FDA pursuant to 21 CFR 312.1 et seq.

"Joint Inventions" shall have the meaning set forth in Section 11.1.

"Joint Patents" shall have the meaning set forth in Section 11.1.

"Know-how" means: (i) techniques, data and information relating to the Substance, the Drug Substance, the Drug Product or the Product within the Field, including, but not limited to, inventions, practices, methods, manufacturing

processes, knowledge, know-how, skill, trade secrets, experience, test data (including pharmacological, toxicological, preclinical and clinical test data); data, records and information derived from Preclinical Development or Clinical Development, regulatory submissions, adverse reactions, analytical and quality control data, marketing, pricing, distribution, cost, sales and manufacturing data or descriptions, and (ii) compound, compositions of matter and assays within the Field relating to the Substance, the Drug Substance, the Drug Product or the Product.

"Losses" shall have the meaning set forth in Section 13.1.

"Manufacture" or "Manufacturing" means all operations required to manufacture, test, release, handle, store and destroy Drug Product or Drug Substance, or any step thereof, as the case may be.

"NDA" means a new drug application filed with the FDA to obtain marketing approval for the Product in the Field in the Territory (as defined hereinafter).

"Net Sales" means gross sales by Exhale or its Affiliates or any sublicensee of Product hereunder as reflected in invoices to unaffiliated Third Parties, less reasonable and customary deductions applicable to the Products for:

(a) transportation charges and insurance charges paid by Exhale;

(b) sales and excise taxes or customs duties or any other governmental charges imposed upon the sale of the Product and paid by Exhale;

(c) allowances or credits to customers on account of governmental requirements, price differences, rejection, rebates, outdating, returns or recalls of the Product.

In the event the Product is sold in the form of a combination product containing one or more active ingredients in addition to the Substance, Net Sales for such combination product will be adjusted by multiplying actual Net Sales of such combination product by the fraction A / (A+B) where A is the invoice price of the Product in which the Substance is the only active ingredient, if sold separately, and B is the invoice price of any other active ingredient or ingredients in the combination, if sold separately. If the other active ingredient or ingredients in the combination are not sold separately, Net Sales shall be calculated by multiplying actual Net Sales of such combination product by the fraction A / C where A is the invoice price of the Product in which the Substance is the only active ingredient if sold separately, and C is the invoice price of the combination product. If neither the Product in which the Substance is the only active ingredient nor the other active component or components of the combination product is sold separately, Net Sales shall be determined by allocating actual Net Sales of the combination product between the Substance and the other matter based upon the total actual sourcing cost thereof.

"Orphan Drug Application" means an application for Orphan Drug

Approval.

"Orphan Drug Approval" means the granting of the orphan drug status for the Product in the Field by the Health Regulatory Authority.

"Orphan Drug Status" means the period during which the Product is approved as an orphan drug.

"Patent Expenses" means the fees, expenses and disbursements and outside counsel and agent fees incurred in connection with the preparation, filing, prosecution and maintenance of Patents including Schering's and Exhale's costs of patent interference, opposition and nullity proceedings.

"Patents" means all patents, patent applications and patent applications hereinafter filed in any country of the world, including any continuation, continuation-in-part, division, provisional or any substitute applications, any patent issued with respect to any such patent applications, any reissue, reexamination, renewal or extension (including any supplemental patent certificate) of any such patent, and any confirmation patent or registration patent or patent of addition based on any such patent, and all foreign counterparts of any of the foregoing.

"Phase 3 Clinical Trials" has the meaning set forth in 21 CFR 312.21(c), as amended.

"Pre-clinical Development" means all activities relating to the planning and execution of non-human studies conducted in *in vitro* or in relevant *in vivo* animal models directed toward obtaining Regulatory Approval of the Product in the Field in the Territory. This includes pre-clinical testing, pharmacokinetics, toxicology, documentary and medical writing directly related to Pre-clinical Development activities, and related regulatory affairs.

"Product" means any pharmaceutical product for inhaled use which includes, as an active ingredient the Substance (hereinafter defined).

"Regulatory Approval" means the approval by the Health Regulatory Authority necessary for the Commercialization of the Product in the Field in the Territory.

"Schering Know-how" means Know-how within the Control of Schering as of the Effective Date or which comes within the Control of Schering during the term of this Agreement and relates to the Development, Manufacture or Commercialization of the Substance, the Drug Substance, the Drug Product or the Product in the Field in the Territory. Notwithstanding anything herein to the contrary, Schering Know-how shall exclude Schering Patents.

"Schering Patents" means any Patents in the Territory owned or Controlled by Schering or its Affiliates as of the Effective Date or which comes within the ownership or Control of Schering or any of its Affiliates during the term of this

Agreement covering the Development, Manufacture, or Commercialization of the Substance, the Drug Substance, the Drug Product or the Product in the Field.

"Specifications" shall mean the tests, standard test methods and acceptance limits for qualitative and quantitative characteristics of Drug Product and Drug Substance as set out in Schedule 4 (attached hereto and made a part hereof), as same may be amended from time to time by mutual agreement of the Parties.

"Substance" means Schering's proprietary compound Iloprost Trometamol.

"Supply Interruption Event" shall be deemed to have occurred upon the completion of either (i) two (2) consecutive quarters, or (ii) any three (3) quarters in a period of seven (7) consecutive quarters, in each case during which Exhale has received less than sixty percent (60%) of the amount of Drug Product or Drug Substance (as applicable) for which Exhale had placed a firm order.

"Territory" means the U.S.

"Third Party" means any entity other than Schering or Exhale and their respective Affiliates.

"Trademark" means any trademark owned and Controlled by Schering and used by Exhale in connection with the marketing of the Product in the Field in the Territory.

"U.S." shall mean the United States of America and its territories and commonwealths and possessions, including without limitation the Commonwealth of Puerto Rico.

"Valid Claim" shall mean a claim in an issued, unexpired Schering Patent which has not been abandoned, withdrawn, canceled or disclaimed, nor held invalid or unenforceable by a court of competent jurisdiction in an unappealed or unappealable decision.

## ARTICLE II

## LICENSES TO PATENTS AND KNOW-HOW

2.1 As of the Effective Date of this Agreement, Schering hereby grants to Exhale the exclusive (even as to Schering) right and license under the Schering Patents and the Schering Know-how to Develop and Commercialize the Product in the Territory and within the Field, subject to the terms and conditions hereof.

The granting of sublicenses by Exhale under the licenses set forth in this Agreement to Affiliates of Exhale or any Third Party shall be subject to

Schering's prior written consent; such consent not to be unreasonably withheld.

2.2 A list of the Schering Patents identified as of the Effective Date is attached hereto as Schedule 1. If at any time during the course of this Agreement any additional Patents are acquired by or come under the Control of Schering that include any claims that are necessary or desirable for the Development, Manufacture or Commercialization of the Product in the Territory in the Field, such shall be added to the list attached hereto as Schedule 1.

2.3 Promptly following the Effective Date, Schering shall disclose and provide to Exhale all Schering Know-how which is available at Schering and required for the Development or Commercialization of the Product in the Field in the Territory (except for the DMF). If at any time during the course of this Agreement any additional Know-how necessary or desirable for the Development or Commercialization of the Product in the Territory in the Field is acquired by, Controlled by, or otherwise becomes available to Schering, Schering shall promptly offer to Exhale to provide all such additional Know-how. If Exhale accepts this offer to receive such additional Know-how and such additional Know-how is acquired from a Third Party against payment of a license or a lump sum fee, such fee shall be borne by Exhale, but fifty (50) percent of such may be deducted from the royalty otherwise payable to Schering pursuant to Article VIII of this Agreement.

2.4 Notwithstanding the rights granted to Exhale pursuant to Section 2.1 above, Schering at all times reserves the right under the Schering Patents and the Schering Know-how to Develop, Manufacture or Commercialize the Substance and/or the Product in any country of the world for any use outside the Field, and outside the Territory for any use either within or outside the Field.

2.5 Exhale covenants that it shall not use any of the Schering Know-how or Schering Patents to carry out any activity or exercise any right other than those expressly licensed by Schering to Exhale pursuant to this Agreement.

## ARTICLE III

## DEVELOPMENT

3.1 Development

(a) From the Effective Date, Exhale shall solely be responsible for and bear all costs of all Development of the Product in the Field in the Territory.

(b) The expected Development to be conducted by Exhale pursuant to Section 3.1 (a) above including, but not limited to the timelines for such

interactions with Health Regulatory Authority. As between the Parties, Exhale shall be the legal and beneficial owner of the Drug Approval Application and the Orphan Drug Application and related Regulatory Approval and Orphan Drug Approval in the Territory.

3.3 Support by Schering

At Exhale's request, Schering shall provide Exhale with reasonable support in the form of consulting services directed toward securing and maintaining Regulatory Approval and Orphan Drug Approval. In the first twelve (12) months after the Effective Date, Schering shall provide fifty (50) person hours per month of such consulting services free of charge as and when reasonably requested by Exhale. Any consulting services by Schering after the first twelve (12) months or beyond fifty (50) hours per month during the first twelve (12) months shall be reimbursed by Exhale for time and expenses at pre-approved fully burdened cost according to general accounting principles. Travel time associated with rendering such services shall be included as consulting time (not more than eight (8) hours per day). The parties agree that membership in the Development and Commercialization Committee is not deemed to be the provision of consulting services and Exhale shall not reimburse any costs related to Schering's participation in the Development and Commercialization Committee.

In addition, from the Effective Date, Exhale shall reimburse to Schering reasonable, pre-approved traveling and accommodation expenses incurred in providing the aforementioned consulting services.

## ARTICLE IV

## COMMERCIALIZATION

4.1 Exhale as Sole Commercialization Party. Exhale shall have the exclusive right to Commercialize the Product, either by itself or through its Affiliates in the Field in the Territory.

4.2 Commercialization Plan. The expected Commercialization to be conducted by Exhale pursuant to this Section 4 shall be set out in the Commercialization Plan attached hereto as Schedule 3. Any material change of or material deviation from this Commercialization Plan and any material redefinition of commercialization goals and strategy requires Schering's prior written consent, which shall not be unreasonably withheld and shall be deemed given if a refusal with a written explanation is not provided to Exhale within fifteen (15) Business Days of Exhale's request for such consent.

4.3 Commercialization Efforts. Exhale agrees to use Best Efforts with respect to the Commercialization of Products in the Field in the Territory as provided hereunder. Without limiting the generality of the foregoing, Exhale shall

determine the pricing for the Product at its sole discretion, provided, however, that Exhale shall not sell the Product as a loss leader.

4.4 Marketing and Sales Infrastructure. Exhale agrees to Commercialize the Product on the basis of a marketing and sales infrastructure which is specifically qualified for and specifically concentrates on the Commercialization of the Product. The Commercialization through a Third Party shall only be permissible upon Schering's prior written consent, except for the use of specialty pharmacies in the normal course of distribution.

4.5 Exhale will not seek customers or establish any branch or commercialization depot for the Product in any country which is outside the Territory. Exhale will not, neither knowingly nor if it gross negligently does not know, supply the Product to any customer outside the Territory or to any customer in the Territory for resale outside the Territory unless such supply is required by law.

Neither Schering nor any of its Affiliates will seek customers or establish any branch or commercialization depot for the Product in the Field in the Territory. Schering and its Affiliates will not, neither knowingly nor if they gross negligently do not know, supply Product to any customer in the Territory or outside the Territory for resale in the Field in the Territory unless such supply is required by law.

## ARTICLE V

## COOPERATION BETWEEN THE PARTIES

5.1 Development and Commercialization Committee. Within thirty (30) days of the Effective Date, Schering and Exhale will establish a Development and Commercialization Committee. The Development and Commercialization Committee will be composed of six (6) members, three (3) representatives appointed by Schering and three (3) representatives appointed by Exhale. Such representatives will include individuals with expertise in areas such as clinical development, regulatory affairs and marketing. The Development and Commercialization Committee will meet (in person, telephonically or via videoconference). Upon reasonable request of either Party, employees of the Parties who have expertise in certain other areas may attend meetings of the Development and Commercialization Committee as guests. Unless otherwise agreed between the Parties, meetings of the Development and Commercialization Committee shall take place quarterly. One of the Exhale members of the Development and Commercialization Committee, chosen at the sole discretion of Exhale, along with one of the Schering members of the Development and Commercialization Committee, chosen at the sole discretion of Schering, shall serve as co-chairs of the Development and Commercialization Committee. Either Party may replace any or all of its representatives at any time upon written notice to the other Party. If any issues or disputes cannot be resolved unanimously within the Development

and Commercialization Committee, these issues shall be referred to Exhale's CEO and the President of the Strategic Business Unit ("SBU") Specialized Therapeutics at Schering's Affiliate Berlipharm, Inc., Montville, New Jersey, U.S.A., for resolution. If Exhale's CEO and the President of the SBU Specialized Therapeutics cannot resolve the issue unanimously, Exhale's CEO shall discuss this issue with the board member of Schering who is responsible for the SBU Specialized Therapeutics. Should Exhale's CEO and Schering's board member not come to an unanimous resolution (i) with respect to an issue that could be reasonably expected to have an adverse effect on Schering's Product business outside the Territory, then Schering shall have the final decision, and (ii) with respect to any other issue, Exhale shall have the final decision, provided that Exhale agrees to solely bear its increased cost or expense resulting from such decision. Each Party will disclose to the other proposed agenda items reasonably in advance of each meeting of the Development and Commercialization Committee. Each Party shall bear its own costs for participation in the Development and Commercialization Committee.

5.2 Functions of Development and Commercialization Committee: The Development and Commercialization Committee shall: (a) discuss and supervise the development of the Product in the Field in the Territory, including the progress and conduct of the Development, meeting Development goals, dealing with obstacles to successful Development, and the status of obtaining the Regulatory Approval; (b) discuss and supervise the Commercialization of the Product, including the progress and conduct of the Commercialization, meeting Commercialization goals and dealing with obstacles to successful Commercialization; (c) discuss and supervise actions planned by Exhale in respect of the Product where such actions could reasonably be expected to have a material impact on the Product in the Territory or outside the Territory; and (d) discuss in good faith other issues relating to the Commercialization of the Product in the Territory and outside the Territory. All discussions and other activities of the Development and Commercialization Committee shall be subject to Article X of this Agreement.

5.3 Reports. Exhale shall provide to Schering no later than two (2) weeks before each meeting of the Development and Commercialization Committee a report detailing and evaluating all issues relating to Sections 5.2 (a) to (d) above. Schering shall inform Exhale no later than one (1) week before each meeting of the Development and Commercialization Committee of any specific issues which it intends to discuss.

5.4 Use of Data. Subject to Article X of this Agreement, Schering shall be authorized to use any and all Know-how generated or acquired by Exhale relating to the Product in the Field under this Agreement in accordance with the license granted in Section 11.3(c) hereof. Exhale shall promptly upon such generation of Know-how offer to Schering to provide such newly generated or acquired Know-how to Schering. If Schering accepts to receive such Know-how and such Know-how is acquired from a Third Party against payment of a

license or a lump sum fee, half of such fee shall be borne by Schering.

## ARTICLE VI

## MANUFACTURE OF CLINICAL AND COMMERCIAL SUPPLY

6.1 Schering shall Manufacture or have Manufactured by an Affiliate or a Third Party and supply to Exhale Drug Product as and when reasonably requested and in accordance with the relevant Specifications, and, subject to the terms of this Article VI (and prior to the Notice Period), Exhale shall purchase exclusively from Schering all Drug Product which is required for conduct of Clinical Development and Commercialization of the Product in the Field in the Territory. With respect to this Manufacture and supply of the Drug Product by Schering, Schering shall provide Exhale priority that is at least as high as the priority Schering applies to its own internal requirements for Drug Product and Drug Substance or any other higher priority Iloprost substance or product. The parties will determine and specify reasonably and in good faith a more detailed process for such Manufacture and supply consistent with the terms of this Article VI in the form of a manufacturing and supply agreement to be completed within two (2) months from the execution of this Agreement (hereinafter the "Manufacturing & Supply Agreement").

6.2 The ex works price for paper, one-color labeled ampoules, packed in a 300-ampoule boxes for Commercialization of Drug Product per ampoule shall be as follows:

- for a firm order of 0.5 to 2 million ampoules per year: EUR 1.12;
- for a firm order of more than 2 to 5 million ampoules per year: EUR 1.09;
- for a firm order of more than 5 million ampoules per year: EUR 1.07.

The ex works price for Drug Substance (if applicable) shall be EUR 10,300.- per gram.

These amounts shall be adjusted from January 1 of each calendar year in order to keep pace with inflation or deflation. The adjustment shall be in accordance with the change of the "Price Index for Cost of Living of all Private Households" by the German Federal Statistical Office for the respective previous year.

6.3 At any time during the term of this Agreement or the Manufacturing & Supply Agreement, Schering may terminate the Manufacture and supply of Drug Product to Exhale if Schering decides to generally cease Manufacture of Drug Product (and/or Drug Substance if Schering decides to generally cease manufacture thereof) with twenty four (24) months' (the "Notice Period") prior written notice to Exhale provided that:

(a) With effect as of the expiry of the Notice Period, Exhale is automatically

granted the non-exclusive right and license under the Schering Patents and the Schering Know-how to Manufacture Drug Substance and/or Drug Product (as applicable) or have Drug Substance and/or Drug Product (as applicable) Manufactured through a contract manufacturer for Clinical Development and Commercialization of the Product in the Field in the Territory (hereafter the "Manufacturing License"). From the beginning of the Notice Period, Exhale is automatically granted the non-exclusive right and license to prepare such Manufacture of Drug Substance or Drug Product (as applicable).

If, after the beginning of the Notice Period, Schering wishes to grant a (non-exclusive) Manufacturing License to a Third Party, Schering shall, before entering into any agreement with any Third Party offer to Exhale in writing to take an exclusive Manufacturing License. Exhale shall within thirty (30) days of receipt of the written offer evaluate its interest in the exclusive Manufacturing License. If, after thirty (30) days, Exhale decides not to take the exclusive Manufacturing License, Schering shall be free to grant a non-exclusive Manufacturing License to any Third Party. If, however, after thirty (30) days, Exhale wishes to take the exclusive Manufacturing License, Schering and Exhale will negotiate reasonably and in good faith binding commercially reasonable terms of an exclusive Manufacturing License within additional forty-five (45) days. Should Schering and Exhale not come to an agreement concerning the exclusive Manufacturing License during this additional forty-five (45) days' period, Schering shall be free to grant a non-exclusive Manufacturing License to any Third Party.

(b) Promptly following its written notice to Exhale pursuant to this Section 6.3, Schering shall disclose and provide to Exhale all Schering Know-how which is available at Schering and required for the Manufacture of the Drug Product and/or Drug Substance (as applicable) in the Field in the Territory. Section 2.3 sentences 2 and 3 shall apply *mutatis mutandis*.

(c) At Exhale's request, Schering shall provide Exhale or its designated contract manufacturer with reasonable support in the form of consulting services directed towards the completion of the transfer of the Manufacture to Exhale or its designated contract manufacturer. This support shall be provided within the framework determined in Section 3.3 above and shall include an additional two hundred and fifty (250) person hours free of charge.

(d) No later than by one (1) month before the expiry of the Notice Period, Schering shall supply to Exhale Drug Substance against payment of EUR 10,300.- per gram in the amount which is required to Manufacture Drug Product required for Commercialization of Product during a period of two (2) years based on Exhale's forecast. This forecast by Exhale must be submitted to Schering no later than six (6) months before the

expiry of the Notice Period. In addition, throughout the Notice Period, Schering shall supply to Exhale on the same terms Drug Substance in the amount required by Exhale to establish Manufacturing operations by the expiry of the Notice Period. The price per gram shall be adjusted pursuant to Section 6.2 sentence 2 above. If Schering has elected to terminate supply of Drug Product in accordance with this Section, but not Drug Substance, Schering's supply and license obligations under this Agreement (and under the Manufacturing and Supply Agreement) shall apply *mutatis mutandis* to Drug Substance in lieu of Drug Product as of the expiry of the Notice Period.

6.4 Schering may permanently cease Manufacture and supply of Drug Substance and/or Drug Product without giving twenty four (24) months' prior written notice if any regulatory authority in any major market country outside the Territory requires the Drug Substance and/or Drug Product to be withdrawn from the market for safety reasons and Schering implements such withdrawal on a worldwide basis. In such event, Schering will give Exhale such notice as is reasonable in the circumstances. Following notice by Schering under this Section 6.4, the provisions of Sections 6.3 (a), (b) and (c) above shall apply *mutatis mutandis* except that the Manufacturing License is granted immediately upon receipt of Schering's respective notice by Exhale.

6.5 The provisions of Sections 6.3 above shall also apply *mutatis mutandis* in the event of a Supply Interruption Event except that the Manufacturing License is granted immediately upon the occurrence of the Supply Interruption Event. This shall, however, not apply if Exhale terminates the Agreement in the event of a Supply Interruption Event pursuant to Section 14.2 (b) hereof.

6.6 The Parties agree that Schering shall not be liable to Exhale for any indirect, incidental, special or consequential damages (including without limitation any damages arising from lost profits) arising out of or in connection with any short fall or disruption of supply of Drug Product or Drug Substance for which Exhale had placed a firm order including, but not limited to a Supply Interruption Event.

6.7 In the event that the provisions of Section 6.3 or 6.5 are triggered, if Exhale incurs Manufacturing or acquisition costs for Drug Product or Drug Substance that exceed the cost that had been paid to Schering therefor by thirty percent (30%), any cost exceeding such thirty percent (30%) cost increase shall be shared equally between Schering and Exhale to the effect that Exhale may deduct the respective amount from the royalty otherwise payable to Schering pursuant to Article VIII hereof; such deduction shall, however, only be permissible up to an amount of twenty five percent (25%) of these royalties otherwise payable to Schering.

6.8 Schering shall be free to change the Manufacturing process for Drug Product or Drug Substance provided that the Specifications of Drug Product or Drug Substance shall be equivalent to or better than the Specifications in existence

prior to such change. Schering shall inform Exhale in advance in writing of any such change of the Manufacturing process.

6.9 Exhale undertakes to include in its firm orders for Drug Product or Drug Substance (as applicable) under the Manufacturing and Supply Agreement capacity in order to ensure the maintenance by Exhale of a continuous safety stock of Drug Product or Drug Substance (as applicable) covering at least Exhale's requirements of Drug Product or Drug Substance (as applicable) for a period of two (2) months as calculated pursuant to the then current forecast for the next two (2) months following the respective firm order.

## ARTICLE VII

## INITIAL PAYMENT AND MILESTONE PAYMENTS

7.1 Initial Payment. Exhale shall pay to Schering a non-refundable signing fee equal to six (6) million US dollars (US$ 6,000,000) within five (5) Business Days of the Effective Date of this Agreement, provided that the payment of the US$ 750,000.— which Exhale paid to Schering following the Memorandum of Understanding between the Parties dated June 20, 2003 shall be credited towards the signing fee.

7.2 Milestone Payments. Exhale shall make the following one-time payments ("Milestone Payments") to Schering within thirty (30) Business Days after the first achievement of each of the following milestones.

| MILESTONES | PAYMENT (US$) |
|---|---|
| Upon first acceptance for filing of the Product NDA in the Field by the Health Regulatory Authority | 7,000,000 |
| Upon Regulatory Approval of the Product in the Field by the Health Regulatory Authority | 9,000,000 |
| When annual Net Sales of the Product first exceed US$ 25 million | 4,000,000 |
| When annual Net Sales of the Product first exceed US$ 100 million | 10,000,000 |

Exhale shall notify Schering promptly in writing of the occurrence of any of the above milestones.

## ARTICLE VIII

## ROYALTIES

8.1 Royalty Rate. In further consideration of the rights and licenses granted to Exhale under Article II of this Agreement, Exhale shall pay to Schering royalties based on Net Sales of the Product in the amount of 20 %. The sums

to be paid by Exhale shall be exclusive of the costs for the supply of the Drug Product or Drug Substance pursuant to Article VI above.

8.2 Royalty Term: Except where expressly provided otherwise in this Agreement, all royalties shall be calculated from the date of the First Commercial Sale of the Product until the later (the "Royalty Expiration Date") of (i) ten (10) years from the First Commercial Sale of Product and (ii) the last to expire of any Patent which includes a Valid Claim applicable to the Product in the Territory.

8.3 Royalty Reduction. Should (1) the Patents and the Orphan Drug Status expire before the Royalty Expiration Date and there be no Patent containing at least one Valid Claim and no Orphan Drug Status and no other statutory exclusivity be in place which would prevent the sale of a generic version of the Product, and should, in this situation, any generic product occur or (2) the Product be approved by the Health Regulatory Authority outside the Field based on an application by Schering, any of Schering's Affiliates or a licensee of Schering other than Exhale (hereinafter the "Second Product"), and should this Second Product be used off-label in the Field, and should sales of these generic products or sales of the Second Product for off-label use in the Field exceed fifteen percent (15%) of Exhale's Net Sales in any six (6) months period (as measured for generic products by IMS data or similar data, and for off-label use through a recognized independent Third Party audit, such as IMS NDTI), then the royalty rate set out in Section 8.1 above shall over the period of three (3) years be reduced to 10 % as follows: (i) by 2.5 percentage points to 17.5 % from the beginning of the calendar quarter following the calendar quarter in which the generic competition or the sales of the Second Product for off-label use in the Field exceeded the threshold of fifteen percent (15%) of Exhale's Net Sales for a period of six (6) months (hereinafter the "Royalty Reduction Date"); (ii) again by 2.5 percentage points to 15 % from the end of the calendar year following the Royalty Reduction Date; (iii) again by 2.5 percentage points to 12.5 % from the end of the second calendar year following the Royalty Reduction Date; and, (iv) from the end of the third calendar year following the Royalty Reduction Date and at any time thereafter, the royalty rate shall again be reduced by 2.5 percentage points and thus be 10 %. The royalty rate shall in no event be reduced to less than 10% under the terms of this Section 8.3. For the avoidance of doubt, it is set forth herein that the royalty reduction set forth in this Section 8.3 will be triggered only once.

8.4 License following Expiration. After the Royalty Expiration Date for the Product, Exhale shall thereafter have an exclusive (even as to Schering), paid-up license to Schering Know-how to Develop, and Commercialize the Product in the Field in the Territory as set out in Article II hereof. Furthermore, if Exhale has taken over Manufacture of Product in the Field in the Territory pursuant to Sections 6.3, 6.4 or 6.5 hereof, Exhale shall thereafter have a non-exclusive, paid up license to Schering Know-How to Manufacture the Product.

8.5 Payment Reports and Payments. Exhale shall make payments to Schering

quarterly within thirty (30) days after the end of each calendar quarter in which Net Sales occurred, such period to be extended to fourty five (45) days if sales are made and recorded by a sublicensee of Exhale. A report summarizing the Net Sales of the Product during the relevant quarter shall be delivered to Schering within thirty (30) days or fourty five (45) days (as applicable) following the end of each calendar quarter for which payments are due.

8.6 Payments; Interest. Payments due under this Agreement shall be due on such date as specified in this Agreement and, in the event such date is not a Business Day, then the next succeeding Business Day, and shall be made by wire transfer of immediately available funds to a bank account designated by Schering at least ten (10) days before payment is due. Any failure by Exhale to make a payment within five (5) Business Days after the date when due, shall obligate Exhale to pay to Schering computed interest, the interest period commencing on the due date and ending on the payment day, at a rate per annum equal to the Prime Rate as publicly announced by Bank of America on REUTERS_screen <USPRIME1> plus three (3) percentage points, or the highest rate allowed by law, whichever is lower. The interest calculation shall be based on the act/360 computation method. The interest rate shall be adjusted whenever there is a change in the Prime Rate quotation on REUTERS screen <USPRIME1> mentioned above. Interest shall be compounded annually in arrears. Such interest shall be due and payable on the tender of the underlying principal payment.

8.7 Taxes. Schering shall pay any and all taxes levied on account of all payments it receives under this Agreement. If laws or regulations require that taxes be withheld, Exhale will (i) deduct those taxes from all remittable payments, (ii) timely pay the taxes to the proper taxing authority, and (iii) send proof of payment to Schering within thirty (30) days of receipt of confirmation of payment from the relevant taxing authority. Exhale agrees to make lawful and reasonable efforts to minimize such taxes to Schering.

8.8 Payment Currency. Except for payments for Drug Product or Drug Substance pursuant to Article VI above, payments by Exhale under this Agreement shall be paid to Schering in U.S. dollars.

8.9 Payments to or Reports by Affiliates. Any payment required under any provision of this Agreement to be made to either Party or any report required to be made by either Party shall be made to or by an Affiliate of that Party if designated by that Party as the appropriate recipient or reporting entity without relieving such Party from responsibility for such payment or report.

8.10 Records of Revenues and Expenses.

(a) Exhale will maintain complete and accurate records relevant to the calculation of revenues under this Agreement. Not more often than once each year, Exhale shall make the said records available for

inspection for the period required by applicable laws, but not less than two (2) years from creation of individual records by a certified public accountant or chartered accountant selected by Schering (subject to the consent of Exhale not to be unreasonably withheld or delayed), for the sole purpose of verifying for Schering the correctness of calculations and classifications of such revenues under this Agreement. Schering shall bear its own costs related to such audit; provided that, for any underpayments greater than five (5) percent by Exhale, Exhale shall pay Schering the amount of underpayment, interest as provided for in Section 8.6 from the time the amount was due and Schering's reasonable out-of-pocket expenses for such audit. For any underpayments of less than five (5) percent by Exhale, Exhale shall pay Schering the amount of underpayment. Any overpayments by Exhale will be refunded to Exhale or credited to future royalties, at Exhale's discretion. Any records or accounting information received from Exhale shall be Confidential Information for the purposes of Article X. Results of any such audit shall be provided to both Parties and shall also constitute Confidential Information for the purposes of Article X, provided that accountants are bound by appropriate confidentiality obligations and may only provide Schering with evidence of any royalty payment discrepancies.

(b) If there is a dispute between the Parties following any audit performed pursuant to Section 8.10 (a), either Party may refer the issue (an "Audit Disagreement") to an internationally recognized independent certified public accountant or chartered accountant for resolution. In the event an Audit Disagreement is submitted for resolution by either Party, the Parties shall comply with the following procedures: (i) the Party submitting the Audit Disagreement for resolution shall provide written notice to the other Party that it is invoking the procedures of this Section 8.10(b); (ii) within thirty (30) Business Days of the giving of such notice, the Parties shall jointly select a recognized international accounting firm to act as an independent expert to resolve such Audit Disagreement. (iii)The Audit Disagreement submitted for resolution shall be described by the Parties to the independent expert, which description may be in written or oral form, within ten (10) Business Days of the selection of such independent expert. (iv) The independent expert shall render a decision on the matter as soon as practicable. (v) The decision of the independent expert shall be final and binding unless such Audit Disagreement involves alleged fraud, breach of this Agreement or construction or interpretation of any of the terms and conditions thereof. (vi) All fees and expenses of the independent expert, including any third party support staff or other costs incurred with respect to carrying out the procedures specified at the direction of the independent expert in connection with such Audit Disagreement, shall be borne by each Party in inverse proportion to the disputed amounts awarded to the Party by the independent expert through such decision (e.g. Schering disputes US$100, the

independent expert awards Schering US$60, then Schering pays forty (40%) percent and Exhale pays sixty percent (60%) of the independent expert's costs).

## ARTICLE IX

## ADVERSE DRUG REACTIONS

9.1 Both parties agree to promptly exchange all information that relates to the safety of the Product and especially all adverse reactions and to comply with all applicable laws and regulations relating to the Product concerning drug safety.

9.2 Within a period of two (2) months from the execution of the Agreement, and before enrolment of the first patient in a Product-related study that is conducted sponsored or cosponsored by Exhale and before the first IND or NDA for the Product is granted to Exhale, the Parties will adopt a standard operating procedure to govern the investigation of and action to be taken with regard to Product-related adverse drug experience reports (from both clinical studies and marketing experience), such that each of the Parties can comply with its legal obligations worldwide. The standard operating procedure will: (i) define responsibilities for adverse experience handling for initial, follow-up and/or periodic submission to government agencies of significant information on the Product from pre-clinical laboratory, animal toxicology and pharmacology studies and pre-clinical and Clinical Development; and (ii) include arrangements for the exchange of serious and non-serious cases including formats and timelines, periodic safety update reports, periodic reports and answers to safety-related queries by health regulatory authorities; and (iii) be promptly amended as changes in legal obligations require or as otherwise agreed to by the Parties.

## ARTICLE X

## CONFIDENTIALITY

10.1 Confidentiality; Exceptions. Except to the extent expressly authorized by this Agreement or otherwise agreed in writing, the Parties agree that the receiving Party shall keep confidential and shall not publish or otherwise disclose or use for any purpose other than as provided for in this Agreement any Know-how and other information and materials furnished to it by the other Party pursuant to this Agreement or any Know-how developed during the course of the collaboration hereunder, or any provisions of this Agreement that are the subject of an effective order of the Securities Exchange Commission granting confidential treatment pursuant to the Securities Act of 1934 as amended (collectively "Confidential Information"), except to the extent that it can be established by the receiving Party that such Confidential Information:

(a) was already known to the receiving Party, other than under an obligation of confidentiality, at the time of disclosure by the other Party; or

(b) was generally available to the public or otherwise part of the public domain at the time of its disclosure to the receiving Party; or

(c) became generally available to the public or otherwise part of the public domain after its disclosure and other than through any act or omission of the receiving Party in breach of this Agreement.

(d) was disclosed to the receiving Party, other than under an obligation of confidentiality, by a Third Party who had no obligation to the disclosing Party not to disclose such information to others; or

(e) was independently discovered or developed by the receiving Party as documented in its corporate records.

10.2 Authorized Disclosure. Each Party may disclose Confidential Information hereunder to the extent such disclosure is reasonably necessary in filing or prosecuting patent applications, prosecuting or defending litigation, filing or updating the drug approval applications or orphan drug applications, complying with applicable governmental laws, rules and regulations or conducting Development or Commercialization, provided that, if a Party is required by law or regulation to make any such disclosures of the other Party's Confidential Information it will, except where impracticable for necessary disclosures, for example in the event of medical emergency, give reasonable advance notice to the other Party of such disclosure requirement and, except to the extent inappropriate in the case of patent applications, will use its reasonable efforts to secure confidential treatment of such Confidential Information required to be disclosed. In addition, and with prior written notice to the other Party of each Third Party with whom a confidential disclosure

agreement is being entered into, each Party shall be entitled to disclose, under a binder of confidentiality, Confidential Information to any Third Party for the purpose of carrying out the purposes of this Agreement. Nothing in this Article X shall restrict any Party from using for any purpose any Confidential Information independently developed by it during the course of the collaboration hereunder, or from using Confidential Information that is specifically derived from pre-clinical or clinical trials to obtain regulatory approval or carry out marketing, sales or professional services support functions as is customary in the pharmaceutical industry. Where materiality of disclosure requires a press release or other disclosure pertaining to this Agreement by one Party, the disclosing Party shall give at least three (3) Business Days' advance notice to the other Party.

10.3 Termination of Prior Agreement and Negotiation Phase. The Parties agree that, as of the Effective Date, the Secrecy Agreement between the Parties dated June 25, 2002 is hereby terminated and superseded by the provisions of this Agreement, and any disclosures made by Schering under the terms of the Secrecy Agreement shall be deemed to have been made under, and be governed solely by the terms of this Agreement. Furthermore, the Parties agree that any disclosures made by either Party during the negotiations for this Agreement shall be deemed to have been made under, and be governed solely by the terms of this Agreement.

10.4 Publications. Any press release or other major publication by Exhale relating to the Development or the Commercialization of the Product in the Field in the Territory shall be provided to Schering at least ten (10) Business Days (or five (5) Business Days in the case of a press release) in advance of publication. Schering shall have the right to review and comment upon the publication and the parties will cooperate in good faith to address any reasonable comments within such period.

10.5 Survival. This Article X shall survive the termination or expiration of this Agreement.

## ARTICLE XI

## OWNERSHIP OF INTELLECTUAL PROPERTY, PATENT RIGHTS, TRADEMARKS, DOMAIN NAMES AND USE OF NAME

11.1 Ownership. Each Party shall solely own, and it alone shall have the right to apply for, Patents within and outside of the Territory for any inventions made solely by that Party's employees or consultants in the course of performing work under this Agreement. Inventions made jointly by employees or consultants of Schering and Exhale relating to the use of the Product in the Field (herein referred to as "Joint Inventions") and any patents resulting therefrom (herein referred to as "Joint Patents") shall be owned by the Parties jointly. Joint Inventions and Joint Patents may be used by either Party without accounting to or further approval of the other Party, subject to Section 11.3(c).

The granting of a license to any Third Party shall be subject to the other Party's consent, such consent not to be unreasonably withheld. Either Party shall, however, be authorized to license such Joint Invention or Joint Patent to any of its Affiliates without the other Party's consent, subject to Section 11.3(c).

11.2 Disclosure of Inventions. Exhale shall disclose to Schering any invention made solely by its own employees or consultants relating to the Substance, Drug Substance, Drug Product or the Product in the Field, and Schering shall disclose to Exhale any invention made solely by its own employees or consultants relating to the Substance, the Drug Substance (as applicable), the Drug Product or the Product in the Field in the Territory reasonably in advance of the intended date for submission of a patent application to a governmental patent authority.

11.3 Patent Filings.

(a) Each Party, at its own cost, shall prepare, file, prosecute and maintain Patents to cover inventions made solely by its own employees or consultants relating to Substance, the Drug Substance, the Drug Product or the Product in the Field ("Inventions") and shall use Commercially Reasonable Efforts to file initially all such applications in and outside the Territory. If either Party elects not to file, prosecute, or maintain any such Patent in any country, it shall give the other Party notice of this election within a reasonable period prior to allowing such Patent to lapse, become abandoned or become unenforceable, and prior to taking any steps which would render such an Invention unpatentable and assign all rights in this Patent related to such country to the other Party allowing this other Party to file, prosecute, and maintain this Patent in such country.

Schering shall have the right to file, prosecute and maintain Joint Patents and to determine the countries in which to file Joint Patents, provided that, in all cases, Schering shall reasonably consult and cooperate with Exhale in connection therewith. Schering shall have the right to direct and control all material actions relating to the prosecution or maintenance of these Joint Patents in any country, including correspondence with patent authorities (Schering's address being named for services), interference proceedings, reexaminations, reissue, opposition and revocation proceedings. If either Party elects not to participate in any such Joint Patent or to quit its participation therein, it shall give notice of this election to the other Party and assign all rights in this Joint Patent to the other Party allowing this Party to file, prosecute and maintain this Joint Patent as being such Party's solely owned Patent.

Each Party shall keep the other informed of all actions taken under this Section 11.3, and provide to the other Party all necessary declarations

and cooperate with the other Party to enable Patents or Joint Patents to be issued or transferred. This Section 11.3 (a) shall survive the termination of this Agreement for any reason.

(b) The Parties agree to use Commercially Reasonable Efforts to ensure that any Patent or Joint Patent (on an Invention or Joint Invention) filed outside of the U.S. prior to filing in the U.S. will be in a form sufficient to establish the date of original filing as a priority date for the purposes of a subsequent filing in the U.S. The Parties agree to use Commercially Reasonable Efforts to ensure that any Patent or Joint Patent (on an Invention or Joint Invention) filed in the U.S. prior to filing outside the U.S. will be in a form sufficient to establish the date of original filing as a priority date for the purpose of a subsequent filing in any contracting state of the Paris Convention.

(c) License Grant. All Inventions by Schering employees or consultants and Schering's rights in all Joint Inventions relating to the Substance, Drug Substance, Drug Product and/or Product in the Field and the Territory shall be subject to the licenses granted to Exhale in Articles II and VI (as applicable) of this Agreement.

Exhale shall grant to Schering a royalty-free, exclusive, sub-licensable license to use these Inventions and any Patents resulting therefrom in connection with the Product in the Field outside the Territory. Furthermore, Exhale shall grant to Schering a royalty-free, exclusive, sub-licensable license to use any Know-how generated by Exhale under this Agreement relating to the Product in the Field in connection with the Product in the Field outside the Territory.

11.4 Enforcement Rights.

(a) Notification of Infringement. If either Party learns of any infringement or threatened infringement by a Third Party of the Schering Patents or a Joint Patent, such Party shall promptly notify the other Party and shall provide such other Party with all available evidence of such infringement.

(b) Enforcement in the Territory. Subject to the next sentence, Schering shall be entitled to defend Schering Patents and Joint Patents in the Territory. Schering shall have the right, but not the obligation, to institute, prosecute and control any action or proceeding with respect to infringement of any Schering Patents or Joint Patents covering the Development, Manufacture or Commercialization of the Product being developed or marketed in the Territory, by counsel of its own choice. Schering shall undertake any such action concerning Schering Patents at its own expense. If such action is related to a Joint Patent, expenses shall equally be shared between the Parties. Exhale shall have the right, at its own expense, to be represented in any action by counsel of

its own choice. If Schering fails to bring an action or proceeding or otherwise take appropriate action to abate such infringement within a period of ninety (90) days of notice by Exhale to Schering requesting action, Exhale will have the right to bring and control any such action or proceeding relating to Schering Patents by counsel of its own choice and Schering will have the right to be represented in any such action by counsel of its own choice and at its own expense. If one Party brings any such action or proceeding, the other Party agrees to be joined as a party plaintiff if necessary to prosecute the action or proceeding and to give the first Party commercially reasonable assistance and authority to file and prosecute the suit. Any damages or other monetary awards recovered pursuant to this Section 11.4 (b) shall be allocated first to the costs and expenses of the Party bringing suit, then to the costs and expenses, if any, of the other Party. In the event that Exhale brings such action, any amounts remaining shall be distributed as follows: compensatory damages shall be treated as Net Sales in the Territory and calendar quarter received, and punitive and exemplary damages shall be paid sixty percent (60%) to Exhale and the remaining forty percent (40%) to Schering. In the event that Schering brings such action, sixty percent (60%) of any amounts remaining shall be payable to Schering and the remaining forty percent (40%) to Exhale.

(c) Settlement with a Third Party. The Party that controls the prosecution of a given action shall also have the right to control settlement of such action, provided however, that no settlement shall be entered into without the written consent of the non-controlling Party if such settlement involves any payment or admission of liability by such non-controlling Party.

11.5 Defense and Settlement of Third Party Claims. If a Third Party asserts that a patent or other intangible right owned by it is infringed by the Product in the Territory, Schering shall be entitled to solely defend against any such assertions at its cost and expense (subject to the provisions of Section 11.4 (b)), but no settlement may be entered into without the written consent of Exhale, which shall not be unreasonably withheld. The costs for any such settlement (including, without limitation, damages, expense reimbursements, compliance, future royalties or other amounts) shall be paid fourty percent (40%) by Schering and sixty percent (60%) by Exhale. If any Third Party is successful in any such claim and Exhale is ordered to make any payments to such Third Party in connection therewith, fifty (50%) percent of any such payments may be offset or deducted from the payment obligations of Exhale under the Agreement.

11.6 Licenses under Third Party Patents.

(a) Determination. Each Party agrees to bring to the attention of the other Party any Third Party Patent it discovers, or has discovered, and which relates to the subject matter of this Agreement. Upon mutual

agreement, the Parties may seek to obtain a license or right under one or more Third Party Patents covering any Product in the Territory in order to avoid infringement. In the event that Exhale determines that it is beneficial for the Parties to obtain a license or right under one or more Third Party Patents covering any Product in the Territory and Schering objects to such determination within twenty (20) Business Days after such determination is made, the Parties shall suspend action for a period of one (1) month unless a shorter period is reasonably required under the circumstances (the "Deferral Period") to allow Schering to present its position to and discuss its position with Exhale. Such discussion shall involve senior management of each Party.

(b) Schering may present such facts, findings, conclusions and other information as it deems necessary to Exhale during the Deferral Period. Upon the earlier of the end of the Deferral Period or Schering's presentation of all of its information, Exhale shall evaluate such information and make a final determination, in its reasonable judgment, as to the desirability of obtaining a license or right under such Third Party Patents. The decision reached by Exhale shall thereafter be final and binding on the Parties.

(c) Licensing. In the event that the Parties agree to seek to obtain a license or right under any Third Party Patents or in the event of final determination by Exhale of the desirability to obtain a license or right under any Third Party Patents, Exhale and Schering will make reasonable efforts to obtain such license or right.

(d) Royalties. Any royalties and fees to be paid by Exhale to the Third Party in consideration of the license or right under the Third Party Patents with respect to the Product sold by Exhale or its Affiliates shall be borne by Exhale but fifty (50%) percent of such may be deducted from the royalty otherwise payable to Schering pursuant to Article VIII of this Agreement.

11.7 Patent Expenses. All worldwide Patent Expenses with respect to Schering Patents shall be borne by Schering, subject to the terms of this Agreement; all worldwide Patent Expenses with respect to Exhale's Patents shall be borne by Exhale. All worldwide Patent Expenses with respect to Joint Patents shall be shared equally between the Parties. Should either Party quit its participation in a Joint Patent pursuant to Section 11.3 (a) above, the other Party acquiring such Joint Patent as being its solely owned Patent (as applicable) shall then take over all payment obligations concerning any co-inventions by employees.

11.8 Trademarks

(a) Schering grants to Exhale an exclusive right to use the Trademark and

Domain Name throughout the term of this Agreement and after expiration hereof (other than for Exhale's breach) provided, however, that Schering and Exhale shall share the Domain Name "... .com" by using a joint web page containing a link to each of the Parties individual web pages; the design of such joint web page to be discussed in and supervised by the Development and Commercialization Committee. Exhale shall use the Trademark only for denomination of the Product in the Field in the Territory. The Parties will cooperate to find an alternative Trademark in the event that either the FDA objects to the use of a Trademark, or the use of a Trademark in connection with the Product in the Field in the Territory potentially infringes or violates a Third Party's rights.

(b) Schering shall be responsible for the registration and maintenance of the Trademark which Exhale employs in connection with the marketing of the Product in the Field in the Territory. Schering shall own and control the Trademark and bear all relevant costs relating thereto.

(c) Exhale recognizes the exclusive ownership by Schering of any proprietary Schering name, logotype or Trademark furnished by Schering (including Schering's Affiliates) for use in connection with the marketing, sale or distribution of the Product. Exhale shall not, either while this Agreement is in effect, or at any time thereafter, register, use or challenge or assist others to challenge the Trademark or attempt to obtain any right in or to any such name, logotype or trademarks confusingly similar to the Product as defined in this Agreement or any other goods and products, notwithstanding that such goods or products have a different use or are dissimilar to the Product as defined in this Agreement.

(d) Exhale shall not materially modify or alter the Trademark or do anything which should reasonably be expected to damage the Trademark.

(e) Exhale shall promptly notify to Schering any actual alleged or threatened infringement of the Trademark or of any unfair trade practices, trade dress limitation, passing off of counterfeit goods, or similar offenses of which it becomes aware. Only Schering will be authorized to initiate at its own discretion legal proceedings against any infringement or threatened infringement of a trademark applicable to the Product as defined in this Agreement. Exhale shall cooperate fully in connection with Schering's actions for the protection of the Trademark, at Schering's expense.

11.9 Domain Names. Schering shall be responsible for the registration, hosting, maintenance and defense of the Domain Names. For the avoidance of doubt, Schering is allowed to register in its own name, to host on its own servers, maintain and defend the Domain Names and use them for websites.

11.10 Use of Names. Neither Party shall use the name of the other Party in relation to this transaction in any public announcement, press release or other public document without the written consent of such other Party, which consent shall not be unreasonably withheld or delayed; provided however, that either Party may use the name of the other Party in any document filed with any Health Regulatory Authority, including the FDA and the Securities and Exchange Commission, in which case Schering shall be referred to as "Schering AG, Germany".

## ARTICLE XII

## REPRESENTATIONS AND WARRANTIES

12.1 Each of the Parties represents and warrants to the other Party as follows:

The Agreement is a legal and valid obligation binding upon such Party and enforceable in accordance with its terms. The execution, delivery and performance of the Agreement by such Party does not conflict with any agreement, instrument or understanding, oral or written, to which it is a party or by which it is bound, nor to such party's knowledge, violates any law or regulation of any court, governmental body or administrative or other agency having jurisdiction over it.

12.2 Exhale hereby represents and warrants to Schering that Exhale:

(a) Has employed and will in the future employ individuals of appropriate education, knowledge, and experience to conduct and oversee the conduct of the Development and Commercialization of the Product in the Territory;

(b) To the best of its knowledge, has not employed, or used a contractor or consultant that employs, any individual or entity debarred by the FDA, or, to the best knowledge of Exhale, any individual who or entity which is the subject of an FDA debarment investigation or proceeding (or similar proceeding of EMEA), in the conduct of the pre-clinical or clinical studies of the Product;

(c) There are no actions, suits, proceedings or unsatisfied judgments outstanding, including, without limitation, those that may be related to war reparations, pending or threatened against or affecting Exhale, which may impair the ability of Exhale to perform its obligations under this Agreement, and Exhale is not aware of any existing ground on which any such action, suit or proceeding might be commenced with any reasonable likelihood of success.

12.3 Schering hereby represents and warrants to Exhale that Schering:

(a) To the best of its knowledge, has not employed, or used a contractor or consultant that employs, any individual or entity debarred by the FDA, or, to the best knowledge of Schering, any individual who or entity which is the subject of an FDA debarment investigation or proceeding (or similar proceeding of EMEA), in the conduct of any activity relevant to the Substance, the Drug Substance or the Product;

(b) Has not granted (and none of its Affiliates has granted), and during the term of this Agreement neither Schering (nor its Affiliates) will grant, any right to any Affiliate or Third Party (or otherwise engage in any activity) in the Field relating to (i) the Schering Patents and/or Schering Know-how or to the Substance, the Drug Substance, the Drug Product or the Product or (ii) any Trademark, in either case which would conflict with the rights granted to Exhale hereunder. Further, neither Schering nor any of its Affiliates will do any of the following (and none of them has authorized or will authorize any Affiliate or Third Party to do any of the following): to sell, license or otherwise engage in any activity only relevant to any prostacyclin drug in the Field in the Territory (other than as expressly specified in this Agreement or the Manufacturing and Supply Agreement);

(c) To the best of its knowledge, (i) is the sole owner of all right, title and interest in and to the Schering Patents and the Schering Know-how; (ii) is not aware of any actual or potential violation, infringement or misappropriation of any Third Party's rights (or any potential claim thereof) by the Drug Substance or the Drug Product; (iii) is not aware of any material questions or challenges with respect to the validity of the Schering Patents; (iv) is not aware of any patents or applications (other than the Schering Patents and Know-how and the Toray patent application WO98/37895) relevant to the Product in the Field in the Territory, excluding, however, any Patents or patent applications relevant to any combination therapies involving the Product; and (v) is not aware of any information or circumstance that could materially and adversely affect the value of the Product in the Field in the Territory (e.g., information regarding safety, efficacy, orphan drug status, or regulatory matters).

12.4 DISCLAIMER. EXCEPT AS EXPRESSLY STATED IN THIS AGREEMENT, NOTHING IN THIS AGREEMENT SHALL BE CONSTRUED AS A WARRANTY OR REPRESENTATION, IN PARTICULAR, EXCEPT AS EXPRESSLY STATED IN THIS AGREEMENT, NOTHING SHALL BE CONSTRUED AS:

(a) A WARRANTY OR REPRESENTATION BY SCHERING AS TO THE VALIDITY OR SCOPE OF ANY SCHERING KNOW-HOW OR SCHERING PATENT OR TRADEMARK OR THAT THE EXERCISE OF THE PATENT RIGHTS WILL NOT INFRINGE UPON THE RIGHTS

OF ANY THIRD PARTY;

(b) A REQUIREMENT THAT SCHERING SHALL FILE ANY PATENT APPLICATION OR TRADEMARK APPLICATION; SECURE ANY PATENT OR TRADEMARK APPLICATION, OR MAINTAIN ANY PATENT OR TRADEMARK APPLICATION IN FORCE;

(c) AN OBLIGATION BY SCHERING TO BRING OR PROSECUTE ACTIONS OR SUITS AGAINST THIRD PARTIES FOR INFRINGEMENT;

(d) GRANTING BY IMPLICATION, ESTOPPEL, OR OTHERWISE BY SCHERING ANY LICENSES OR RIGHTS UNDER PATENTS OR KNOW-HOW OR TRADEMARK OTHER THAN AS EXPRESSLY SET FORTH IN THIS AGREEMENT;

(e) A REPRESENTATION OR WARRANTY BY SCHERING OF THE ACCURACY, SAFETY, OR USEFULENESS FOR ANY PURPOSE OF ANY INTELLECTUAL PROPERTY AT ANY TIME MADE AVAILABLE TO EXHALE.

## ARTICLE XIII

## INDEMNIFICATION

13.1 Subject to Section 13.3, Exhale hereby agrees to indemnify, save, defend and hold Schering and its officers, directors, consultants, agents and employees harmless from and against any and all suits, claims, actions, demands, liabilities, expenses and/or losses, including reasonable legal expenses and attorneys' fees, each to the extent paid by Schering to a Third Party (collectively, "Losses" and each a "Loss"), resulting from or arising out of Exhale or its Affiliates' or sublicensees Development or Commercialization or Manufacture (as applicable) of the Product in the Field in the Territory except to the extent such Losses result from or arise out of (i) the inaccuracy of any representation of Schering set forth in this Agreement; (ii) the breach of any warranty or covenant contained in this Agreement by Schering; or (iii) the negligence or willful misconduct of Schering.

13.2 Schering hereby agrees to indemnify, save, defend and hold Exhale and its officers, directors, consultants, agents and employees harmless from and against any and all Losses resulting from or arising out of (i) the inaccuracy of any representation of Schering set forth in this Agreement; (ii) the breach of any warranty or covenant contained in this Agreement by Schering; or (iii) the negligence or willful misconduct of Schering.

13.3 Each indemnified Party agrees to give the indemnifying Party prompt written notice of any Loss or discovery of fact upon which such indemnified Party

intends to base a request for indemnification under Sections 13.1 or 13.2. Each Party shall furnish promptly to the other copies of all papers and official documents received in respect of any Loss. With respect to any Loss relating solely to the payment of money damages and which will not result in the indemnified Party becoming subject to injunctive or other relief or otherwise adversely affecting the business of the indemnified Party in any manner, and as to which the indemnifying Party shall have acknowledged in writing the obligation to indemnify the indemnified Party hereunder, the indemnifying Party shall have the sole right to defend, settle or otherwise dispose of such Loss, on such terms as the indemnifying Party, in its sole discretion, shall deem appropriate. The indemnifying Party shall obtain the written consent of the indemnified Party, which shall not be unreasonably withheld or delayed, prior to ceasing to defend, settling or otherwise disposing of any Loss if as a result thereof the indemnified Party would become subject to injunctive or other equitable relief or any remedy other than the payment of money, which payment would be the responsibility of the indemnifying Party. The indemnifying Party shall not be liable for any settlement or other disposition of a Loss by the indemnified Party which is reached without the written consent of the indemnifying Party. The reasonable costs and expenses, including reasonable fees and disbursements of counsel incurred by any indemnified Party in connection with any Loss, shall be reimbursed on a quarterly basis by the indemnifying Party, without prejudice to the indemnifying Party's right to contest the indemnified Party's right to indemnification and subject to refund in the event the indemnifying Party is ultimately held not to be obligated to indemnify the indemnified Party.

13.4 Insurance. Each Party agrees to obtain and maintain in effect a policy or policies of insurance relating to the subject of its indemnity obligations hereunder. Such policies shall be issued by one or more reputable insurers, and shall contain reasonable terms of coverage in light of the obligations set forth above. Exhale undertakes to obtain and maintain in effect a policy or policies of insurance covering during the Clinical Development of the Product a minimum of USD 3 Mio. per single damage, and during the Commercialization of the Product a minimum of USD 10 Mio. per single damage. Upon the request of the other Party to this Agreement, each Party shall provide evidence of insurance coverage in compliance with this Section to the other Party. In lieu of the insurance coverage described above, Schering shall have the right to undertake a program of self-insurance to cover its indemnity obligations hereunder, with financial protection comparable to that arranged by it for its own protection with regard to other products in its product line.

13.5 This Article XIII shall survive the termination or expiration of this Agreement.

## ARTICLE XIV

## TERM, TERMINATION AND CHANGE OF CONTROL

14.1 Term. This Agreement shall commence as of the Effective Date and, unless sooner terminated as provided herein, shall continue in effect until no royalties are payable to Schering under Article VIII hereunder. If Exhale has not within ten (10) Business Days from the execution of this Agreement by both Parties provided written proof to Schering that it has entered into an agreement with investors for at least USD 15 million of additional funding available for the Development and Commercialization of the Product in the Field in the Territory, this Agreement shall remain null and void, and Schering shall be free to grant all rights and licenses referred to in this Agreement to any Third Party.

14.2 Termination

(a) Exhale may terminate the Agreement within sixty (60) days from its Pre-NDA meeting with the Health Regulatory Authority concerning the Product by advance written notice to Schering if, as a result of this Pre-NDA meeting, Exhale determines that additional Phase 3 Clinical Trials beyond those conducted prior to the date hereof will be required for Regulatory Approval of the Product in the Field by the Health Regulatory Authority.

(b) Failure of Exhale or Schering to comply with any of their respective material obligations contained in this Agreement which constitutes a material breach (e.g. on the part of Exhale, its obligation to pursue the Development Plan pursuant to Section 3.1 (b) and (c) above or the Commercialization Plan pursuant to Section 4.2 and 4.3 above), shall entitle the other Party to give the Party a default notice requiring it to cure such default. If such default is not cured within ninety (90) days after receipt of such notice, the notifying Party shall be entitled (without prejudice to any of its other rights conferred on it by this Agreement) to terminate this Agreement. Notwithstanding the foregoing, in the event of a non-monetary default, if the default is not reasonably capable of being cured within the ninety (90) day cure period by the defaulting Party and such defaulting Party is making a good faith effort to cure such default, the notifying Party may not terminate this Agreement, provided however, that the notifying Party may terminate this Agreement if such default is not cured within one hundred eighty (180) days of such original notice of default. The right of either Party to terminate this Agreement as herein above provided shall not be affected in any way by its waiver of, or failure to take action with respect to any previous default.

(c) In the event that one of the Parties hereto shall go into liquidation, a receiver or a trustee be appointed for the property or estate of that Party and said receiver or trustee is not removed within one hundred twenty (120) days, or the Party makes an assignment for the benefit of

creditors, and whether any of the aforesaid bankruptcy events be the outcome of the voluntary act of that Party, or otherwise, the other Party shall be entitled to terminate this Agreement.

(d) In the event that this Agreement is terminated by Exhale in accordance with Section 14.2(a) or by either Party in accordance with Sections 14.2(b) or (c) hereof, Exhale will: (i) deliver to Schering the Schering Know-How and assign to Schering its rights in said Schering Know-How, Schering Patents, Trademarks and Domain Names if any; (ii) not use the Schering Know-How as long as it has to be kept confidential pursuant to Article X hereof; (iii) not infringe any of the Schering Patents; (iv) make all payments accrued under this Agreement prior to the effective termination date; (v) transfer all regulatory filings and approvals and all Orphan Drug Act petitions, designations and exclusivity related to the Product, to Schering upon Schering's written request for same; (vi) refrain from filing an ANDA for a generic of the Product; and (vii) sell to Schering, at any time within ninety (90) days of such termination, all or any portion of the inventory of the Substance, the Drug Substance, the Drug Product and/or the Product owned by Exhale or its Affiliates which are intended for sale in the Territory at a price equal to Exhale's or its Affiliate's fully burdened costs for such inventory. If Exhale has terminated the Agreement pursuant to Section 14.2(b) above, Schering shall be obligated to purchase such inventory. Otherwise, Exhale shall only sell and Schering shall only purchase all or any portion of the inventory at Schering's election. Such election shall be made by Schering in writing in a notice to Exhale, and within thirty (30) days of such termination. If Schering purchases such Exhale inventory, Exhale shall ship at Schering's cost and direction such inventory to Schering. Schering shall pay for such inventory in advance of receipt of such inventory.

(e) Each Party agrees (to the extent that it may lawfully do so) that it will not at any time insist upon, or plead, or in any manner whatsoever claim to take the benefit or advantage of, any stay or extension law or any other law wherever enacted, now or at any time hereinafter in force, which would prohibit the termination of this Agreement by the other Party as provided in this Agreement, in any way modify the effects of termination by such Party as provided in this Agreement, or prohibit or impede the exercise by such Party of any other rights set forth in this Article XIV or elsewhere in this Agreement. Each Party (to the extent it may lawfully do so) hereby expressly waives all benefit and advantage of any such law and covenants that it will not hinder, delay or impede the execution of any power granted to the other Party in this Agreement, but will permit the execution by such Party of every power granted to such Party in this Agreement as though such law had not been enacted.

(f) In the event that Exhale intends to pursue potential transactions as a

result of which (i) the majority of the outstanding voting securities or substantially all of the assets or business of Exhale would become owned by a pharmaceutical company that sells a pulmonary hypertension drug that is directly competitive with the Product (a "Competitor Pharmaceutical Company") that did not own a majority of the voting securities of Exhale as of the Effective Date; or (ii) the actual power to direct or cause the direction of the management and policies of Exhale through ownership of the outstanding voting securities would become vested in a Competitor Pharmaceutical Company that did not possess such power as of the Effective Date (hereinafter collectively the "Change of Control Event"), Schering will have the option to exercise an exclusive right of first negotiation to acquire Exhale as described below (the "Option"). Before entering a transaction with any Third Party which would result in a Change of Control Event, Exhale shall notify Schering that it may pursue such potential transactions and Schering shall have ten (10) Business Days from the date of such notice to provide Exhale written notice that it has exercised its Option. If Schering does not provide written notice that it has exercised its Option within such ten (10) Business Day period, then Exhale shall have no further obligation with respect to the Option and shall be free to negotiate and enter into any transaction which results in a Change of Control Event with any Third Party. If Schering properly exercises the Option as described above, then the Parties shall negotiate reasonably and in good faith concerning the acquisition of Exhale by Schering for a period of forty-five (45) days. If the parties do not execute and deliver an agreement for the acquisition of Exhale by Schering within such forty-five (45) days' period, then Exhale shall be free to negotiate and enter into any transaction which results in a Change of Control Event with any Third Party; provided that if such Third Party transaction is, when taken as a whole, materially and substantially less favorable to Exhale than the terms last offered to Exhale by Schering, then Exhale will offer Schering such transaction for a period of ten (10) days before entering such transaction with a Third Party.

(g) Except where expressly provided for otherwise in this Agreement, termination or expiration of this Agreement shall not relieve the Parties hereto of any liability, including any obligation to make payments hereunder, which accrued hereunder prior to the effective date of such termination or expiration, nor preclude either Party from pursuing all rights and remedies it may have hereunder or at law or in equity with respect to any breach of this Agreement nor prejudice any Party's right to obtain performance of any obligation.

14.3 Surviving Rights. The rights and obligations set forth in this Agreement shall extend beyond the termination of the Agreement only to the extent expressly provided for herein as follows: Sections 6.6 and 8.4, Article IX, Article X, the last sentence of Section 11.1, Sections 11.3(a), and (c), 11.8(a), 11.10, and 12.4, Article XIII, Sections 14.2(d), (e) and (g), 14.3 and Article XV.

## ARTICLE XV

## MISCELLANEOUS

15.1 Assignment.

(a) Subject to compliance with Section 14.2 (f) above, either party may assign any of its rights or obligations under this Agreement to any of its Affiliates or to a successor to all or substantially all of such party's business or assets; provided, however, that such assignment shall not relieve such party of its responsibilities for performance of its obligations under this Agreement. Except as provided herein, neither Party to this Agreement shall have the right to assign its rights or obligations under this Agreement.

(b) This Agreement shall be binding upon and inure to the benefit of the permitted assigns of the Parties. Any purported assignment not in accordance with this Agreement shall be void.

15.2 Force Majeure. Neither Party shall lose any rights hereunder or be liable to the other Party for damages or losses on account of failure of performance by the defaulting Party if the failure is occasioned by government action, war, fire, explosion, flood, strike, lockout, embargo, act of God or any other cause beyond the reasonable control of the defaulting Party, provided that the Party claiming force majeure has extended reasonable efforts to avoid or remedy any such force majeure, continues to employ such efforts and promptly notifies the other Party of such force majeure event.

15.3 Further Actions. Each Party agrees to execute, acknowledge and deliver such further instruments and to do all such other acts, as may be necessary or appropriate in order to carry out the purposes and intent of this Agreement.

15.4 No Trademark Rights. Except as otherwise provided herein, no right, express or implied, is granted by this Agreement to use in any manner the names "Exhale" or "Schering" or any other trade name or trademark of the other Party or its Affiliates in connection with the performance of this Agreement.

15.5 Notices. All notices hereunder shall be in writing, effective upon receipt, and shall be delivered personally, mailed by registered or certified mail (return receipt requested, postage prepaid), or sent by express courier service, to the other Party at the following addresses (or at such other address for a Party as shall be specified by like notice):

(a) If to Exhale:

1301 Shoreway Road

Suite 320
Belmont, California
94002, U.S.A.

(b) If to Schering:

Schering AG
Attn. Dr. Bernhard Fritz-Zieroth
Muellerstraße 178
D-13353 Berlin
Germany

With copy to:

Schering AG
Legal Department
Muellerstraße 178
D-13353 Berlin
Germany

15.6 Waiver. Except as specifically provided herein, the waiver from time to time by either of the Parties of any of their rights or their failure to exercise any right or remedy shall not operate or be construed as a continuing waiver of same or of any other of such Party's rights or remedies provided in this Agreement.

15.7 Severability. Each Party hereby agrees that it does not intend, by its execution hereof, to violate any public policies, statutory or common laws, rules, regulations, treaties or decisions of any government agency or executive body thereof of any country or community or association of countries. Should one or more provisions of this Agreement be or become invalid, the Parties hereto shall substitute, by mutual consent, valid provisions for such invalid provisions, which valid provisions in their economic and other effects are sufficiently similar to the invalid provisions that it can be reasonably assumed that the Parties would have entered into this Agreement with such valid provisions. In case such valid provisions cannot be agreed upon, the invalidity of one or several provisions of this Agreement shall not affect the validity of this Agreement as a whole or the validity of any portions hereof, unless the invalid provisions are of such essential importance to this Agreement that it is to be reasonably assumed that the Parties would not have entered into this Agreement without the invalid provision.

15.8 Ambiguities. The Parties acknowledge and agree that: (a) each Party and its counsel reviewed and negotiated the terms and provisions of this Agreement and have contributed to its revision; (b) the rule of construction to the effect that any ambiguities are resolved against the drafting Party shall not be employed in the interpretation of this Agreement; and (c) the terms and

provisions of this Agreement shall be construed fairly as to the Parties hereto and not in favor of or against any Party, regardless of which Party was generally responsible for the preparation of this Agreement.

15.9 Governing Law and Place of Jurisdiction. This Agreement shall be governed by and construed in accordance with the laws in force in the State of New York, U.S., without giving effect to the choice of laws provisions thereof. Any legal action arising under this Agreement shall be instituted in the state or U.S. district Courts for the Southern District of New York and each Party consents to the jurisdiction of such courts for the purposes of any such action.

15.10 Headings. The Section and Paragraph headings contained herein are for the purposes of convenience only and are not intended to define or limit the contents of said Sections or Paragraphs.

15.11 Counterparts. This Agreement may be executed by the Parties in one or more counterparts. Such counterparts may be exchanged by facsimile (provided that each executed counterpart is transmitted in one complete transmission). Where there is an exchange of executed counterparts, each Party shall be bound by this Agreement notwithstanding that original copies of this Agreement may not be exchanged immediately. The Parties shall cooperate after execution of this Agreement and exchange by facsimile to ensure that each Party obtains an original, executed copy of this Agreement.

15.12 Entire Agreement; Amendments. This Agreement, including all Schedules attached hereto, all documents and things incorporated herein by reference and all of the documents delivered concurrently herewith set forth all the covenants, promises, agreements, warranties, representations, conditions and understandings between the Parties hereto and supersede and terminate all prior agreements and understandings between the Parties. No subsequent alteration, amendment, change or addition to this Agreement shall be binding upon the Parties hereto unless reduced to writing and signed by the respective authorized officers of the Parties.

15.13 Expenses. Except as otherwise specified in this Agreement, all costs and expenses, including, without limitation, fees and disbursements of counsel, financial advisers and accountants, incurred in connection with this Agreement and the transactions contemplated hereby shall be paid by the Party incurring such costs and expenses.

15.14 Independent Contractors. The status of the Parties under this Agreement shall be that of independent contractors. Neither Party shall have the right to enter into any agreements on behalf of the other Party, nor shall it represent to any person that it has any such right or authority. Nothing in this Agreement shall be construed as establishing a partnership or joint venture relationship between the Parties.

IN WITNESS WHEREOF, Exhale and Schering have caused this Agreement to be executed as of October 2, 2003 by their respective duly authorized representatives.

SCHERING AKTIENGESELLSCHAFT

Date: October 2, 2003

Dr. Barbara Putz
Head CCD STH Eur.

Dr. Ulrich Koch
Head Corp. Bus. Dev.

EXHALE THERAPEUTICS, INC.

Date: October 2, 2003

Name: DONALD J. SAMTEL
Title: PRESIDENT & CEO

**Schedules:**

1. List of Schering Patents
2. Development Plan
3. Commercialization Plan
4. Specifications of Drug Product and Drug Substance

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**Schedule 1**
**to Exhale Agreement**

## List of Schering Patents

1. Product Patent No. US 4,692,464;
2. Process Patent No. US 4,894,336;
3. Process Patent No. US 5,200,530.

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**Schedule 2**
**to Exhale Agreement**

# Exhale Therapeutics
# Development Plan for Ventavis® (Iloprost)

## Registration Strategy

- **Establish FDA Division of Cardio-Renal Drug Products as the reviewing division for Iloprost Inhalation Solution, and have a pre-IND meeting with the Division at the earliest time to obtain agreement for the registration strategy**
- **File IND with Schering pre-clinical, CMC and clinical data with protocols for Phase 1 QT study (if needed) and Phase 3 iloprost add-on study (if needed)**
- **Request an end-of-Phase 2 meeting with FDA to obtain agreement on completeness of existing clinical data for approval**
- **Initiate a second Phase 3 pivotal trial if the Agency clearly states (at either the pre-IND meeting or the end-of-Phase 2 meeting) that the existing clinical data is not adequate for filing. This trial would serve as a back-up to the Tracleer study if significance is not reached in that trial.**
- **Submit NDA based on European submission with additional clinical analyses to support labeling for Stage III and IV Pulmonary Arterial Hypertension (PAH) as long term goal; short term goal could be approval for PPH stage III and label extenison to PAH stages III and IV by ongoing clinical studies (e.g. iloprost add-on study)**
- **File Orphan application to achieve additional marketing exclusivity**

### *Introduction*

The Division of Cardio-Renal Drug Products has reviewed all 3 currently available drugs for pulmonary hypertension (Flolan®, Tracleer®, and Remodulin®). To date, there has been no interaction with that division concerning Iloprost Inhalation Solution. Berlex, the Schering subsidiary in the US, conducted an End of Phase II meeting in July 1999 with the Division of Gastrointestinal and Coagulation Drug Products.

Exhale plans to meet with the Division of Cardio-Renal Drug Products as soon as possible (mid-November) in a pre-IND meeting to discuss the pre-clinical and CMC information required for initiating clinical trials in the U.S. The potential need to conduct an additional Phase I study will be discussed - a study to assess the effect of iloprost on the QT interval (a recent proposed requirement for all new chemical entities). We are also planning to conduct a iloprost add-on study under the IND. See Attachment 1 for a list of clinical studies.

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We will state that we contemplate no additional trials, other than the Phase I trial (if needed) and ask if the Division thinks this is a reasonable approach. In this way, we will be able to obtain early feedback on the FDA's view of the completeness of the available data package, which will be submitted in the IND.

As discussed with Dr. Ray Lipicky, the former head of the Cardio-Renal Division, at the pre-IND meeting we will propose that an End of Phase II meeting be held early next year (prior to the completion of the QT study) to discuss submitting the NDA based on the European marketing application (MAA).

## *Preclinical*

A full complement of preclinical pharmacology and toxicology studies of iloprost (administered by parenteral and oral dosing in a variety of species) will be submitted in the IND, along with a 6 month inhalation toxicity study in rats conducted by Schering. The NDA may require a 28-day inhalation study in dogs sponsored by Exhale, if the FDA believes that such a study is necessary.

## *Clinical Pharmacology*

The pharmacokinetic data for iloprost given by inhalation are limited to a single Phase I crossover study of 3 nebulizers in 12 patients. No pharmacokinetic data were obtained in the Phase III study.

At the End of Phase II meeting with the GI/Coagulation Division on 7/99, the FDA representatives noted that dose-blood level data should be provided in order to evaluate systemic side effects. According to Schering personnel, further discussion on this point centered on the conduct of a pharmacokinetic/ pharmacodynamic study linking the inhaled formulation to iloprost given intravenously.

We will provide a strong justification that this study is not necessary for the following reasons:

- The Exhale drug product will be identical to the Schering drug product, supplied by the Schering facility in Spain. Schering will continue to manufacture the drug substance and drug product, so there are no CMC changes from the EMEA submission.

- In the Phase III study, doses of iloprost were titrated upwards (to a top dose of 5 µg 9 times daily) as tolerated by each patient individually. This is similar to the up-titration utilized for both Flolan and Remodulin. Systemic concentrations of iloprost have no role in this individualized dosing.

- Extensive pharmacokinetic information is available for Schering's intravenous iloprost product administered for the treatment of peripheral

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arterial obstructive disease. Furthermore, robust pharmacokinetic data was obtained from the Phase I crossover study with inhaled iloprost, albeit limited to a single dose of 5 µg. These data show area under the curve (AUC) concentrations of approximately 50 pg·h/ml. This value is approximately half of the AUC obtained after a 2 ng/kg/min intravenous dose which is commonly used for peripheral arterial obstructive disease.

**Potential QT interval study**

A "Preliminary Concept Paper" was issued by the FDA in November 2002 that outlined the proposed requirement for rigorous characterization of the effects of a new chemical entity on the QT interval (to assess the potential to affect cardiac repolarization and certain types of arrhythmias). We will review the ECG data generated by Schering AG in support of iloprost given by both inhalation and intravenous infusion. However, it is likely that this dataset will be inadequate to convince the FDA that we have fully characterized the effect of iloprost on cardiac repolarization as no positive control was included. Therefore, we will be prepared to conduct a well-standardized study (with both positive and placebo control) to assess this.

## *Clinical*

The clinical program consisted of three controlled studies (Phase I crossover, Phase II, and Phase III), long-term open label extensions of the Phase II and III studies, and additional supportive safety data from intravenous iloprost use in about 7000 patients, including 155 patients with pulmonary hypertension. This data will be filed with the IND (allowing adequate review time by the Agency) and will serve as basis of the clinical section of the NDA. Additional analyses will be performed to support the proposed labeling (see below).

**A) Rationale for Adequacy of Single Pivotal Trial**

We believe that there is a reasonable chance that the single completed pivotal trial will be sufficient for FDA review and approval, based on the following:

- At the End of Phase II meeting held with Berlex, the FDA noted that a single pivotal trial would be adequate if the results were consistent and persuasive.
- The efficacy data from the pivotal trial are robust (solid p values using several statistical methods) and persuasive (internally consistent across multiple endpoints).
- The results are also consistent across the treatment sites and subgroups (with the exception of chronic thromboembolic disease; see next bullet).
- The CPMP gave a positive opinion for iloprost based on the single pivotal trial.

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**B) Iloprost add-on study**

At the pre-IND meeting, we will get a sense of the FDA's feedback on the adequacy of the dataset. In the event that the FDA insists that a second pivotal study is necessary prior to filing the NDA, we will be prepared to discuss with them the adequacy of using data from an iloprost add-on trial to serve as that second pivotal. The planned add-on trial will be a Phase 3 placebo-controlled study of iloprost added to common therapy including approved disease specific therapies such as Tracleer in patients who are inadequately controlled on Tracleer alone. Pilot experience of iloprost add-on therapy in patients already treated with Tracleer will form a basis for the final study design. Importantly, we plan to initiate this study in March 2004 for the following reasons:

- This study will serve as a contingency study in the event the FDA insists upon a second pivotal study, either during the pre-IND meeting or during the end of Phase II meeting.
- The concept of an add-on therapy is well supported by the differing mechanisms of action.
- Two recently published studies (BREATHE-2 and Hoeper 2003) support the concept of additive effects for Tracleer and a prostacyclin. Therefore, pilot experience of an iloprost add-on therapy in patients already on bosentan might further facilitate the design of an add-on study.
- Efficacy and safety data on the combination is important for profiling iloprost in this age of evidence-based medicine
- This will give important opinion leaders a chance to use the drug in a clinical trial setting prior to launch.

**C) Repeat pivotal placebo-controlled study**

If at the pre-IND meeting or the end-of-phase 2 meeting the FDA insists that a second confirmatory placebo-controlled pivotal trial similar to the pivotal trial (AIR study published by Olschewski in the NEJM) is required, we will initiate such a placebo-controlled trial in PAH patients . This study will be a contingency study in the event that the iloprost add-on study results are not robust enough to serve as a second pivotal trial. A placebo-controlled study in PAH patients who are not taking other disease targeting drug such as Tracleer has a lower risk of failing to achieving a significant p value, but will require a much longer period of time to recruit. This is due to the competition for newly diagnosed patients to be recruited into ongoing or planned clinical trials for the oral agents ambrisentan, sitaxsentan, or sildenafil. The option of using international sites except Europe will also be fully explored. Assuming that the iloprost add-on study yields positive results sufficient for NDA approval, the repeat placebo-controlled trial will be closed to further recruitment, and all patients will be offered open-label iloprost.

**D) Support for labeling of Stage III and IV Pulmonary Arterial Hypertension**

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Schering AG obtained an EMEA approvalbased on the efficacy data obtained from the pivotal Phase III study. However, the CPMP restricted the labeling to NYHA Class III patients with Primary Pulmonary Hypertension.

Although the pivotal study enrolled Class III and IV patients, the restriction to Class III patients was based on the opinion that the Class IV patients (mean walk distance 270 meters) had milder disease than typical Class IV patients seen by clinicians. This restriction is similar to that applied to Tracleer in Europe (Remodulin is not approved in Europe); the CPMP believes that Class IV patients should be treated with Flolan. We will justify that the labeling for Iloprost Inhalation Solution should include both Class III and Class IV because the latter were well represented in the Phase III study (approximately half the patients) and showed a similar response to the drug. This strategy follows the precedent set by the FDA with both Tracleer and Remodulin.

The European restriction to Primary Pulmonary Hypertension is based on the data in the Phase III patients (approximately half) who had pulmonary hypertension secondary to chronic thromboembolic disease (CTED), collagen vascular disease, or appetite suppressants. The results for the 6 minute walk distance were not statistically significant for this secondary PH subgroup as a whole. However, we will assert that Iloprost Inhalation Solution should be approved for primary arterial hypertension (PAH) (which includes primary PH and secondary PH but excludes CTED) for the following reasons:

- CTED is a different pathophysiologic group, according to the most recent WHO classification system. In the Phase III study, these patients tended to be older with a longer duration of disease. The efficacy of vasodilators in this subgroup has never been shown in a controlled trial.

- The efficacy of iloprost for PAH (total patient group excluding CTED) is well supported by the Phase III data.

- Tracleer and Remodulin were both approved for pulmonary hypertension and not restricted to PPH despite having that group dominate the demographics.

In case of receiving the PPH indication alone, Exhale will conduct a post-marketing study to gain the PAH indication. Exhale's focus is to obtain agreement on the labeling strategy as early as possible.

## *CMC*

Drug substance will be manufactured and provided by Schering AG under a separate commercial supply agreement using a European-approved manufacturing procedure. Schering will file a DMF containing all CMC information, including drug product and all stability data that was filed in their

MAA. The drug product will also be manufactured by Schering in their Madrid facility through at least approval and launch. A US-based company has been identified and could be qualified as a second drug product manufacturer shortly after launch.

The IND will reference the Schering DMF for the drug substance and contain information drug product manufacturing procedures and specifications, along with aerosol characterization data obtained by Schering using the HaloLite and ProDose nebulizers. A 510k application has been filed by the manufacturer of the ProDose nebulizer and is expected to get approved by Oct. 2003.

### *Orphan application*

Exhale will file an Orphan Drug Designation Request (similar to that obtained for iloprost in the EU), which will support 7 years of marketing exclusivity.

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# Attachment 1 — Iloprost Clinical Plan

| Protocol Number/ Phase | Study Description | No. Subjects | Endpoints | Est. Cost | Target Dates for Start and Data Avail. | Status |
|---|---|---|---|---|---|---|
| Pilot Ventavis/Tracleer combination study | Iloprost add-on to Tracleer study | | Clinical effects: 6 minute walk distance and other useful variables, first hints for safety/tolerability | | | • Pilot study as basis for iloprost add-on study |
| E200-TBD | QT Interval Assessment (if needed) | N = ~120 | QT interval | $2.5M | Start Apr 04 Data Sep 04 | • Need for study contingent on FDA discussions at pre-IND meeting |
| E200-002 Phase II/III | Tracleer Add-on; Iloprost vs. Placebo added to Tracleer; 12 weeks Rx | N = 140 (75 per Rx) | 6 minute walk distance plus usual secondary endpoints; Echo/Doppler | $4.5M | Start Mar 04 Data Mar 05 | • Contingency study to serve as second pivotal if required by FDA<br>• Will provide important use data for U.S. marketing |
| E200-004 Phase III | Repeat Pivotal (Iloprost vs. Placebo); 12 weeks Rx | N=190 (95 per Rx) | 6 minute walk distance plus usual secondary endpoints | $5 M | Start Apr 04 Data Jan 06 | • Back-up to iloprost Add-on study, if FDA requires second pivotal |
| E200-TBD Phase II | Viagra Pilot; Iloprost frequency – 3X/day, 4X/day, 6X/day; 4 weeks Rx | N = 45 (15 per Rx) | 6 minute walk distance | $750K | Start TBD Data 9 mos | • Study start post NDA submission |
| E200-TBD Phase II | IPF pilot Iloprost vs. Placebo in addition to | N = 40 (20 per Rx) | Integrated 6 min walk with oxygen saturation | $750K | Start TBD Data 12 mos | • Study start post NDA submission |

| Protocol Number/ Phase | Study Description | No. Subjects | Endpoints | Est. Cost | Target Dates for Start and Data Avail. | Status |
|---|---|---|---|---|---|---|
| | standard care; 4 weeks Rx | | | | | |
| E200-TBD Phase III | Viagra confirmatory; Viagra plus Ilioprost at frequency from pilot study vs. Placebo; 12 weeks Rx | N = 140 (70 per Rx) | 6 min walk distance | $4M | Start TBD Data 20 mos | • Study contingent on data from pilot study |



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**Schedule 3 to**
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# Exhale Therapeutics
# Commercialization Plan for Ventavis® (Iloprost)

## Executive Summary

Ventavis will be positioned in the US as the preferred prostacyclin for the treatment of Pulmonary Arterial Hypertension (PAH) in a market that is projected to grow to over $750 million per annum by 2008. There is considerable enthusiasm among physicians and patients for Ventavis, to be used either alone or in combination with other agents, as an effective and safe inhaled prostacyclin to manage symptom control, improve exercise tolerance, improve the quality of life and potentially prolong the lives of those suffering from PAH.

Exhale will build a commercial team to conduct pre-launch market development activities and execute a launch campaign that will insure rapid adoption and success of Ventavis in the US. At launch, a "1-800-Ventavis Access Hotline" will provide reimbursement support and 24 hour Ventavis patient support. The Ventavis hotline and distribution will be managed via a closed distribution through specialty pharmacy partners, which will provide ongoing care for Ventavis patients.

Post Ventavis launch, Exhale will expand the PAH market opportunity through education by increasing the number of pulmonologists diagnosing and treating PAH patients, as well as encouraging other medical specialties to be involved in early diagnosis of PAH. The 5 year peak revenue forecast for Ventavis in the US is conservatively set at $105 million, requiring approximately 1,600 patients or 10% of the current US PAH patient base. Ventavis is poised for success in the US market.

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**Market Dynamics**

The US prevalence of PAH is approximately 50,000. Of these patients, approximately 25 % (12,500) have primary disease and 75 % (37,500) have secondary disease. The number of diagnosed and treated and patients at the beginning of 2003 was approximately 15,000. This number doubled in 2002 due to the availability of new therapies and pharmaceutical manufacturer sponsored education and promotion. Physicians diagnosing and treating PAH patients also increased. The number of physicians treating PAH patients is relatively small with 80 % of PAH patients being managed by less than 200 physicians ("high prescribers"). There are approximately 6,000 practicing pulmonologists in the U.S.

The majority (80%) of currently diagnosed and treated PAH patients are late stage (Class III/IV). However, the availability of new treatments and education are projected to improve early diagnosis and increase the diagnosed prevalence to nearly 22,000 patients by 2008. The current value of the US market for PAH is approximately $400 million in 2003, and is projected to grow to $750 million by 2008. Actelion, Tracleer (bosentan), is the only company with a dedicated field sales force, with over 40 representatives involved in education and promotion.

Combination therapy is becoming standard of care within the PAH market. Throughout their lifetime, following diagnosis, most PAH patients will be on a combination of anticoagulants, digoxin, diuretics, calcium channel blockers, endothelin antagonists, and prostacyclins. Most therapies for mild to moderate PAH patients are oral. However, the currently available prostacyclins, Flolan (epoprostenol) from GSK and Remodulin (treprostinil) from United Therapeutics require intravenous and subcutaneous administration respectively. These agents are therefore reserved for the more severe PAH patients.

The average cost per year for the branded agents is: Tracleer ($28,000), Remodulin ($55,000 – $80,000), and Flolan ($55,000-$80,000). Due to the orphan classification, the life threatening nature of PAH and the paucity of agents to treat the disease, reimbursement is favorable, with the majority patients having either commercial, federal, or state coverage for medications.

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**Exhale Sales Organization**

Exhale plans to launch Ventavis with a U.S. field based selling team of 12 pulmonary representatives, 1 sales director, and 1 national accounts manager. Each of the 12 pulmonary sales representatives will be responsible for approximately 16 "high prescribers" at launch, and additional "high potential" prescribers for PAH market development activity.

Exhale has conducted extensive analysis of the U.S. pulmonary market using IMS prescription data and ICD diagnosis codes (ProMetrics - Philadelphia, PA) for field sales based territory creation, alignment, and optimization. Exhale currently has market maximization maps by representative placement in the U.S. for the PAH market utilizing 4 scenarios: 12, 24, 36, and 48 field based representatives.

As Ventavis launches and market development activity expands the prescriber base for PAH therapies, Exhale will expand the field selling force in groups of 12 as needed to efficiently manage Rx growth, while minimizing disruption to the field selling effort.

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**Strategic Imperatives**

- 100% Pre-Launch Awareness
  - Pulmonologists
  - Cardiologists
  - PAH Patients
  - Payors

- Advocacy Support
  - Key Opinion Leader Support
  - PHA Support

- Universal Reimbursement Coverage
  - Private payors
  - State payors
  - Federal payors

- Patient-Friendly Product Support and Distribution
  - Ventavis "800" Access Hotline
  - Specialty Pharmacy Partner Distribution Network
    - Priority Health Care Pharmacy
    - Care Mark Pharmacy
    - Nova Factor Pharmacy

- Product Positioning:
  - "Ventavis represents an advance in treatment of patients with pulmonary arterial hypertension. The unsurpassed efficacy, pulmonary targeted delivery, ease of administration, and decreased systemic adverse events associated with systemically delivered prostacyclins make Ventavis the first line prostacylin for pulmonary arterial hypertension patients, as monotherapy or in combination with ETR Antagonists and/or PDE 5 Inhibitors"

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**Pre-Launch Tactics**

- Patient Awareness
  - PHA
  - Advocacy Development

- Conventions
  - CHEST Scientific Exhibit Booth
  - American Thoracic Society Scientific Exhibit Booth
  - American College of Cardiology Scientific Exhibit Booth
  - Pulmonary Hypertension Association Scientific Exhibit Booth

- Continuing Medical Education
  - Monograph on PAH and Emerging Therapies
  - Patient Education

- Key Opinion Leader Development
  - Education
  - Speaker Preparation and Training

- Reimbursement Coverage Initiatives
  - American Hospital Formulary Service Monograph
  - Commercial Payor Presentations
  - State and Federal Payor Presentations

- Specialty Pharmacy Distribution Network*
  - Priority Health Care / Caremark / NovaFactor
    - 800 Access Hotline
    - Reimbursement Assistance
    - Patient Training
    - 24 Hour Patient Care Assistance
    - Inventory Management
    - Data Management

- National Sales and Marketing Team Development
  - Chief Commercial Officer
    - Marketing Director
      - Marketing Manager
    - National Accounts Director
    - Sales Director
      - 12 Pulmonary Specialist Representatives

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**Launch Tactics**

- Ventavis Commercial Team Headcount
  - 3 Marketing and Management
  - 14 Sales and Management

- Conventions
  - CHEST Mail Drop at Physicians' hotel rooms (2003)
  - CHEST Scientific Promotional Booth (2004 and beyond)
  - American Thoracic Society Promotional Booth
  - American College of Cardiology Promotional Booth
  - Pulmonary Hypertension Association Booth

- Ventavis Promotional Pieces
  - Detail Aids
    - Sell Sheet
    - Slim Jim
    - Reprints
  - Journal Ads
    - CHEST
    - AJRCCM
    - JACC

- Continuing Medical Education
  - CHEST Meeting CME Symposia
  - ATS Meeting CME Symposia

- Ventavis National Consultants / Speaker Training Meetings
  - 100 Pulmonologists

- Ventavis Community Advisory Panel Programs
  - 250 Pulmonologists

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*Specialty pharmacies in the US such as Priority Healthcare, Novafactor, and Caremark currently manage patients on agents such as Flolan (GSK), Remodulin (United Therapeutics), and Tracleer (Actelion). These specialty pharmacies provide support to healthcare practitioners and also complete patient care including reimbursement services, disease specific training, product specific training, and ongoing support for patients under their care. In addition to improved care for patients on their respective pharmaceutical products, pharmaceutical manufacturers, like Exhale, also benefit from this type of closed distribution network through access to patient and physician specific data and through product inventory control. Many US pharmaceutical companies that distribute biologic agents with special storage needs or that sell to special patient populations use the services of specialty pharmacy distribution partners. For more information please refer to:
http://www.accredohealth.net/nova/
http://www.priorityhealthcare.com
http://www.rxpower.com/caremark.html

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**Revenue Forecast**

| Year | 2006 | 2007 | 2008 | 2009 |
|---|---|---|---|---|
| $ (millions) | $40 | $65 | $85 | $105 |
| Patients | 696 | 1,082 | 1,354 | 1,600 |

**Pre-Launch Development and Launch Year Expenses**

| Expense | Description | Expense |
|---|---|---|
| FTE (Head Count) | Sales and Marketing Staff | $3,800,000 |
| Conventions and Symposia | ATS, CHEST, ACC, PHA | $250,000 |
| Promotional Materials | Detail Aids, Journal Ads | $250,000 |
| CME | New Therapies in PAH | $100,000 |
| National Speaker Training Meetings | 100 MDs | $500,000 |
| Community Advisory Panel Meetings | 250 MDs | $250,000 |
| **Total** | | **$5,150,000** |

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Date: 17 Aug 2001

# Iloprost, pure (variant)

**ZK No. 00036374**

| | | | |
|---|---|---|---|
| Release: | Gabriele Kadenbach<br>sgd. | Responsible: | Dr. Moede<br>sgd. |

This Quality Specification takes effect on 01 Nov 2001.

| | |
|---|---|
| **Note:** | Caution: highly potent drug substance<br>Avoid any contamination<br>store at -18°C<br>Observe the safety data sheet (SKD No. 1038 in the Schering safety database. |
| Art. No. | 01645167 |
| This replaces: | Quality Specification of Testing Standard No 0040 g, issued 12 Sep 1991 (Iloprost, pure, Art No. 00288878)<br>Quality Specification No. 0040, issued 14 Aug 1991 (iloprost, reference standard)<br>Quality Specification (shelf-life) of Testing Standard No. S 0061 d, issued 16 Aug 1991 (Iloprost, pure, Art No. 00288878)<br>Quality Specification No. LL64E250<br>Quality Specification No. LL64EG10 (for Germany) |

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| | **Release** | **Shelf-life:** |
|---|---|---|
| Appearance: | oily substance | oily substance |
| Identification of iloprost: (HPLC 4) | positive | positive |
| Identification of iloprost: IR spectroscopy | matches IR reference spectrum | matches IR reference spectrum |
| Specific optical rotation: (polarimetry) | $[\alpha]_D^{20}$: +93° to +102°, calculated on the anhydrous and solvent-free basis | $[\alpha]_D^{20}$: +93° to +102°, calculated on the anhydrous and solvent-free basis |
| 2-propanol: (GC) | ≤ 0.1% | ≤ 0.1% |
| Methylene chloride: (GC) | ≤ 0.01% | ≤ 0.01% |
| Ethyl acetate: (GC) | ≤ 5.0% | ≤ 5.0% |
| Hexane: (GC) | ≤ 0.01% | ≤ 0.01% |
| Methyl-tert.-butyl ether: (GC) | ≤ 0.01% | ≤ 0.01% |
| Acetic acid: (HPLC 1) | ≤ 0.5% | ≤ 0.5% |
| Water: (Karl Fischer method, coulometry) | ≤ 2.0% | ≤ 2.0% |

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| | Release | Shelf-life: |
|---|---|---|
| Related substances/decomposition products of iloprost (except Z-isomers): (HPLC 2 and HPLC 3) | 15-oxo-iloprost ≤ 0.2%, 15ß-OH-iloprost ≤ 0.2%, iloprost-11-iloprost ester ≤ 0.2%, iloprost-15-iloprost ester ≤ 0.2%, iloprost-11-acetate ≤ 0.2%, iloprost-15-acetate ≤ 0.2%, other identified, single ≤ 0.2%, unidentified, single ≤ 0.2%, sum of unidentified ≤ 0.5%, sum of identified and unidentified ≤ 1.2% | 15-oxo-iloprost ≤ 0.2%, 15ß-OH-iloprost ≤ 0.2%, iloprost-11-iloprost ester ≤ 0.2%, iloprost-15-iloprost ester ≤ 0.2%, iloprost-11-acetate ≤ 0.2%, iloprost-15-acetate ≤ 0.2%, other identified, single ≤ 0.2%, unidentified, single ≤ 0.2%, sum of unidentified ≤ 1.5%, sum of identified and unidentified ≤ 2.0% |
| Z-isomers (ZK 00036375) (HPLC 4) | ≤ 2.0%, relative to iloprost | ≤ 2.0%, relative to iloprost |
| Isomer ratio of the E isomers: (HPLC 4) | methyl diastereomer E(4R): 52% to 58%, methyl diastereomer E(4S): 42% to 48% | methyl diastereomer E(4R): 52% to 58%, methyl diastereomer E(4S): 42% to 48% |
| Iloprost: (HPLC 4) | 95.0% to 102.0%, calculated on the anhydrous and solvent-free basis | 94.0% to 102.0%, calculated on the anhydrous and solvent-free basis |

**Test procedure(s):**

Conduct the tests as per Testing Standard No. LL64E150.

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Date: 08 Oct 2001

# Ilomedin-10, solution for nebulizer

**SH No.: L00401N**

| | | | |
|---|---|---|---|
| Release: | Dr. Maja Hertsch<br>sgd. | Responsible: | Dr. Moede<br>sgd. |

This Quality Specification takes effect on 01 Dec 2001.

This Quality Specification applies for:

Ilomedin-10, solution, 2.0 ml solution for inhalation, 3-ml glass ampul

| | |
|---|---|
| **Note:** | Caution: Highly potent medicinal product.<br>Observe the safety data sheet SKD No. 1038 for iloprost from the Schering safety database. |
| This replaces: | Quality Specification No. MP81E230. |

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| | **Release** | **Shelf-Life** |
|---|---|---|
| Appearance / visible particles: (visual test 1) | clear, free of particles | clear, free of particles |
| Identification of iloprost: (TLC) | positive | positive |
| Identification of iloprost: (HPLC 3) | positive | positive |
| Identification of trometamol: (TLC) | positive | positive |
| Identification of sodium: (flame coloration) | positive | positive |
| pH: (potentiometry) | 7.3 to 8.5 | 7.3 to 8.5 |
| Filling volume: (volumetry) | $\overline{V}$ : ≥ 2.00 and ≤ 2.30 ml | $\overline{V}$ : ≥ 2.00 and ≤ 2.30 ml |
| Color: (visual test 2) | not more intense in color than reference solution Y5 or BY5 | not more intense in color than reference solution Y5 or BY5 |
| Related substances / decomposition products of iloprost (except Z-isomers): (HPLC 1 and HPLC 2) | 15-oxo-iloprost ≤ 0.2%, 15ß-OH-iloprost ≤ 0.2%, other identified, single ≤ 0.2%, unidentified, single ≤ 0.5%, Σ sum of unidentified ≤ 1.5%, sum of identified and unidentified ≤ 2.0% | 15-oxo-iloprost ≤ 0.2%, 15ß-OH-iloprost ≤ 0.2%, other identified, single ≤ 0.2%, unidentified, single ≤ 0.5%, Σ sum of unidentified ≤ 1.5%, sum of identified and unidentified ≤ 2.0% |
| Iloprost: (HPLC 3) | 9.50 to 10.50 µg per ml solution (95% to 105%) | 9.50 to 10.50 µg per ml solution (95% to 105%) |
| Sterility: (membrane filtration) | sterile; no viable microorganisms detectable | sterile; no viable microorganisms detectable |

**Test procedures:**

Conduct the tests as per Testing Standard No. MP81E130.

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