IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF ILLINOIS
EASTERN DIVISION

COBALT PHARMACEUTICALS INC. and COBALT LABORATORIES INC.,

Plaintiffs,

v.

BAYER AKTIENGESELLSCHAFT and BAYER PHARMACEUTICALS CORP.,

Defendants.

07CV5875
JUDGE CASTILLO
MAG. JUDGE VALDEZ

COMPLAINT FOR DECLARATORY JUDGMENT

Plaintiffs Cobalt Pharmaceuticals Inc. and Cobalt Laboratories Inc. (collectively "Cobalt"), for their complaint against Bayer Aktiengesellschaft ("Bayer AG") and Bayer Pharmaceuticals Corporation (collectively, "Bayer"), allege as follows:

Nature Of The Action

1. Cobalt brings—and is entitled by statute to maintain—this action for declaratory judgment of patent non-infringement and invalidity under, *inter alia*, the Declaratory Judgment Act and 21 U.S.C. § 355(j)(5)(C)(i), which is part of the Hatch-Waxman Amendments to the Federal Food, Drug, and Cosmetic Act ("FFDCA"), as amended by Title XI of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Pub. L. No. 108-173, 117 Stat. 2066 (2003) ("MMA").

2. This action arises out of, *inter alia*, Cobalt's submission of an Abbreviated New Drug Application ("ANDA") to the U.S. Food and Drug Administration ("FDA") seeking approval to market a generic version of Bayer's brand-name drug Precose®, known generically as acarbose.

3. Bayer purports to own U.S. Patent No. 4,904,769 ("the '769 patent"), a true and accurate copy of which is attached hereto as Exhibit A. Upon submission by Bayer, the '769 patent was listed in FDA's list of *Approved Drug Products with Therapeutic Equivalents Evaluations*, more commonly known as the "Orange Book." As a consequence of such listing, Bayer has affirmatively represented to the world that the '769 patent claims the approved drug, Precose®, or a method of using that drug, and that a claim for patent infringement could reasonably be asserted against any generic ANDA applicant, including Cobalt, attempting to market a generic acarbose product before patent expiration. Moreover, Bayer has enforced and continues to vigorously enforce its intellectual property rights against other generic pharmaceutical companies.

4. Cobalt has designed around the '769 patent with its proposed generic acarbose ANDA product and so, as required by statute, has certified to FDA that Cobalt's product will not infringe the '769 patent and has further notified Bayer of the legal and factual bases for that certification. Cobalt's submission of an ANDA containing a so-called "paragraph IV" certification to the '769 patent constitutes an artificial act of patent infringement. This regulatory submission created the necessary case or controversy and subject matter jurisdiction for Bayer to sue Cobalt for patent infringement. It likewise created the necessary case or controversy for Cobalt to file and maintain an action for declaratory judgment of patent non-infringement and invalidity.

5. There is an actual, substantial, and continuing justiciable case and controversy between Cobalt and Bayer regarding infringement and validity of the '769 patent, over which this Court can and should exercise jurisdiction and declare the rights of the parties.

6. Cobalt is entitled by law to bring and maintain this action for declaratory judgment of patent non-infringement and invalidity under the Declaratory Judgment Act and the MMA where, as here, Bayer did not sue Cobalt within 45 days of receipt of Cobalt's notice of paragraph IV certification to the '769 patent, and Cobalt has offered Bayer an Offer of Confidential Access to Cobalt's ANDA for generic acarbose tablets.

7. Cobalt is entitled to a judicial declaration that the manufacture, sale, offer for sale, use, or importation of Cobalt's proposed generic acarbose product does not and will not infringe the '769 patent and that such patent is invalid.

Parties

8. Plaintiff Cobalt Pharmaceuticals Inc. is a corporation organized and existing under the laws of Canada and having a place of business at 6500 Kitimat Road, Mississauga, Ontario, Canada L5N 2B8.

9. Plaintiff Cobalt Laboratories Inc. is a corporation organized and existing under the laws of Delaware and having a place of business at 24840 South Tamiami Trail, Bonita Springs, FL 34134.

10. On information and belief, Defendant Bayer AG is a corporation organized under the laws of the Federal Republic of Germany, with a place of business at D-51368 Leverkusen, Germany. On information and belief, Defendant Bayer AG, through its various agents, affiliates, representatives, subsidiaries and/or alter egos, develops, manufactures, and sells pharmaceutical products throughout the world, including in the United States and in this District. On information and belief, Bayer AG also allegedly owns United States patents that purport to cover pharmaceutical products sold in the United States and in this District, and from which Bayer AG derives substantial revenue exceeding $5 billion in the United States alone in 2006.

11. On information and belief, Defendant Bayer Pharmaceuticals Corporation is a corporation organized under the laws of the State of Indiana, with a place of business at 400 Morgan Lane, West Haven, Connecticut 06516. On information and belief, Bayer Pharmaceuticals Corporation is the agent, affiliate, representative, subsidiary and/or alter ego of, and/or acts in concert with, Bayer AG, for purposes of marketing, distributing, and selling patented pharmaceutical products within the United States and in this District on behalf of Bayer AG, and from which Bayer AG generates billions of dollars in yearly revenue.

Jurisdiction and Venue

12. This action arises under, *inter alia*, the Patent Laws of the United States, 35 U.S.C. § 1 *et seq.*; the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202; and the MMA (21 U.S.C. § 355(j)(5)(C)(i) and 35 U.S.C. § 271(e)(5)).

13. This Court has original jurisdiction over the subject matter of this action under 28 U.S.C. §§ 1331 and 1338(a), because it involves substantial claims arising under the United States Patent Act, 35 U.S.C. § 1 *et seq.*; under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202, because it is an actual controversy concerning the infringement and validity of the patent-in-suit; and under the MMA (21 U.S.C. § 355(j)(5)(C)(i) and 35 U.S.C. § 271(e)(5)), because Congress has directed that district courts maintain and exercise jurisdiction in such cases.

14. There exists a substantial and continuing actual, justiciable case or controversy between Cobalt and Bayer regarding infringement and validity of the '769 patent.

15. This Court can and should declare the rights and legal relations of the parties regarding non-infringement of the '769 patent pursuant to, *inter alia*, the Declaratory Judgment

Act, 28 U.S.C. §§ 2201 and 2202, and the MMA (21 U.S.C. § 355(j)(5)(C)(i) and 35 U.S.C. § 271(e)(5)).

16. Cobalt has the statutory right to bring and maintain this declaratory judgment action under 21 U.S.C. § 355(j)(5)(C)(i). This Court can and should exercise its declaratory judgment jurisdiction over Cobalt's claims pursuant to 35 U.S.C. § 271(e)(5).

17. This Court has personal jurisdiction over Bayer AG and Bayer Pharmaceuticals Corporation because both conduct substantial business in, and have regular and systematic contact with, this District.

18. Venue is proper in this District under 28 U.S.C. §§ 1391(b) and 1400(b).

Background

I. Statutory Scheme For Approval Of New And Generic Drugs.

19. The approval of new and generic drugs is governed by the applicable provisions of the FFDCA, 21 U.S.C. §§ 301 *et seq.*, as amended by the Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (1984) (commonly known as the "Hatch-Waxman Amendments" or "Hatch-Waxman"), and subsequently amended by the MMA (codified as amended in relevant part at 21 U.S.C. § 355 and 35 U.S.C. § 271).

A. New drugs and patent listing requirements.

20. Before marketing an original new drug in the United States, the FFDCA, as amended by Hatch-Waxman and the MMA, requires that an applicant submit, and that FDA approve, a new drug application ("NDA") under 21 U.S.C. § 355(b). The NDA must include, *inter alia*, technical data on the composition of the drug, the means for manufacturing it, clinical trial results to establish the safety and efficacy of the drug, and labeling relating to the use of the drug for which approval is requested.

21. An NDA applicant is required, within its NDA, to submit information (*e.g.*, the patent number and expiration date) regarding each patent that claims the drug or method of using the drug that is the subject of the NDA and for which a claim of patent infringement could reasonably be asserted if a person not licensed by the patent owner engaged in the manufacture, use, or sale of the drug product. 21 U.S.C. § 355(b)(1); *see also id.* § 355(c)(2).

22. FDA publishes patent information submitted by an NDA-holder in the Patent and Exclusivity Information Addendum of FDA's publication, *Approved Drug Products with Therapeutic Equivalence Evaluations* (commonly known as the "Orange Book").

23. By filing an NDA and submitting a patent for listing in the Orange Book, the NDA-holder/patent owner, by law, necessarily maintains that the listed patent claims the approved NDA drug, or a method of using that drug, and that an infringement suit could reasonably be asserted against anyone who engages in the manufacture, use, or sale of the drug, and, in particular, against any company that is seeking to make a generic bioequivalent of the NDA drug before patent expiration.

24. Thus, the NDA-holder/patent owner necessarily puts all prospective generic ANDA applicants on notice that a suit for infringement can and will be asserted against any ANDA applicant that attempts to seek approval for and market a generic version of the NDA drug before patent expiration.

B. Generic drugs and patent certification requirements.

25. The FFDCA, as amended by Hatch-Waxman and the MMA, provides for an ANDA approval process that enables generic pharmaceutical manufacturers to obtain regulatory approval of lower-cost generic versions of previously approved brand-name or NDA drugs on an expedited basis, thereby benefiting the U.S. health-care system and American consumers. The

ANDA process is a streamlined version of the full NDA procedure and results in a generic drug product that is normally marketed under the chemical name of the active drug ingredient.

26. An applicant may invoke this procedure for expedited FDA approval of a generic version of an already-approved NDA drug by submitting an ANDA to FDA under 21 U.S.C. § 355(j).

27. Instead of repeating the clinical studies of safety and efficacy conducted for the previously-approved NDA drug, a generic applicant submitting an ANDA is required to establish, among other details, that its proposed generic product is bioequivalent to the already-approved NDA drug (*i.e.*, has no significant difference in rate and extent of absorption) and that it has the same active ingredient, dosage form, dosage strength, route of administration, and labeling (with certain exceptions) as the approved NDA drug. 21 U.S.C. § 355(j)(2)(A).

28. An ANDA applicant also is required to address each patent listed in the Orange Book in connection with the approved NDA drug. In particular, Hatch-Waxman requires an ANDA applicant to submit one of four types of patent certifications: (I) that the NDA-holder/patent owner has not submitted any patent information to FDA; (II) that the listed patent has expired; (III) that the patent will expire on a future date, and that the generic applicant will not market its product until after the expiration date; or, (IV) that the listed patent is invalid and/or will not be infringed by the manufacture, use, or sale of the generic drug for which the ANDA is submitted (commonly referred to as a "paragraph IV certification"). 21 U.S.C. §§ 355(j)(2)(A)(vii)(I)-(IV). This last type of certification, a paragraph IV certification, signifies that the generic ANDA applicant intends to market its generic product prior to expiration of the subject patent. Such certification constitutes an act of patent infringement. 35 U.S.C. § 271(e).

29. When an ANDA applicant submits a paragraph IV certification for a listed patent, the generic applicant must notify the NDA-holder/patent owner that it has filed an ANDA to obtain regulatory approval of a generic version of the NDA drug, and that the ANDA contains a paragraph IV certification for a listed patent (indicating that the ANDA applicant intends to market its generic product before expiration of the listed patent). 21 U.S.C. § 355(j)(2)(B). This notice must contain a detailed statement of the factual and legal bases for the ANDA applicant's certification that the listed patent is invalid and/or will not be infringed by the manufacture, use, or sale of the generic applicant's generic drug product. 21 U.S.C. § 355(j)(2)(B)(iv).

30. The submission of a paragraph IV certification has two important consequences.

31. First, an applicant that is first to submit an ANDA containing a paragraph IV certification for a listed patent is entitled to 180 days of generic market exclusivity during which no other ANDA for that drug product will be approved. 21 U.S.C. § 355(j)(5)(B)(iv).

32. Second, the submission of a paragraph IV certification for a listed patent constitutes an act of infringement that creates the necessary case or controversy and subject matter jurisdiction to enable an NDA-holder/patent owner to file, and a district court to resolve, an action for patent infringement—before the generic drug is actually made, used, or sold—to determine whether the generic drug, if marketed and sold in accordance with the ANDA, would infringe the relevant patent.

33. The submission of a paragraph IV certification likewise creates the necessary case or controversy and subject matter jurisdiction for an ANDA applicant to file a declaratory judgment action against the NDA-holder/patent owner if the ANDA applicant is not sued within the applicable 45-day period, as set forth below.

34. Upon receiving notice of a paragraph IV certification for a listed patent submitted by an ANDA applicant, the NDA-holder/patent owner may file suit for infringement of the listed patent under 35 U.S.C. § 271(e)(2)(A) within 45 days of receiving such notification. Such a suit automatically delays FDA from issuing final approval of the ANDA for up to thirty (30) months. 21 U.S.C. § 355(j)(5)(B)(iii). An ANDA applicant is statutorily prohibited from seeking a declaratory judgment during the 45-day period in which the NDA-holder/patent owner may bring suit after receiving notification of the ANDA and paragraph IV certification. *Id.*

35. If the NDA-holder/patent owner does not file such a suit, the ANDA applicant can file and maintain a suit for declaratory judgment against the NDA-holder/patent owner to obtain patent certainty. Indeed, as explained below, Congress explicitly mandated that an ANDA-filer is entitled to maintain a declaratory judgment action when it is not sued. 21 U.S.C. § 355(j)(5)(C).

36. Congress enacted Hatch-Waxman and the ANDA approval process in order to expedite the marketing of lower-priced generic drug products. Congress intended that the generic manufacturing and marketing of a drug should be allowed as soon as it is determined that the particular generic drug does not violate patent rights.

II. Congress Explicitly Mandated That An ANDA-Filer May Bring And Maintain A Declaratory Judgment Action When The Brand Company Does Not Bring An Infringement Action.

37. On December 8, 2003, the MMA was signed into law. Title XI of the MMA, labeled "Access to Affordable Pharmaceuticals," amended provisions of the FFDCA and, in particular, Hatch-Waxman.

38. Under the MMA, an ANDA applicant who has filed a paragraph IV certification is statutorily entitled to institute and maintain an action for declaratory judgment against an

NDA-holder/patent owner if: (1) the 45-day period has passed since notice of the paragraph IV certification was received; (2) neither the patent owner nor the NDA-holder/patent owner brought an action for infringement of the patent within the 45-day period; and (3) the notice of paragraph IV certification contains an Offer of Confidential Access to the ANDA. 21 U.S.C. §§ 355(j)(5)(C)(i)(I)(aa)-(cc).

39. Once these three conditions are met, the MMA specifically and unequivocally provides that an ANDA applicant "may, in accordance with section 2201 of Title 28 [of the United States Code] bring a civil action under such section against the owner or holder referred to in such subclause . . . for a declaratory judgment that the patent is invalid or will not be infringed by the drug for which the applicant seeks approval . . . ." 21 U.S.C. § 355(j)(5)(C)(i)(II).

40. An ANDA applicant may exercise its right to file and maintain a declaratory judgment action under the MMA regardless of whether or not the Offer of Confidential Access to Application is accepted.

41. The new declaratory judgment provision contained in the MMA, Section 1101 of the MMA, 117 Stat. 2066, 2454-2456, applies to all ANDAs pending on or after December 8, 2003, which includes these proceedings.

42. Congress' intent in amending 21 U.S.C. § 355(j)(5)(C)(i) and 35 U.S.C. § 271(e)(5) was to extend to ANDA applicants, like Cobalt here, the right to file and maintain a declaratory judgment action for patent non-infringement and/or invalidity against an NDA-holder/patent owner, and grant the court subject matter jurisdiction in such an action.

III. The Patent-In-Suit.

43. On or about February 27, 1990, the U.S. Patent and Trademark Office ("PTO") issued the '769 patent, entitled "Highly Pure Acarbose," to Erich Rauenbusch.

44. Bayer purports and claims to own the '769 patent.

45. Bayer purports and claims to have the right to enforce the '769 patent.

IV. Bayer's Precose® (Acarbose).

46. Bayer is the holder of approved NDA No. 20-482 for acarbose tablets, which are sold under the brand name Precose®.

47. Precose® (acarbose) is indicated for, among other things, the treatment of hyperglycemia in patients afflicted with type-2 diabetes mellitus.

48. FDA approved Precose® in 1995. Today, Precose® remains the only acarbose tablet product on the market.

49. Bayer purports and claims to be the owner of the '769 patent, the term of which expires on or about September 6, 2009, according to FDA's Orange Book.

50. Bayer submitted information regarding the '769 patent to FDA for listing in the Orange Book. By virtue of that submission, FDA listed the '769 patent in the Orange Book in connection with Bayer's approved NDA for Precose® (acarbose) tablets.

51. By listing the '769 patent in the Orange Book, Bayer has affirmatively represented to the world, that the '769 patent claims Precose® (acarbose) tablets, or a method of using that drug, and that an infringement suit could reasonably be asserted against any generic ANDA applicant, including Cobalt, that attempts to seek approval for, and market, a generic version of Precose® before patent expiration.

52. The listing of the '769 patent in the Orange Book alone objectively creates the necessary case or controversy and subject matter jurisdiction for an ANDA-filer to file and maintain a declaratory judgment action if it is not sued by Bayer within the requisite 45-day period.

V. Cobalt's ANDA For Acarbose.

53. Cobalt has submitted an ANDA to FDA seeking approval to market a generic version of Precose® (acarbose) tablets in 25 mg, 50 mg, and 100 mg strengths for the treatment of hyperglycemia in individuals with type-2 diabetes mellitus.

54. Cobalt devoted considerable resources researching, developing, and testing its generic acarbose product, all toward compiling the information necessary to submit its ANDA for generic acarbose tablets.

55. Bayer submitted the '769 patent to FDA for listing in the Orange Book prior to the filing of Cobalt's ANDA for generic acarbose tablets. By law, Cobalt was required to include in its ANDA a certification to the '769 patent.

56. Cobalt ANDA, as originally filed, contains a paragraph IV certification to the '769 patent, stating that the '769 patent will not be infringed by the manufacture, use, offer for sale, sale, or importation of Cobalt's generic acarbose tablets and/or that the '769 patent is invalid. This certification signified that Cobalt intends to market and commercialize its generic acarbose product prior to the expiration of the '769 patent.

57. Cobalt's ANDA is substantially complete and was accepted for filing by FDA.

58. Cobalt intends, and is prepared, to market its generic acarbose product before expiration of the '769 patent.

59. In accordance with 21 U.S.C. § 355(j)(2)(B), Cobalt provided Bayer with notice that it submitted ANDA and a paragraph IV certification to the '769 patent. This notice included a detailed statement setting forth the factual and legal bases why the '769 patent will not be infringed by the manufacture, use, offer for sale, sale, or importation of Cobalt's generic acarbose tablets.

60. Upon receipt of Cobalt's notice of paragraph IV certification to the '769 patent, Bayer did not sue Cobalt within the 45-day period for instituting an infringement suit under 21 U.S.C. § 271(e).

VI. Cobalt's Offer Of Confidential Access To Application.

61. Cobalt—by letter and as required under 21 U.S.C. § 355(j)(5)(C)—extended to Bayer an Offer of Confidential Access to Application to access certain information in Cobalt's ANDA for acarbose tablets.

62. By providing this Offer of Confidential Access to Application, and because Bayer did not sue Cobalt within 45 days of receipt of Cobalt's notice of paragraph IV certification, Cobalt is statutorily entitled to file and maintain a declaratory judgment action against Bayer under 28 U.S.C. §§ 2201 and 2202, pursuant to 21 U.S.C. § 355(j)(5)(C).

VII. Bayer's Attempt to Delist The '769 Patent From FDA's Orange Book.

63. On information and belief, Bayer has, without justification, attempted to remove the '769 patent from FDA's Orange Book, which removal could deprive Cobalt of any marketing exclusivity Cobalt may be entitled pursuant to the filing of its ANDA for generic acarbose tablets.

64. Bayer cannot lawfully remove the '769 patent from the Orange Book, *inter alia*, in light of marketing exclusivity that may attach to the filing of Cobalt's ANDA.

VIII. There Is A Substantial And Continuing Justiciable Controversy Between Cobalt And Bayer Regarding The '769 Patent.

65. By preparing and filing Cobalt's ANDA No. 77-532, Cobalt has substantially prepared to commercialize generic acarbose tablets in the United States. Cobalt is prepared to begin commercialization of its competing generic product upon issuance of final FDA approval.

66. By submitting its ANDA to commercialize generic acarbose tablets before the expiration of the '769 patent, as well as submitting a paragraph IV certification to said patent, Cobalt has committed an artificial act of patent infringement sufficient to create case or controversy jurisdiction pursuant to 35 U.S.C. § 271(e)(2) and Article III of the Constitution.

67. Bayer's listing of the '769 patent and Cobalt's paragraph IV certification to that patent satisfy Article III of the Constitution by creating the necessary case or controversy between Bayer and Cobalt regarding infringement of the '769 patent.

68. To avoid legal uncertainty, to protect its substantial investment, and to protect its anticipated future investments in its manufacturing process for generic acarbose tablets, Cobalt has initiated this action and is entitled to a declaration of the rights of the parties with respect to the '769 patent.

COUNT I
(Declaratory Judgment of Non-Infringement of the '769 Patent)

69. Cobalt repeats and incorporates by reference the allegations contained in paragraphs 1 through 68 of its Complaint as though fully set forth herein.

70. There is an actual, substantial, and continuing justiciable case or controversy between Cobalt and Bayer regarding infringement of the '769 patent.

71. The manufacture, use, sale, offer for sale, or importation of the acarbose tablets that are the subject of Cobalt's ANDA does not and will not infringe (either literally or under the doctrine of equivalents) any valid and enforceable claim of the '769 patent.

72. Cobalt is entitled to a judicial declaration that the manufacture, use, sale, offer for sale, or importation of the acarbose tablets that are the subject of Cobalt's ANDA does not and will not infringe (either literally or under the doctrine of equivalents) any valid and enforceable claim of the '769 patent.

COUNT II
(Declaratory Judgment of Invalidity of the '769 Patent)

73. Cobalt repeats and incorporates by reference the allegations contained in paragraphs 1 through 72 of its Complaint as though fully set forth herein.

74. There is an actual, substantial, and continuing justiciable case or controversy between Cobalt and Bayer regarding the validity of the '769 patent.

75. The claims of the '769 patent are invalid for failure to satisfy one or more conditions for patentability under the patent laws.

76. Cobalt is entitled to a judicial declaration that the claims of the '769 patent are invalid.

COUNT III
(Declaratory Judgment Precluding the Delisting of the '769 Patent from FDA's Orange Book)

77. Cobalt repeats and incorporates by reference the allegations contained in paragraphs 1 through 76 of its Complaint as though fully set forth herein.

78. There exists an actual, substantial, and continuing justiciable case or controversy between Cobalt and Bayer regarding the listing of the '769 patent in FDA's Orange Book.

79. Pursuant to statute, Bayer duly submitted the '769 patent for listing in FDA's Orange Book, and certified to FDA that the '769 patent claims the drug (acarbose) or method of using the drug that is the subject of the NDA (acarbose) and for which a claim of patent infringement could reasonably be asserted if a person not licensed by the patent owner engaged

in the manufacture, use, or sale of the drug product. 21 U.S.C. § 355(b)(1); *see also id.* § 355(c)(2).

80. As a consequence of that listing, Cobalt undertook the risk and expense of challenging the '769 patent by submitting a paragraph IV certification to the '769 patent.

81. Because Cobalt was the first generic applicant to submit an ANDA for acarbose tablets with a paragraph IV certification to the '769 patent, Cobalt is entitled to the 180-day generic marketing exclusivity for acarbose tablets.

82. On in formation and belief, on or about April 16, 2007, Bayer purportedly requested that FDA "delist" the '769 patent as to Precose®.

83. Such delisting, if permitted, could deprive Cobalt of the 180-day exclusivity to which it is lawfully entitled under the FFDCA.

84. By law, Bayer is not permitted to delist the '769 patent because Cobalt has submitted a paragraph IV certification that entitles Cobalt to the 180-day exclusivity.

85. Cobalt is entitled to a judicial declaration that the Bayer's delisting request is improper and that Bayer may not remove the '769 patent from the Orange Book until after the natural expiration of Cobalt's 180-day exclusivity.

WHEREFORE, Cobalt respectfully prays for judgment in its favor and against Bayer Aktiengesellschaft and Bayer Pharmaceuticals Corporation as follows:

(a) Declaring that the manufacture, use, sale, offer for sale, or importation of the acarbose tablets that are the subject of Cobalt's ANDA does not and will not infringe (either literally or under the doctrine of equivalents) any valid, enforceable and unexpired claim of the '769 patent;

(b) Declaring that the claims of the '769 patent are invalid;

(c) Declaring that Bayer's "delisting" request for the '769 patent is improper and that Bayer may not remove the '769 patent from the Orange Book; and

(d) Awarding Cobalt such other and further relief as the Court may deem just and proper.

Dated: October 17, 2007.

Respectfully submitted,

COBALT PHARMACEUTICALS INC. and
COBALT LABORATORIES INC.

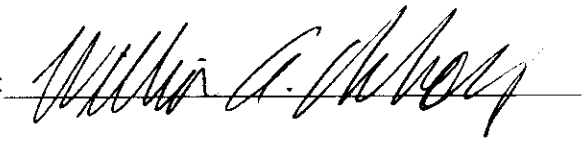
By: 

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EXHIBIT A

United States Patent [19]

Rauenbusch

[11] **Patent Number: 4,904,769**

[45] **Date of Patent: Feb. 27, 1990**

[54] **HIGHLY PURE ACARBOSE**

[75] Inventor: **Erich Rauenbusch**, Wuppertal, Fed. Rep. of Germany

[73] Assignee: **Bayer Aktiengesellschaft**, Leverkusen, Fed. Rep. of Germany

[21] Appl. No.: **940,713**

[22] Filed: **Dec. 11, 1986**

[30] **Foreign Application Priority Data**

Dec. 13, 1985 [DE] Fed. Rep. of Germany 3543999

[51] **Int. Cl.**[4] **C07H 3/08; A61K 31/70**

[52] **U.S. Cl.** **536/17.2**

[58] **Field of Search** 536/127, 55.3, 18.7, 536/25, 17.2; 514/23, 54

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,062,950	12/1977	Frommer	536/18.7
4,174,439	11/1979	Rauenbusch	536/55.3
4,526,784	7/1985	Heiker	536/18.5
4,536,493	8/1985	Junge	536/17.9
4,666,776	6/1987	Lange	528/304

Primary Examiner—Ronald W. Griffin

Attorney, Agent, or Firm—Sprung, Horn, Kramer & Woods

[57] **ABSTRACT**

A purified acarbose which contains less than 10% by weight of sugar-like secondary components is obtained by column chromatograph of a solution of prepurified acarbose with a pH 4 to 7. The column contains as a packing material a weakly acid cation exchanger which has carboxyl groups and is based on dextran, agarose and cellulose or exchangers which are derived from the latter with the addition of polyamide.

11 Claims, 1 Drawing Sheet

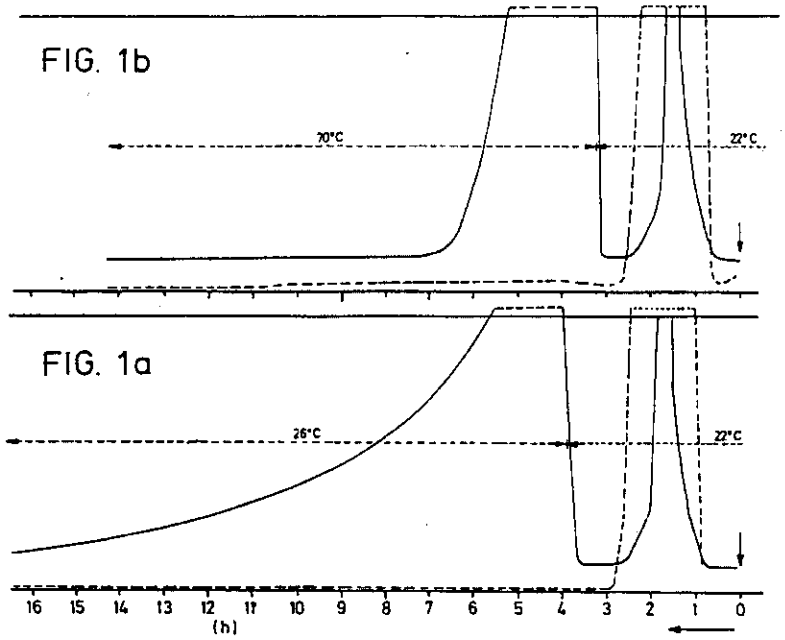


FIG. 1b
70°C
22°C
FIG. 1a
26°C
22°C
16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0
(h)

HIGHLY PURE ACARBOSE

The invention relates to highly pure acarbose, to a process for its preparation and to its use in and for the preparation of medicaments.

Acarbose is an inhibitor of the saccharase enzyme complex of the human small intestine and is used in medicine for the treatment of diabetes.

Acarbose is O-4,6-didesoxy-4-[(1S,4R,5S,6S)-4,5,6-trihydroxy-3-(hydroxymethyl)-2-cyclohexen-1-yl amino]-α-D-glucopyranosyl-(1→4)-O-α-D-glucopyranosyl(1→4)-D-glucopyranose.

The inhibitor is obtained by fermentation of Actinoplanes species (see German Patent Specification 2,209,832, German Patent Specification 2,209,834, German Patent Specification 2,064,092) and has to be isolated from the fermentation broth. Purification processes have been described for this purpose (see German Patent Specification 2,347,782 and German Patent Specification 2,719,912).

In these purification processes, the acarbose is bound to strongly acid cation exchangers and is eluted with salt solutions or, mainly, with dilute acid. The acarbose obtained after neutralization with anion exchangers has a content of 78–88% of acarbose in the dry matter (HPLC method). These preparations still contain impurities in the form of about 10–15% of secondary components giving color reactions for sugars, 1–4% of ash and some coloring constituents. Even higher degrees of purity are necessary for use in human medicine, but, with knowledge of the abovementioned state of the art, these cannot be achieved simply by replacing the strongly acid cation exchangers by weakly acid cation exchangers, since the latter exchangers do not bind the very weakly basic acarbose adequately and it emerges unpurified in the effluent.

It has now been found, surprisingly, that acarbose which has been prepurified in accordance with the state of the art can, after all, be purified, in one step, from residual salts, coloring matter and the sugar-containing basic secondary components on very particular weakly acid hydrophilic cation exchangers in narrowly restricted pH ranges. The content of acarbose after this increases to at least 90% by weight, preferably to 95–98% by weight and more, the sulphated ash decreases to 0–0.5%, and the sugar-like secondary components diminish to less than 10% by weight, preferably 2–5% by weight and less.

Hence the invention relates to acarbose containing less than 10% by weight of sugar-like secondary components.

Acarbose containing 2 to 5% by weight of sugar-like secondary components is preferred, and the invention particularly preferably relates to acarbose containing less than 2% by weight of sugar-like secondary components.

For the preparation of the acarbose according to the invention using this specific type of chromatography, use is made of a solution of prepurified acarbose obtained by, for example, the process which has been described in German Patent Specification 2,719,912. This solution is applied to a column in a concentration of 1–20% and at a pH of 3.5–6.5, preferably 4.0–5.5. Suitable as packing are weakly acid cation exchangers which have carboxyl groups and are based on dextran, agarose and cellulose, or exchangers derived from these components with the addition of polyacrylamides, such as, for example, the commercially available types CM-Sephadex ®, CM-Sepharose ®, CM-Cellulose ®, CM-Cellufine ®, inter alia. Remarkably, the commercially available weakly acid exchangers which contain carboxyl groups and are based on polystyrene, polyacrylic acid or polymethacrylic acid cannot be used for this purification.

Accordingly, the invention furthermore relates to a process for the preparation of acarbose which contains less than 10% by weight of sugar-like secondary components, which is characterized in that prepurified acarbose in a 1 to 20% by weight aqueous solution with a pH of 4 to 7 is applied to a column which contains as packing material weakly acid cation exchangers which have carboxyl groups and are based on dextran, agarose and cellulose or exchangers which are derived from the latter with the addition of polyamide, the column is eluted exclusively with degassed, distilled water and, where appropriate, the acarbose is isolated from the eluate in customary manner.

The volume of the aqueous solution of prepurified acarbose which is applied to the column is restricted. The maximum volume which can be applied corresponds to the filling volume of the column, and preferably less than 60% of the column volume is applied. For this reason, in order to purify a preparative amount of acarbose, the concentrations used are not too low. The concentration is limited in the upward direction by the fact that the ion exchangers best suited for the purification are prone to shrinkage. Concentrations of 7–20% are preferred.

After the application, the column is eluted exclusively with degassed, distilled water. During this there is elution first of salts, neutral sugars and coloring concomitants, and subsequently, more slowly, the acarbose in a relatively broad peak. The sugar-like basic secondary components remain on the column and are not removed until it is regenerated. Thus the acarbose is in the form of a purely aqueous solution at a pH of 6–7 and can be concentrated in a customary manner and dried in a highly pure form.

The behaviour of acarbose on the column depends on several factors of which, surprisingly, those crucial for the practical procedure are the pH of equilibration of the column packing and the temperature during the chromatography.

Alteration of the pH of the column packing alters the capacity and the elution behaviour of acarbose. At neutral pH values, the slowing of acarbose compared with the salts is insufficient, and separation is inadequate. At acid pH values around 3.5–4, the acarbose is greatly slowed down and is only incompletely eluted with water. Carrying out the process in practice requires an optimization of the pH for each particular exchanger. In generaly, pH values between 4.3 and 5.0 are suitable. The pH values which are to be preferred are around 4.6 with high loading and around 4.9 with low loading and maximum yield.

The second important factor is the temperature. The lower the temperature the more strongly acarbose is held back by the ion exchanger, but the greater the capacity of the column the slower the elution of acarbose. This means that an asymmetric peak is obtained and the volume of the acarbose fraction is very large. Hence it is expedient to apply the substance at, or even below, room temperature, and, after the elution of the salts and colouring constituents, to heat the column to

about 25° to 90° C., preferably to 40°–70° C. This results ih rapid elution of the acarbose with good yields.

Buffers are used for the regeneration of the ion exchanger, for example sodium acetate buffer in the pH range necessary for the equilibration and in a concentration of 0.1 to 0.5M. Thereafter, the column is washed with pure, degassed water until the conductivity has fallen to about 0.1 mS/cm (room temperature).

In the depictions of the separations, the time is plotted on the abscissa in hours against the refractive index of the eluate and its conductivity (broken line). In addition, the temperature marking is indicated.

The content of acarbose in the final product was determined, in particular, by liquid chromatography (HPLC method) and related to the anhydrous substance.

The method was carried out as follows:	
	High-pressure liquid chromatograph with thermostated column oven, Stainless steel metal column Length: 25 cm internal diameter: 4 mm packed with: aminophase 5 µm (for example LiChrosorb NH_2, E. Merck, or Hypersil APS, Shandon)
Reagents	1. Acetonitrile (for example LiChrosolv, E. Merck) 2. Potassium dihydrogen phosphate, analytical grade 3. Disodium hydrogen phosphate dihydrate, analytical grade
Test solution	Dissolve about 200 mg of substance, accurately weighed, in a graduated flask and make up to 10.0 ml with water. 20 mg/ml
Comparison solution	Dissolve the contents of one ampoule of standard substance in the volume of water indicated for the standard.
Eluent	Acetonitrile/phosphate buffer (71 + 29, volumes). Phosphate buffer: dissolve 600 mg of potassium dihydrogen phosphate and 350 mg of disodium hydrogen phosphate-dihydrate and make up to 1000 ml with water. Filter the solution through a 0.8 µm type AAWP Millipore filter.
Flow rate	2.2 ml/min.
Temperature of the column oven	35° C.
Detection	UV, 210 nm
Amount injected	10 µl, 0.2 mg in 10 µl
Full-scale deflection of recorder	About 0.25 AUFS (absorbance units full scale)
Calculation of the acarbose content	$G = \frac{P_p \times C \times 100{,}000}{P_r \times E_p \times (100 - b)}$
	G = Content of acarbose in percent, calculated on the basis of the anhydrous substance
	P_p = acarbose peak area from the test solution
	P_r = acarbose peak area from the comparison solution (standard)
	W_p = weight of the sample in mg
	C = concentration of the comparison solution in mg of acarbose per ml
	b = water content of the sample in percent

The inhibitory action of acarbose was determined in the saccharase inhibition assay and reported in saccharase inhibition assay and reported in saccharase inhibition units (SIU). The assay is described by L. Müller, B. Junge et al. in Enzyme Inhibitors, U. Brodbeck ed., Verlag Chemie, 1980, page 109.

The present invention includes pharmaceutical preparations which in addition to non-toxic, inert pharmaceutically suitable excipients contain the active compound according to the invention or which consist of the active compound according to the invention and processes for the production of these preparations.

The present invention also includes pharmaceutical preparations in dosage units. This means that the preparations are in the form of individual parts, for example tablets, dragees, capsules, pills, suppositories and ampoules, of which the content of active substance corresponds to a fraction or a multiple of an individual dose. The dosage units can contain, for example, 1, 2, 3 or 4 individual doses or ½, ⅓ or ¼ of an individual dose. An individual dose preferably contains the amount of active compound which is given in one administration and which usually corresponds to a whole, a half or a third or a quarter of a daily dose.

By non-toxic, inert pharmaceutically suitable excipients there are to be understood solid, semi-solid or liquid diluents, fillers and formulation auxiliaries of all kinds.

Tablets, dragees, capsules, pills, granules, suppositories, solutions, suspensions and emulsions, pastes, ointments, gels, creams, lotions, powders and sprays may be mentioned as preferred pharmaceutical preparations.

Tablets, dragees, capsules, pills and granules can contain the active compound or compounds alongside the customary excipients such as (a) fillers and extenders, for example starches, lactose, sucrose, glucose, mannitol and silica, (b) binders, for example carboxymethylcellulose, alginates, gelatine and polyvinylpyrrolidone, (c) humectants, for example glycerine, (d) disintegrating agents, for example agar-agar, calcium carbonate and sodium bicarbonate, (e) solution retarders, for example paraffin, and (f) resorption accelerators, for example quaternary ammonium compounds, (g) wetting agents, for example cetyl alcohol or glycerine monostearate, (h) adsorbents, for example kaolin and bentonite, and (i) lubricants, for example talc, calcium stearate and magnesium stearate and solid polyethylene glycols, or mixtures of the substances listed under (a) to (i).

The tablets, dragees, capsules, pills and granules can be provided with the customary coatings and shells, optionally containing opacifying agents, and can also be of such composition that they release the active compound only, or preferentially, in a certain part of the intestinal tract, optionally in a delayed manner, examples of embedding compositions which can be used being polymeric substances and waxes.

The active compound or compounds, optionally together with one or more of the abovementioned excipients, can also be in a micro-encapsulated form.

Suppositories can contain, in addition to the active compound, the customary water-soluble or water-insoluble excipients, for example polyethylene glycols,

fats, for example cacao fat, and higher esters (for example C_{14}-alcohol with C_{16}-fatty acid) or mixtures of these substances.

Ointments, pastes, creams and gels can contain the customary excipients in addition to the active and eucalyptus oil, and sweeteners, for example saccharin.

The therapeutically active compounds should preferably be present in the abovementioned pharmaceutical preparations in a concentration of about 0.1 to 99.5, preferably of about 0.5 to 95, percent by weight of the total mixture.

The abovementioned pharmaceutical preparations are manufactured in the usual manner according to known methods, for example by mixing the active compound or the active compounds with the excipient or excipients.

The present invention also includes the use of the active compound according to the invention and of pharmaceutical preparations which contain the active compound according to the invention in human and veterinary medicine for the prevention, amelioration and/or cure of illnesses.

The active compound or its pharmaceutical preparations can be administered locally, orally, parenterally, intraperitoneally and/or rectally, preferably parenterally, especially intravenously.

In general it has proved advantageous both in human medicine and in veterinary medicine to administer the active compound in total amounts of about 1 to about 40, preferably 2 to 8, mg/kg of body weight every 24 hours, optionally in the form of several individual administrations, in order to achieve the desired results. An individual administration contains the active compound preferably in amounts of about 0.1 to about 4, especially of 0.2 to 2, mg/kg of body weight. However, it can be necessary to deviate from the dosages mentioned and in particular to do so as a function of the nature and body weight of the subject to be treated, the nature and the severity of the illness, the nature of the preparation and if the administration of the medicine, and the time or interval over which the administration takes place. Thus it can suffice in some cases to manage with less that the abovementioned amount of active compound whilst in other cases the abovementioned amount of active compound must be exceeded. The particular required optimum dosage and the type of administration of the active compound can easily be decided by anyone skilled in the art, on the basis of his expert knowledge.

EXAMPLE 1

A chromatography column of diameter 2.6 cm and length 40 cm (Pharmacia K 26/40) was packed with CM-Sephadex ® C 25. The CM-Sephadex ® C 25 had previously been equilibrated in 0.2M sodium acetate buffer pH 4.7. After the column had been packed it was washed with distilled, degassed water until the conductivity had fallen to 0.1 mS/cm. The height of the packing in the column was then 34 cm. The test substance used was 5.2 g of prepurified acarbose which, in addition to water, also contained salts and other impurities. The acarbose was dissolved in about 40 ml of distilled water, the pH was adjusted to 4.7 by addition of a little hydrochloric acid, and the solution was made up to 50 ml. The inhibitor content was 446,550 SIU, corresponding to 5.75 g of pure anhydrous acarbose. The substance was applied at a flow rate of 100 ml/h (18.8 cm/h) to the column and was washed and eluted with distilled water at 26° C. The course of the separation is shown in FIG. 1*a*. The main fraction was combined and resulted in a yield of 5.87 g containing 399,300 SIU, which is 89% of the inhibitor employed. The specific activity was 72 SIU/mg of dry matter. The HPLC method showed a content of 93% in the dry matter.

The column was regenerated with 800 ml of 0.2M sodium acetate buffer, pH 4.7, and the latter was subsequently washed out with 600 ml of distilled, degassed water.

EXAMPLES 2–5

All the examples in Table 1 were carried out in accordance with Example 1, but the temperature of the column jacket was varied during the elution. The elution was such that, three hours after the start of the application, the thermostat of the column heating was switched on and reached, depending on the temperature set, the target figure in 3–12 minutes. The decrease in the volume of the main fraction is indicated in Table 1, and Example 5 with an elution temperature of 70° C. is in FIG. 1*b*.

TABLE 1

Chromatography of acarbose on CM-Sephadex ® C 25
Dependence of the elution volume on the temperature

Example	Temperature of elution °C.	Volume of main fraction ml	yield g	yield %	Content by HPLC %
1	26	1,163	5.87	89	95
2	40	840	6.25	100	92
3	50	570	6.04	91	90
4	60	460	5.92	86	92
5	70	380	6.62	99	94

EXAMPLE 6

A chromatography column (Pharmacia K 26/70) was packed as in Example 1 with CM-Sephadex ® C 25 which had, however, been equilibrated and washed at pH 4.3. The height of the packing was 47 cm. The test substance used was again, as in Example 1, a prepurified acarbose, 579,000 SIU being applied in 200 ml of water. The flow rate was 117 ml/h (22 cm/h). The elution was carried out with water; as in Example 1, there was elution first of salt-containing fractions and subsequently of acarbose. The gap between the end of the salt-containing fractions and the start of the rise for acarbose was 162 ml. The rate of elution of acarbose was increased by heating the column to 45° C. the volume of the acarbose fraction was 1048 ml, and the yield was 577,000 SIU, which is 100% of the amount applied.

EXAMPLE 7

As in Example 6, a chromatography column was packed with CM-Sephadex ® C 25 which had, however, been equilibrated and washed at pH 4.9. 200 ml of the test solution containing 579,000 SIU were applied, and the substances were eluted with water. The gap between the salt-containing fractions and the start of the acarbose fraction was now only 23 ml. The volume of the main fraction was 707 ml, the temperature again being increased to 45° C. The yield was 577,000 SIU, which is 100% of the amount applied.

EXAMPLE 8

A chromatography column (Pharmacia K 26/40) was packed with CM-Sepharose ® Cl 6B fast flow, equilibrated at pH 4.5 with 0.2M sodium acetate solution and

washed with water. 40.5 ml of a solution of prepurified acarbose with an inhibitory action of 247,300 SIU were applied. The flow rate was 100 ml/h (18.8 cm/h). The elution was carried out with degassed, distilled water, the column having been heated to 45° C. at the start of the acarbose elution. The gap between the salt fraction and the acarbose fraction was 38 ml, and the volume of the main fraction was 600 ml. The yield of acarbose was 247,000 SIU, which is 100% of the amount used. The content by the HPLC method was 98% in the dry matter.

EXAMPLE 9

A chromatography column as in Example 8 was packed with carboxymethylcellulose CM 52 ® (Whatman), equilibrated to pH 4.5 with 0.2M sodium acetate solution, and washed with water. The height of the packing was 36 cm. 62 ml of a solution of prepurified acarbose with an inhibitory action of 394,000 SIU were applied, and eluted as in Example 8. The acarbose fraction followed immediately after the salt fraction. The volume of the acarbose fraction was 850 ml, and the yield was 322,000 SIU, which is 82% of the amount used. Content by the HPLC method 90% in the dry matter.

EXAMPLE 10

A chromatography column as in Example 8 was packed with Matrex-Cellufine CM ® (Amicon), equilibrated to pH 4.5 with 0.2M sodium acetate solution, and washed with water. The height of the packing was 37 cm. 62 ml of a solution of prepurified acarbose with an inhibitory action of 394,000 SIU were applied, and eluted as in Example 8. The acarbose fraction followed the salt fraction after a gap of 23 ml. The volume of the acarbose fraction was 960 ml, and the yield was 350,000 SIU, which is 89% of the amount applied. Content by the HPLC method 98% in the dry matter.

What is claimed is:

1. A purified acarbose composition which, apart from water, has an acarbose content of about 93–98% by weight.

2. An acarbose composition according to claim 1, which, apart from water, contains 2 to 5% by weight of sugar-like secondary components.

3. An acarbose composition according to claim 1, which, apart from water, contains less than 2% by weight of sugar-like secondary components.

4. A process for the preparation of a purified acarbose composition according to claim 1, comprising applying a prepurified acarbose in a 1 to 20% by weight aqueous solution with a pH of 3.5 to 7 to a column which contains as packing material a weekly acid cation exchanger which has carboxyl groups and is based on dextran, agarose and cellulose or exchangers which are derived from the latter with the addition of polyamide, eluting the column exclusively with degassed, distilled water and isolating the purified acarbose composition from the eluate.

5. A process according to claim 4, wherein the volume of prepurified acarbose solution which is applied corresponds to the filling volume of the column.

6. A process according to claim 4, wherein the volume of prepurified acarbose solution is less than 60% of the column volume.

7. A process according to claim 4, wherein the pH of the prepurified acarbose solution is 3.5 to 6.0.

8. A process according to claim 4, wherein the pH of the prepurified acarbose solution is 4.0 to 5.5.

9. A process according to claim 4, wherein the prepurified acarbose solution is applied at temperatures up to room temperature, and, the column is heated to 25° to 95° C. after the salts and coloring constituents have been eluted therefrom.

10. A process according to claim 9, wherein the prepurified acarbose solution is applied at temperatures in the range from 4° to 25° C., and, after the salts and coloring constituents have been eluted, the column is heated to 40° to 70° C.

11. A pharmaceutical composition comprising an effective amount of an acarbose composition according to claim 1, said acarbose, apart from water, contains less than 10% by weight of sugar-like secondary components and a pharmaceutically acceptable excipient therefor.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE EXTENDING PATENT TERM UNDER 35 U.S.C. § 156

PATENT NO.	:	4,904,769
ISSUED	:	February 27, 1990
INVENTOR(S)	:	Erich Rauenbusch
PATENT OWNER	:	Bayer Aktiengesellschaft

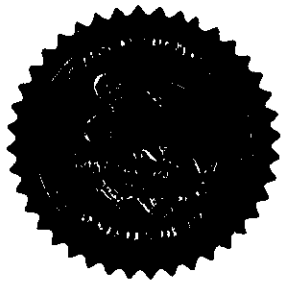
This is to certify that there has been presented to the

COMMISSIONER OF PATENTS AND TRADEMARKS

an application under 35 U.S.C. § 156 for an extension of the patent term. Since it appears that the requirements of the law have been met, this certificate extends the term of the patent for the period of

922 days

from the original expiration date of the patent, February 27, 2007, with all rights pertaining thereto as provided by 35 U.S.C. § 156(b).



I have caused the seal of the Patent and Trademark Office to be affixed this 21st day of April 1997.

Bruce A. Lehman
Assistant Secretary of Commerce and
Commissioner of Patents and Trademarks

Disclaimer

4,904,769 — Erich Rauenbusch, Wuppertal, Fed. Rep. of Germany. HIGHLY PURE ACARBOSE. Patent dated Feb. 27, 1990. Disclaimer filed Dec. 20, 2006, by the assignee, Bayer Healthcare AG.

Hereby enters this disclaimer to all claims of said patent.

(*Official Gazette February 27, 2007*)