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Attorneys for Plaintiff
Abraxis BioScience, Inc.

**UNITED STATES DISTRICT COURT**
**DISTRICT OF NEW JERSEY**

| | |
|---|---|
| ABRAXIS BIOSCIENCE, INC.,<br><br>Plaintiff,<br><br>v.<br><br>NAVINTA LLC,<br><br>Defendant. | Civil Action No. 3:07-cv-01251-JAP-TJB |

**FIRST AMENDED COMPLAINT**

Plaintiff Abraxis BioScience, Inc. (hereinafter "Abraxis") amends its Complaint against Navinta LLC (hereinafter "Navinta") as follows:

**THE PARTIES**

1. Abraxis is a corporation organized and existing under the laws of the State of Delaware, having a principal place of business at 11755 Wilshire Blvd., Suite 2000, Los Angeles, California 90025.

2. On information and belief, Navinta is a limited liability corporation organized and existing under the laws of the State of New Jersey, having a principal place of business at 1499 Lower Ferry Road, Ewing, New Jersey, 08618.

## NATURE OF THE ACTION

3. This is a civil action for patent infringement that arises under the Patent Laws of the United States, 35 U.S.C. § 1 *et seq*. and under the Declaratory Judgment Act, 28 U.S.C. § 2201 and 2202. This action relates to an Abbreviated New Drug Application ("ANDA") filed by Navinta with the United States Food and Drug Administration ("FDA") for the approval to market generic versions of Abraxis' Naropin® Injection products.

## JURISDICTION AND VENUE

4. This Court has jurisdiction over the subject matter of this action under 28 U.S.C. §§ 1331, 1338(a), 2201, and 2202.

5. Navinta is subject to personal jurisdiction within this district because Navinta has availed itself to the laws of New Jersey and conducts business in New Jersey, including within this district.

6. Venue is proper in this Court pursuant to 28 U.S.C. §§ 1391(b) and (c), and 28 U.S.C. § 1400(b).

## THE PATENTS

7. United States Patent No. 4,870,086 ("the '086 patent") (attached hereto as Exhibit A), entitled "Optically Pure Compound and a Process for Its Preparation," was duly and legally issued by the United States Patent and Trademark Office ("USPTO") on September 26, 1989.

8. The '086 patent was granted, by the USPTO, a patent term extension pursuant to 35 U.S.C. § 156 to restore a portion of the loss of effective patent protection resulting from the time during the regulatory review period leading to FDA's approval of Naropin® Injection. The patent term will be extended for the period of 1,400 days from November 24, 2006, which was

the original expiration date of the '086 patent. As such, the '086 patent will expire on or about September 24, 2010.

9. United States Patent No. 5,670,524 ("the '524 patent") (attached hereto as Exhibit B), entitled "Methods and Compositions for the Treatment of Pain Utilizing Ropivacaine," was duly and legally issued by the USPTO on September 23, 1997. The '524 patent will expire on or about September 23, 2014.

10. United States Patent No. 5,834,489 ("the '489 patent") (attached hereto as Exhibit C), entitled "Methods and Compositions for the Treatment of Pain Utilizing Ropivacaine," was duly and legally issued by the USPTO on November 10, 1998. The '489 patent will expire on or about September 23, 2014.

11. By way of assignment, Abraxis owns all rights, title and interest in and to the '086 patent, the '524 patent, and the '489 patent, including the right to sue and recover for patent infringement.

**COUNT I: INFRINGEMENT OF THE '086 PATENT**

12. Abraxis holds an approved New Drug Application ("NDA") 20-553 for Naropin® Injection, which contains the active ingredient ropivacaine hydrochloride. Naropin® Injection was approved by the FDA on September 24, 1996, and is indicated for the production of local or regional anesthesia for surgery and for acute pain management.

13. According to the prescribing information for Naropin® Injection, ropivacaine hydrochloride is chemically described as (S)-(–)-1-propyl-2,6'-pipecoloxylidide hydrochloride monohydrate.

14. The '086 patent discloses and claims, among other things, (S)-(–)-1-propyl-2,6'-pipecoloxylidide hydrochloride in the form of its monohydrate, a process for its preparation, and a method for inducing local anesthesia.

15. On information and belief, Navinta submitted an ANDA to the FDA under the provisions of 21 U.S.C. § 355(j), seeking approval to engage in the commercial manufacture, use and/or sale of generic ropivacaine hydrochloride injection products.

16. On information and belief, Navinta submitted its ANDA to the FDA for the purpose of obtaining approval to engage in the commercial manufacture, use, or sale of its generic ropivacaine hydrochloride injection products before the expiration of the '086 patent.

17. By filing an ANDA under 21 U.S.C. § 355(j) for the purpose of obtaining approval to engage in the commercial manufacture, use, or sale of its generic ropivacaine hydrochloride injection products before the expiration of the '086 patent, Navinta has committed an act of infringement under 35 U.S.C. § 271(e)(2)(A). Further, the commercial manufacture, use, offer for sale, sale and/or importation of the generic ropivacaine hydrochloride injection products for which Navinta seeks approval in its ANDA will also infringe one or more claims of the '086 patent.

18. On information and belief, Navinta made, and included in its ANDA, a certification under 21 U.S.C. § 355(j)(2)(A)(vii)(IV) that, in its opinion and to the best of its knowledge, the '086 patent is not infringed by Navinta's generic ropivacaine hydrochloride injection products.

19. Navinta sent a notice to Abraxis, purporting to comply with the provisions of 21 U.S.C. § 355(j)(2)(B)(iv)(II) and the FDA regulations relating thereto, in which Navinta represented that it had filed an ANDA for its generic ropivacaine hydrochloride injection

products, including its certification with respect to the '086 patent, and that it sought approval of its ANDA prior to the expiration of the '086 patent.

20. Abraxis is entitled to the relief provided by 35 U.S.C. § 271(e)(4), including an order of this Court that the effective date of any approval of the aforementioned ANDA relating to Navinta's generic ropivacaine hydrochloride injection products be a date which is not earlier than the expiration of the '086 patent, including any extensions.

21. On information and belief, when Navinta filed its ANDA, it was aware of the '086 patent and that the filing of its ANDA seeking approval from FDA prior to the expiration of the '086 patent was an act of infringement of this patent.

22. This is an exceptional case and Abraxis is entitled to an award of reasonable attorneys fees under 35 U.S.C. § 285.

**COUNT II: INFRINGEMENT OF THE '524 PATENT**

23. Abraxis repeats and incorporates by reference, as if fully set forth herein, the allegations contained in paragraphs 1 through 22 above.

24. The '524 patent discloses and claims, among other things, a method of treatment using a salt of ropivacaine and a pharmaceutical composition containing a salt of ropivacaine.

25. On information and belief, Navinta submitted an Abbreviated New Drug Application ("ANDA") to the Food and Drug Administration ("FDA") under the provisions of 21 U.S.C. § 355(j), seeking approval to engage in the commercial manufacture, use and/or sale of generic ropivacaine hydrochloride injection products.

26. On information and belief, Navinta submitted its ANDA to the FDA for the purpose of obtaining approval to engage in the commercial manufacture, use and/or sale of generic ropivacaine hydrochloride injection products before the expiration of the '524 patent.

27. By filing an ANDA under 21 U.S.C. § 355(j) for the purpose of obtaining approval to engage in the commercial manufacture, use, or sale of its generic ropivacaine hydrochloride injection products before the expiration of the '524 patent, Navinta has committed an act of infringement under 35 U.S.C. § 271(e)(2)(A).

28. Abraxis is entitled to the relief provided by 35 U.S.C. § 271(e)(4), including an order of this Court that the effective date of any approval of the aforementioned ANDA relating to Navinta's generic ropivacaine hydrochloride injection products be a date which is not earlier than the expiration of the '524 patent, including any extensions.

29. On information and belief, when Navinta filed its ANDA, it was aware of the '524 patent and that the filing of its ANDA seeking approval from the FDA prior to the expiration of the '524 patent was an act of infringement of this patent.

30. On information and belief, Navinta's commercial manufacture, use, offer for sale, sale, and/or importation of its generic ropivacaine hydrochloride injection products, upon approval by FDA, would infringe one or more claims of the '524 patent under 35 U.S.C. § 271.

31. On information and belief, the use of Navinta's generic ropivacaine hydrochloride injection products to be distributed and/or sold by Navinta would infringe one or more claims of the '524 patent under 35 U.S.C. § 271.

32. On information and belief, this infringing use of generic ropivacaine hydrochloride injection products under the '524 patent will occur at Navinta's active behest, and with its intent, knowledge and encouragement, and Navinta will actively induce, encourage, contribute to, aid and abet this administration with knowledge that it is in contravention of Abraxis' rights under the '524 patent.

33. As a result, upon FDA approval, Navinta would be indirectly liable for inducing and/or contributing to infringement of the '524 patent under 35 U.S.C. § 271(b) and/or (c).

34. Abraxis will be substantially and irreparably harmed if Navinta is not enjoined from infringing the '524 patent.

35. Abraxis is entitled to the relief provided by 35 U.S.C. § 283, including an injunction preventing Navinta from infringing the '524 patent.

36. This is an exceptional case and Abraxis is entitled to an award of reasonable attorneys fees under 35 U.S.C. § 285.

**COUNT III: INFRINGEMENT OF THE '489 PATENT**

37. Abraxis repeats and incorporates by reference, as if fully set forth herein, the allegations contained in paragraphs 1 through 36 above.

38. The '489 patent discloses and claims, among other things, a method of treatment using a salt of ropivacaine.

39. On information and belief, Navinta submitted an Abbreviated New Drug Application ("ANDA") to the Food and Drug Administration ("FDA") under the provisions of 21 U.S.C. § 355(j), seeking approval to engage in the commercial manufacture, use and/or sale of generic ropivacaine hydrochloride injection products.

40. On information and belief, Navinta submitted its ANDA to the FDA for the purpose of obtaining approval to engage in the commercial manufacture, use and/or sale of generic ropivacaine hydrochloride injection products before the expiration of the '489 patent.

41. By filing an ANDA under 21 U.S.C. § 355(j) for the purpose of obtaining approval to engage in the commercial manufacture, use, or sale of its generic ropivacaine

hydrochloride injection products before the expiration of the '489 patent, Navinta has committed an act of infringement under 35 U.S.C. § 271(e)(2)(A).

42. Abraxis is entitled to the relief provided by 35 U.S.C. § 271(e)(4), including an order of this Court that the effective date of any approval of the aforementioned ANDA relating to Navinta's generic ropivacaine hydrochloride injection products be a date which is not earlier than the expiration of the '489 patent, including any extensions.

43. On information and belief, when Navinta filed its ANDA, it was aware of the '489 patent and that the filing of its ANDA seeking approval from the FDA prior to the expiration of the '489 patent was an act of infringement of this patent.

44. On information and belief, the use of Navinta's generic ropivacaine hydrochloride injection products to be distributed and/or sold by Navinta would infringe one or more claims of the '489 patent under 35 U.S.C. § 271.

45. On information and belief, this infringing use of generic ropivacaine hydrochloride injection products under the '489 patent will occur at Navinta's active behest, and with its intent, knowledge and encouragement, and Navinta will actively induce, encourage, contribute to, aid and abet this administration with knowledge that it is in contravention of Abraxis' rights under the '489 patent.

46. As a result, upon FDA approval, Navinta would be indirectly liable for inducing and/or contributing to infringement of the '489 patent under 35 U.S.C. § 271(b) and/or (c).

47. Abraxis will be substantially and irreparably harmed if Navinta is not enjoined from infringing the '489 patent.

48. Abraxis is entitled to the relief provided by 35 U.S.C. § 283, including an injunction preventing Navinta from infringing the '489 patent.

49. This is an exceptional case and Abraxis is entitled to an award of reasonable attorneys fees under 35 U.S.C. § 285.

**PRAYER FOR RELIEF**

**WHEREFORE**, Plaintiff Abraxis BioScience, Inc. respectfully requests the following relief:

A. Judgment that Navinta has infringed one or more claims of the '086, '524, and '489 patents by filing the aforementioned ANDA relating to Navinta's generic ropivacaine hydrochloride injection products;

B. An order, pursuant to 35 U.S.C. § 271(e)(4)(A), that the effective date of any approval of the aforementioned ANDA relating to Navinta's generic ropivacaine hydrochloride injection products be a date that is not earlier than the expiration date of the '086, '524, and '489 patents, including any extensions;

C. A permanent injunction restraining and enjoining Navinta and its officers, agents, attorneys and employees, and those acting in privity or concert with it, from engaging in the commercial manufacture, use, offer for sale, or sale within the United States, or importation into the United States, of generic ropivacaine hydrochloride injection products as claimed in the '086, '524, and '489 patents, prior to the expiration of the '086, '524, and '489 patents, including any extensions;

D. Judgment that Navinta's generic ropivacaine hydrochloride injection products, if approved by the FDA, would infringe of one or more claims of the '524 and '489 patents;

E. A permanent injunction restraining and enjoining Navinta and its officers, agents, attorneys and employees, and those acting in privity or concert with it, from engaging in further

acts of direct infringement, inducement of infringement, and contributory infringement of the '524 and '489 patents;

F. Monetary damages for any acts of infringement beyond those specified in 35 U.S.C. § 271(e)(1);

G. Judgment that this is an exceptional case and that Abraxis is entitled to its reasonable attorneys fees pursuant to 35 U.S.C. § 285;

H. The costs and expenses in this action; and

I. Such other and further relief as the Court may deem just and proper.

**JURY DEMAND**

Pursuant to Fed. R. Civ. P. 38 and Loc. Civ. R. 38.1, Plaintiff hereby formally demands a trial by jury as to all issues contained herein.

Dated: November 16, 2007

By: _____

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# EXHIBIT A

# United States Patent [19]

**Sandberg**

[11] **Patent Number: 4,870,086**

[45] **Date of Patent: Sep. 26, 1989**


[54] **OPTICALLY PURE COMPOUND AND A PROCESS FOR ITS PREPARATION**


[75] Inventor: **Rune V. Sandberg**, Järna, Sweden

[73] Assignee: **Astra Lakemedel Aktiebolag**, Sodertalje, Sweden



[21] Appl. No.: **934,114**

[22] Filed: **Nov. 24, 1986**

[30] **Foreign Application Priority Data**

Jan. 3, 1986 [SE] Sweden ..... 8600017

[51] **Int. Cl.**[4] ..... **A61K 31/445**

[52] **U.S. Cl.** ..... **514/330**; 546/225

[58] **Field of Search** ..... 546/225; 514/330



[56] **References Cited**

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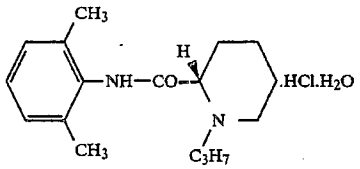
*Primary Examiner*—Richard L. Raymond

*Attorney, Agent, or Firm*—White & Case



[57] **ABSTRACT**

Optically pure S-(−)-1-propyl-2′,6′-pipecoloxylidide hydrochloride monohydrate, with the structural formula




a process for the preparation thereof and the use for inducing local anesthesia.


**6 Claims, No Drawings**

# OPTICALLY PURE COMPOUND AND A PROCESS FOR ITS PREPARATION

## FIELD OF THE INVENTION

The present invention is directed to a new optically pure compound, a process for its preparation and its use in the manufacture of pharmaceutical preparations.

## BACKGROUND OF THE INVENTION

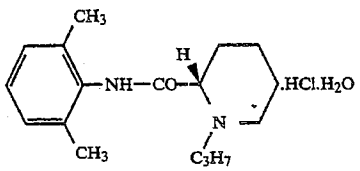
A new local anesthetic namely (S)-(−)-1-propyl-2′,6′-pipecoloxylidide hydrochloride is described in WO 85/00599. The new compound has an unexpected long duration compared to the racemate and the corresponding (R)-(+)-enantiomer. The preparation method described in WO 85/00599 gives however a product which contains about 10% of the (R)-(+)-enantiomer. This means that the product from a physical chemical point of view, contains only about 80% of the (S)-(−)-enantiomer, while the residual about 20% constitutes the racemic form. In addition the product obtained is hygroscopic and thus not stable and contains about 2% of water. One mole of water of crystallization implies a water content of 5,5%. A product having a varying content of water has the drawback that the percentage of water must be analyzed each time a pharmaceutical formulation shall be prepared. As the (S)-(−)-enantiomer is the most potent enantiomer a product containing less (R)-(+)-enantiomer was wanted. One object of this invention is thus to produce the compound in a form, which is stable and which does not change by storing at ordinary room temperature and humidity. A second object of this invention is to obtain a product consisting of the substantially pure (S)-(−)-ennantiomer.

## OUTLINE OF THE INVENTION

The present invention is related to the monohydrate of (S)-(−)-1-propyl-2′,6′-pipecoloxylidide hydrochloride. By means of a specific method of preparing the named hydrate, the (S)-(−)-enantiomer is obtained in high optical purity, namely ≧99.5%, even from an optically highly contaminated preparation. This specific method is a further aspect of this invention. The monohydrate of (S)-(−)-1-propyl-2′,6′-pipecoloxylidide hydrochloride has the further advantage that it is very stable and hardly affected by drying in a desiccator over calcium chloride at room temperature and 0.5 mm Hg. Only when the compound was heated at 75° C. for 16 hours, other conditions being equal, the water of crystallization was removed. No further change of the compound was noticed.

## PREPARATION

The monohydrate of (S)-(−)-1-propyl-2′,6′-pipecoloxylidide hydrochloride with the structural formula




is prepared according to the invention by dissolving (S)-(−)-1-propyl-2′,6′-pipecoloxylidide hydrochloride in water, whereupon hot acetone is added. The solution is then filtered as hot as possible and left for crystallization. At the preparation the starting compound is dissolved in an amount of water, which corresponds to about 1–3 times of the weight of the added compound and the volume of acetone added is 5–15 times of the water volume. If more water is added, that is an amount of water, which corresponds to up to 4 times of the weight of the added compound, the volume of the acetone added is 15–20 times of the water volume. It is especially preferred to make the preparation in the following way: The starting compound is heated with an amount of water equal to the weight of the starting compound. Hot acetone in such an amount that the compound is completely dissolved is added. Additional acetone to a volume of ten times of the volume of the added water is then poured into the solution, whereafter the solution is filtered and left for crystallization. The proportion between water and acetone is important. If too much acetone is added the product obtained is less pure and more recrystallizations are needed. When acetone less than 10 times the volume of water is added on the other hand the yield diminishes. The acetone added is hot preferably boiling (b.p. 56° C.). Acetone having a temperature between 45°–56° C. can be used according to the invention.

The invention also relates to pharmaceutical preparations containing the new pure compound as active ingredient: to the use of the new compound in therapy, especially for obtaining local anesthesia in mammals including man; to a method for obtaining local anesthesia in mammals including man by administering the new compound; and to the use of the new compound in the manufacture of pharmaceutical preparations having local anesthetic effect.

For the preparation of pharmaceutical preparations the new compound is dissolved in a liquid diluent, which is suitable for injection. The preparations used are aqueous solutions which contain between 1.25 and 15.0 mg/ml of the active compound calculated as the hydrochloride salt. In some applications a vasoconstrictor, epinephrine, is included in concentrations between 2.0 and 20.0 μg/ml calculated as the base. The solutions are made isoosmotic with physiologic saline by the addition of an appropriate amount of sodium chloride. Solutions containing epinephrine will also contain sodium metabisulphite in order to protect epinephrine from oxidation. pH of solutions without epinephrine is adjusted to approximately 5.5 wheras pH in solutions containing epinephrine is adjusted to approximately 3.6.

The invention is illustrated by the following examples.

Example 1 illustrates a specially preferred way of carrying out the process according to the invention.

## EXAMPLE 1

Preparation of the monohydrate of (S)-(−)-1-propyl-2′,6′-pipecoloxylidide hydrochloride. 82 g of the hydrochloride of (S)-(−)-1-propyl-2′,6′-pipecoloxylidide containing 10% of the (R)-(+)-enantiomer was dissolved in 85 ml of water, whereupon acetone heated to its boiling point was added to a final volume of 850 ml. The solution was filtered and left for crystallization. This first recrystallization yielded 71,7 g. Another recrystallization was carried out by dissolving the obtained product in 72 ml of $H_2O$, whereupon boiling acetone to a final volume of 750 ml was added. The solution was filtered

and left for crystallization. The final yield was 62.3 g (76%) of an optically pure (≧99.5%) product containing 5.4–5.6% of water, being the monohydrate of (S)-(−)-1-propyl-2',6'-pipecoloxylidide hydrochloride, melting interval 266°–267.5° C.

EXAMPLE 2

| | |
|---|---|
| (S)-(−)-1-propyl-2', 6'-pipecoloxylidide hydrochloride monohydrate | 2.64 mg |
| Sodium chloride | 8.53 mg |
| Sodium hydroxide to pH | 5.5 |
| Water for injection to | 1.0 ml |

2.64 mg of the monohydrate of (S)-(−)-1-propyl-2',6'-pipecoloxylidide hydrochloride was dissolved in 1 ml of sterile water. 8.53 mg of sodium chloride was added and the solution was adjusted to pH 5.5 with sodium hydroxide.

EXAMPLE 3

| | |
|---|---|
| (S)-(−)-1-propyl-2', 6'-pipecoloxylidide hydrochloride monohydrate | 5.29 mg |
| Epinephrine hydrogentartrate | 10.0 μg |
| Sodium chloride | 7.89 mg |
| Hydrochloric acid to pH | 3.6 |
| Water for injection to | 1.0 ml |

The preparation was prepared as described in Example 2

FURTHER ATTEMPTS TO PURIFY THE COMPOUND

In order to try to purify the product described in WO 85/00599 further recrystallizations from 2-propanol, the solvent used according to that patent application, were performed. Although water was added it was not possible to obtain an optically more pure or, with respect to the water contents, more well defined product.

Other common solvents such as methanol and ethanol are not suitable because of the too high solubility of the hydrochloride of (S)-(−)-1-propyl-2',6'-pipecoloxylidide in methanol and ethanol. In solvents such as ethyl acetate and dioxan on the other hand the compound is almost insoluble.

I claim:

1. (S)-(−)-1-propyl-2',6'-pipecoloxylidide hydrochloride, wherein the compound is in the form of its monohydrate.

2. The compound according to claim 1, wherein it is substantially optically pure.

3. The compound according to claim 1, wherein it contains less than 0.5% by weight of the corresponding (R)-(+)-enantiomer.

4. A process for the preparation of substantially optically pure monohydrate of (S)-(−)-1-propyl-2',6'-pipecoloxylidide hydrochloride, which comprises:

dissolving (S)-(−)-1-propyl-2',6'-pipecoloxylidide hydrochloride in a volume of water which is 1 to 3 times its weight;

adding acetone to the dissolved mixture in an amount which is 5 to 15 times the volume of the water added, wherein the temperature of the acetone is between 45° C. and its boiling point; and

isolating the monohydrate of (S)-(−)-1-propyl-2',6'-pipecoloxylidide hydrochloride.

5. The process according to claim 4, wherein the weight of the volume of water is equal to the weight of the (S)-(−)-1-propyl-2',6'-pipecoloxylidide hydrochloride and the volume of the acetone is 10 times the volume of the added water.

6. A method for inducing local anesthesia, which comprises adminstering to mammals including man needing local anesthesia an anesthetizing amount of the compound according to claim 1.

* * * * *

# UNITED STATES PATENT AND TRADEMARK OFFICE

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

| | | |
|---|---|---|
| PATENT NO. | : | 4,870,086 |
| ISSUED | : | September 26, 1989 |
| INVENTOR(S) | : | Rune V. Sandberg |
| PATENT OWNER | : | Astra Läkemedel Aktiebolag |

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

1,400 days

from November 24, 2006, the original expiration date of the patent, subject to the provisions of 35 U.S.C. § 41(b), 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 27th day of August 1998.

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

# EXHIBIT B

US005670524A

# United States Patent [19]

Eek

[11] Patent Number: 5,670,524

[45] Date of Patent: Sep. 23, 1997

[54] **METHODS AND COMPOSITIONS FOR THE TREATMENT OF PAIN UTILIZING ROPIVACAINE**

[75] Inventor: **Arne Torsten Eek**, Trosa, Sweden

[73] Assignee: **Astra AB**, Sweden

[21] Appl. No.: **256,319**

[22] PCT Filed: **May 26, 1994**

[86] PCT No.: **PCT/SE94/00496**

§ 371 Date: **Jun. 28, 1994**

§ 102(e) Date: **Jun. 28, 1994**

[87] PCT Pub. No.: **WO95/00148**

PCT Pub. Date: **Jan. 5, 1995**

[30] **Foreign Application Priority Data**

Jun. 28, 1993 [SE] Sweden ..... 9302218

[51] **Int. Cl.**[6] ..... **A61K 31/445**

[52] **U.S. Cl.** ..... **514/330**

[58] **Field of Search** ..... 514/330

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*Attorney, Agent, or Firm*—Michael A. Sanzo; Vinson & Elkins

[57] **ABSTRACT**

Use of a pharmaceutically acceptable salt of ropivacaine for the manufacture of a pharmaceutical preparation with sensoric block and minimal motor blockade.

**10 Claims, No Drawings**

# METHODS AND COMPOSITIONS FOR THE TREATMENT OF PAIN UTILIZING ROPIVACAINE

This application is a 371 of PCT/SE94/00469 filed May 26, 1994.

1. Field of the Invention

The present invention is related to the use of a low concentration of a pharmaceutically acceptable salt of ropivacaine in the manufacture of pharmaceutical preparations for pain relief post operatively and in labour.

2. Background of the Invention

Post operative pain relief is still a problem within modern surgery. According to a newly published study about 70% of all patients treated surgically felt moderate to severe pain after the surgical treatment.

The need for qualified pain relief is greatest during the first 24 hours after the surgical treatment. The traditional method to treat the patients is to give narcotics intramuscularly or intravenously. Such treatment is often insufficient as narcotic analgetics have many negative effects. One disadvantage is depression of the breathing, which may occur even after treatment. This means that the patient must be intensively looked after by specialists.

A patient, who has been treated with morphine is tired, apathetic and is often feeling sick. The patient thus has no interest in things around him. It is thus difficult to take care of the patient and make him participate in respiratory exercises and prophylaxis for thromboses.

One method is administration epidurally, by infusion or intermittent injections of local anaesthetics. Such treatments can only be carried out on patients with epidural catheters being taken care of at an intensive care or post surgical unit by specially trained persons.

There has been a long felt need at ward level to be able to give a greater group of patients qualified pain relief by epidural infusion of e.g. local anaesthetics instead of opiates.

Normally, with local anaesthetics a good blockade of the pain is obtained. The drawback is the motor blockade in the legs, which is disturbing to the patients, who wants to give up the pain relief treatment in advance. Among other effects the motor blockade means that the patient cannot leave his bed without assistance as the legs will not bear.

## Outline of the invention

According to the present invention it has surprisingly been found that the local anaesthetic agent ropivacaine, described e.g. in WO/85/00599, in form of its hydrochloride can be given to the patient in a dosage which gives pain relief with minimal effect on motor function. This is at a dosage of lower than 0.5% by weight, especially from 0.01% to 0.45% by weight. Such low dosages are normally considered to be ineffective. The normal dosage is from 0.5–2% by weight.

The local anaesthetic compound used according to the invention is in the form of its pharmaceutically acceptable salts. It is especially preferred to use ropivacaine hydrochloride.

The local anaesthetic is incorporated into a solution.

The local anaesthetic composition contains less than 0.5% by weight of the local anaesthetic compound, preferably from 0.01 up to 0.45% by weight, especially preferred 0.1–0.3% by weight.



## Pharmaceutical Preparations

EXAMPLES 1–3

Solution 5 mg/ml, 3 mg/ml, 2 mg/ml

| | Examples | | |
|---|---|---|---|
| | 1 | 2 | 3 |
| Ropivacaine hydrochloride monohydrate | 0.53 kg | 0.32 kg | 0.21 kg |
| Sodium hydroxide 2M to pH 5.0–6.0 | | | |
| Purified water qs ad | 100 kg | 100 kg | 100 kg |

Ropivacaine is dissolved in the water. Sodium hydroxide is added to pH 5.0–6.0. The resulting solution is autoclaved.

The best mode of carrying out the invention known at present is to use the preparations according to Example 3.

Biological test

A double blind study of sensory and motor blockade with 0.1%, 0.2%, 0.3% ropivacaine and 0.25% bupivacaine during continuous epidural infusion in healthy male volunteers.

Background

The aim of the study was to find a low concentration of ropivacaine giving a sufficient sensory block but as little or no motor block at all during continuous epidural infusion. This study is a first step towards finding a low concentration of ropivacaine which later will be used for treatment of post operative pain in patients. 37 volunteers participated in the study. They were divided into 5 treatment groups, receiving either 0.1%, 0.2% or 0.3% ropivacaine or 0.25% bupivacaine. There was also a control group receiving 0.9% saline. All solutions were first given as a bolus dose of 10 ml, followed by a continuous epidural infusion at a rate of 10 ml/hour for 21 hours. During the infusion both motor and sensory blockade was tested using different methods. The postural stability of the volunteers was also evaluated.

Preliminary results

Group 1. No motor and sensory block was achieved in the volunteers receiving saline.

Group 2. Bupivacaine 0.25% gave a good segmental spread (from the lower part of the abdomen to the lower part of the extremities) of sensoric block during the infusion. All of the volunteers had a high degree of motor block and 75% (6/8) could not stand up at any occasion during the infusion.

Group 3. Ropivacaine 0.3% gave an equal duration of sensory blockade compared to bupivacaine 0.25%. The upper segmental spread of sensoric block was somewhat higher than for bupivacaine. The lower segmental spread of sensoric block was, after 10 hours of continuous infusion, shifted up to just below the knees compared to bupivacaine and at the end of infusion was found above the knees. The motorblock was somewhat less profound compared to bupivacaine. 5 out of 7 volunteers could not stand at any occasion during the infusion to perform the postural stability tests.

Group 4. Ropivacaine 0.2% gave an equal sensory block compared to bupivacaine 0.25% in the lower part of the abdomen, but showed a less sensory block around the ankles. After 10 hours of continuous infusion the sensory block was less than for both ropivacaine 0.3% and bupivacaine. The motor block was less profound compared to the 0.3% ropivacaine as well as to the 0.25% bupivacaine solution. 25% (2/8) of the volunteers could not at any occasion stand up whereas the rest of the volunteers (6/8) could at some point during the infusion make some of the postural tests.

Group 5. Ropivacaine 0.1% gave, during the first 5 hours of the infusion, a more narrow spread of the sensory block compared to the 0.2% ropivacaine solution. Normal sensation returned after 8 hours of the epidural infusion.

No serious or unexpected adverse events could be noted in any of the test groups.

It was found that bupivacaine gives 75% higher motor blockade than ropivacaine, which only gives 25% at comparable dosage levels.

At the dosages 0.3% and 0.2% ropivacaine gives about the same motor blockade. At the dosage 0.1% it is less.

Conclusion

From the unique effect of ropivacaine the conclusion can be drawn that said compound is especially useful for administering at low dosage to patients in the need of post surgical and labour pain treatment, with good balance between sufficient sensoric block and a desirable minimal degree of motor block.

I claim:

**1**. A method for treating a human experiencing pain, said method comprising: administering to said human a composition comprising a pharmaceutically acceptable salt of ropivacaine, wherein said ropivacaine is present in said composition at a concentration of less than 0.25% by weight.

**2**. The method of claim **1**, wherein said composition is administered at a site permitting direct interaction between said ropivacaine and nerves in the spinal column of said human.

**3**. The method of claim **1**, wherein said composition is administered epidurally.

**4**. The method of any one of claims **1–3**, wherein said pharmaceutically acceptable salt of ropivacaine is ropivacaine hydrochloride.

**5**. The method of any one of claims **1–3**, wherein said composition is administered by continuous infusion.

**6**. The method of claim **5**, wherein said continuous infusion is at a flow rate of about 10 ml per hour.

**7**. The method of any one of claims **1–3**, wherein said composition is administered for post-surgical pain.

**8**. The method of any one of claims **1–3**, wherein said composition is administered for labor pain.

**9**. A pharmaceutical composition for use in acute pain management with minimal motor blockade, comprising a pharmaceutically acceptable salt of ropivacaine at a concentration lower than 0.25% by weight.

**10**. The pharmaceutical composition of claim **9**, wherein said pharmaceutically acceptable salt of ropivacaine is ropivacaine hydrochloride.

* * * * *

# EXHIBIT C

US005834489A

# United States Patent [19]

Eek

[11] Patent Number: 5,834,489

[45] Date of Patent: *Nov. 10, 1998

[54] **METHODS AND COMPOSITIONS FOR THE TREATMENT OF PAIN UTILIZING ROPIVACAINE**

[75] Inventor: **Arne Torsten Eek**, Trosa, Sweden

[73] Assignee: **AB Astra**, Sweden

[ * ] Notice: The term of this patent shall not extend beyond the expiration date of Pat. No. 5,670,524.

[21] Appl. No.: **851,062**

[22] Filed: **May 5, 1997**

**Related U.S. Application Data**

[63] Continuation of Ser. No. 256,319, May 26, 1994, Pat. No. 5,670,524.

[30] **Foreign Application Priority Data**

Jun. 28, 1993 [SE] Sweden ..... 9302218

[51] **Int. Cl.**[6] ..... **A61K 31/445**

[52] **U.S. Cl.** ..... **514/330**

[58] **Field of Search** ..... 514/330

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[57] **ABSTRACT**

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**7 Claims, No Drawings**

# METHODS AND COMPOSITIONS FOR THE TREATMENT OF PAIN UTILIZING ROPIVACAINE

## CROSS REFERENCE TO RELATED APPLICATIONS

The present application is a continuation of U.S. application Ser. No. 08/256,319, filed May 26, 1994, now U.S. Pat. No. 5,670,524.

## FIELD OF THE INVENTION

The present invention is related to the use of a low concentration of a pharmaceutically acceptable salt of ropivacaine in the manufacture of pharmaceutical preparations for pain relief post operatively and in labour.

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At the dosages 0.3% and 0.2% ropivacaine gives about the same motor blockade. At the dosage 0.1% it is less.

Conclusion

From the unique effect of ropivacaine the conclusion can be drawn that said compound is especially useful for administering at low dosage to patients in the need of post surgical and labour pain treatment, with good balance between sufficient sensoric block and a desirable minimal degree of motor block.



I claim:

1. A method of treating a human so as to relieve pain with minimal motor blockade, said method comprising epidurally administering to said human a composition comprising a pharmaceutically acceptable salt of ropivacaine, wherein said ropivacaine is present in said composition at a concentration of less than 0.5% by weight.

2. The method of claim 1, wherein said ropivacaine is present in said composition at a concentration of between 0.01% and 0.45% by weight.

3. The method of claim 1, wherein said ropivacaine is present in said composition at a concentration of between 0.01% and 0.3% by weight.

4. The method of claim 1, wherein said ropivacaine is present in said composition at a concentration of about 0.25%.

5. The method of claim 1, wherein said ropivacaine is present in said composition at a concentration of about 0.3%.

6. The method of claim 1, wherein said pharmaceutically acceptable salt of ropivacaine is ropivacaine hydrochloride.

7. The method of any one of claims 1–6, wherein said composition is administered by continuous infusion.

* * * * *