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SUPERINTENDENCIA

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PATENTE DE INVENCION

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21. EXPEDIENTE No.

54. TÍTULO Composiciones terapéuticas para la
administración Intranasal de Ketorolac.

KETOROLAC

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31/167 AG/K 9108 AG/P 25/06.

71. SOLICITANTE Roxro Pharma Inc.

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22. BOGOTÁ, D. C., Mayo 24/07.

N. 27-07-2007

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☒ Patente de invención

☐ Modelo de Utilidad

☐ Capítulo I.

☒ Capítulo II.

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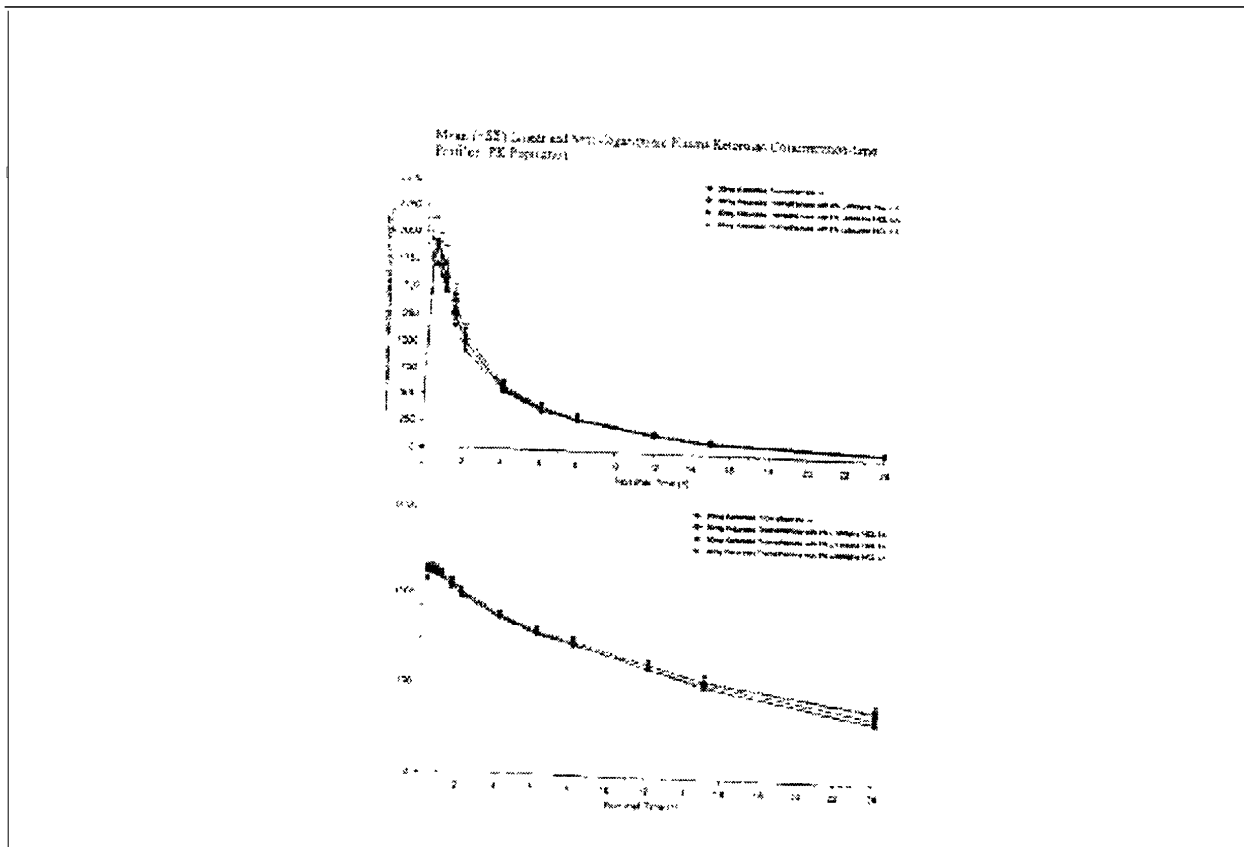
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10)

ANEXOS

- ☒ Comprobante de pago de la tasa de presentación de la solicitud
- ☐ Comprobante de pago por reivindicación de prioridad
- ☐ Documento que acredite la existencia y representación legal cuando el solicitante sea persona Jurídica
- ☐ Poderes, si fuera el caso
- ☐ Documento de cesión del inventor al solicitante o a su causante
- ☐ Declaraciones
- ☒ Copia de la solicitud Internacional. (Resumen, descripción, reivindicación, Dibujos).
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicación, Dibujos)
- ☐ Copia del examen preliminar efectuado por la IPEA
- ☐ De ser el caso, copia del contrato de acceso
- ☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas
- ☐ De ser el caso, certificado de depósito del material biológico
- ☐ Arte final 12 x 12 y 6 x 6 cm
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionados parcial o totalmente con la invención de esta solicitud.
- ☒ Otros:
 1. Reporte internacional de búsqueda

11) FIGURA CARACTERÍSTICA:



12) Solicitud concesión de la patente,

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FIRMA:

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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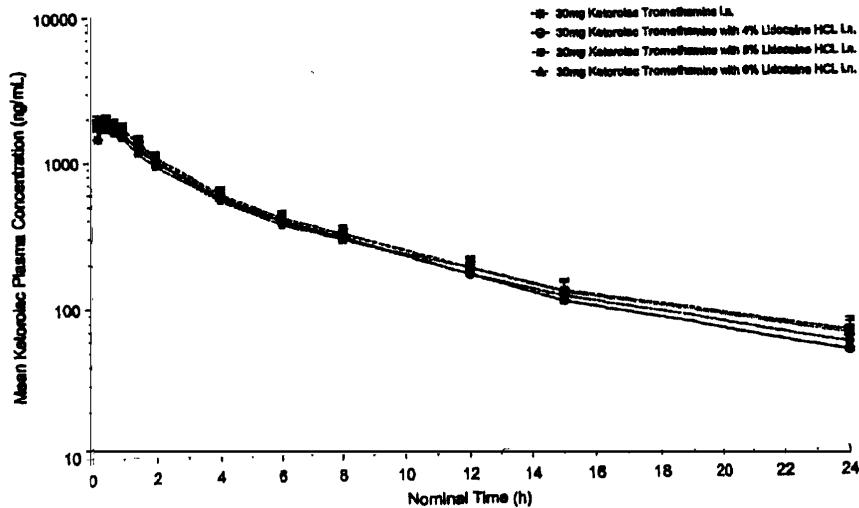
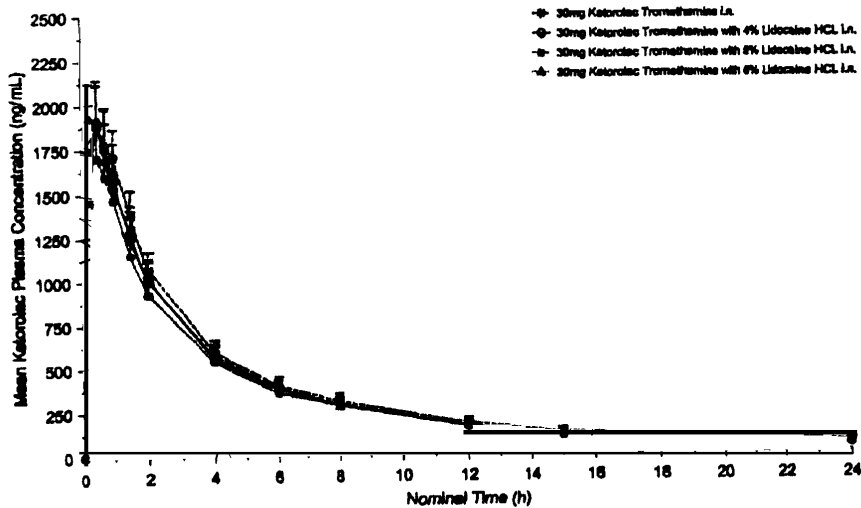
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[Continued on next page]

(54) Title: THERAPEUTIC COMPOSITIONS FOR INTRANASAL ADMINISTRATION OF KETOROLAC

Mean (+SE) Linear and Semi-logarithmic Plasma Ketorolac Concentration-time
Profiles: PK Population



(57) Abstract: Therapeutic compositions, particularly sprayable aqueous compositions, comprise ketorolac or a pharmaceutically acceptable salt, in combination with a local anesthetic, such as lidocaine hydrochloride. The compositions are nasally administered to a subject in need thereof to treat pain or inflammation and have the benefit of reduced stinging and improved efficacy, compared to known nasally administered compositions.

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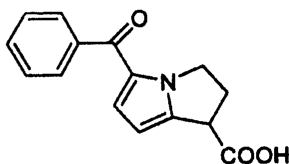
THERAPEUTIC COMPOSITIONS FOR INTRANASAL ADMINISTRATION OF KETOROLAC

Field of the Invention

5 [0001] This invention relates to therapeutic compositions with analgesic and anti-inflammatory activity, suitable for intranasal administration, which include ketorolac or its pharmaceutically acceptable salts as the active ingredient and a local anesthetic to reduce the sensation of stinging and to improve efficacy. This invention also relates to a therapeutic method that provides for the nasal administration of the composition to a subject to treat
10 pain, wherein the subject has a reduced sensation of stinging and the efficacy is improved compared to a known composition.

Background of the Invention

[0002] Ketorolac or 5-benzoyl-2,3-dihydro-1H-pyrrolizine-1-carboxylic acid has the following formula (I):



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It has been known for several years (U.S. Patent No. 4,089,969) and is used in human therapy as an analgesic and an anti-inflammatory as the tromethamine salt. U.S. 4,089,969 is incorporated herein by reference.

20 [0003] Both the racemic form and each of the dextro and levo isomers of this compound are known. Many pharmaceutically acceptable salts, the most commonly used of which is the tromethamine (2-amino-2-hydroxymethyl-1,3-propanediol) salt, are also known. Hereinafter, the name ketorolac shall encompass individually or collectively the racemic mixture or either optically active compound and shall encompass the free acid as

well as the tromethamine salt or any other pharmaceutically acceptable salt of any one of the foregoing.

[0004] Ample literature is available on ketorolac (for instance, "Ketorolac - A review of its pharmacodynamic and pharmacokinetic properties and its therapeutic potential", Drugs 39(1): 86-109, 1990). It is described as a drug with considerably higher analgesic activity than many other non-steroidal anti-inflammatory drugs. Most significantly, it has analgesic activity comparable to that of the opiates, such as morphine, without the well-known side effects of the latter.

[0005] It's known that ketorolac can be formulated as a nasally administratable composition. See U.S. Patent 6,333,044 to Recordati. However, it is found that in some subjects there is an adverse local reaction in the nasal passages that results in the sensation of stinging or irritation. While the nasal composition of ketorolac has many advantages discussed in the Recordati patent, to help patient acceptance, any stinging sensation should be minimized while at the same time not adversely affecting the pharmacokinetic profile of the nasal formulation.

[0006] A number of substances are known as local anesthetics and are applied topically in various situations to deaden the sensation of pain. These local anesthetics are generally known not to be active in solution and thus are generally applied as suspensions or in some topical formulation wherein the active anesthetic is not dissolved. Surprisingly, it has now been found that a solution of a local anesthetic can be used with ketorolac to minimize the stinging sensation in certain people who experience stinging when ketorolac is nasally administered.

[0007] US Patent Application Publication No. 2003/0022894 A1 describes a composition that is a combination of a cGMP PDE V inhibitor in combination with a local anesthetic for nasal administration. As discussed in that publication, there are certain problems in attempting to administer a PDE V inhibitor (e.g., Viagra®). The PDE V inhibitors are vasodilators, and nasal administration leads to multiple dilation of the vessels of the nasal mucosa, and this, it is claimed, results in itching, stinging, eye watering, or other irritation in certain patients. The amount of the local anesthetic used in that dosage

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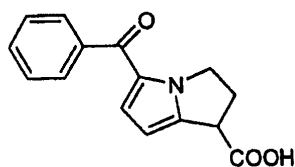
form is generally distinctly less than that necessary to obtain topical anesthesia.

Specifically, in paragraph [0072] of U.S. Patent Publication 2003/0022894 A1, it is taught that "the compositions. . . contain the local anaesthetic(s) in lower concentrations than the standard amount in commercially available topical preparations for surface anaesthesia, namely in a concentration of less than 4% (m/v)." Contrary to the teaching of that US patent publication, we have found that the stinging due to the ketorolac administration (ketorolac not being a vasodilator) can be decreased by using an amount more than 4% w/v (i.e., weight volume, which is interchangeable with mass volume – m/v and is defined as the mass of a substance in grams ("g") divided by the volume of the solution in liters ("L") times 100%: % g/L) in the composition as a solution to reduce the stinging problem as experienced by certain members of the population.

[0008] UK patent application GB 2315673 A is drawn to the treatment of migraine by administering a local anesthetic and a 5-HT_{1D} agonist intranasally. This is based on the hypothesis that the absorption of the 5-HT_{1D} agonist will be enhanced by the presence of the local anesthetic, which is thought to have a vasodilative effect. It is claimed that increased absorption should lead to faster distribution and onset of action of the 5HT_{1D} agonist. No data is provided to support this hypothesis, and no mention is made regarding the time that the maximum concentration of the 5HT_{1D} is reached. Surprisingly, it has now been found that in preferred formulations of the invention the time (T_{max}) for ketorolac to reach its maximum, or peak, concentration (C_{max}) is shortened thus providing better pain relief.

Summary of the Invention

[0009] One aspect of this invention is a composition for nasal administration that comprises an effective amount of the compound 5-benzoyl-2,3-dihydro-1H-pyrrolizine-1-carboxylic acid, of the formula (I)



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an optically active form thereof, the racemic mixture, or a pharmaceutically acceptable salt thereof, in combination with a pharmaceutically acceptable diluent and 4% - 10% w/v of a local anesthetic, e.g., lidocaine hydrochloride. Preferably the compound is ketorolac tromethamine present at a level of about 2.5 - 22.5% (w/v), the anesthetic is present at a level of 5% to 10% w/v, and the composition is a sprayable aqueous solution.

[0010] Another aspect of this invention is a composition for spraying into a human subject's nasal passage that comprises

- (a) water;
- (b) the compound 5-benzoyl-2,3-dihydro-1H-pyrrolizine-1-carboxylic acid, an optically active form thereof, a racemic mixture, or a pharmaceutically acceptable salt (e.g., tromethamine) wherein the compound is dissolved in water at a level sufficient to be absorbed by the subject to treat pain or inflammation;
- (c) a local anesthetic (e.g., lidocaine hydrochloride) dissolved in the water at a level sufficient to reduce any stinging sensation caused by nasally administering the compound alone to the subject; and
- (d) optionally other pharmaceutically acceptable excipients.

[0011] Another aspect of this invention is a method for treating pain or inflammation in a subject in need of such treatment, which comprises intranasally administering the composition of this invention to the subject.

[0012] Another aspect of the invention is the composition of the invention in a vessel equipped with a device for spraying the composition into a patient's nasal passage.

[0013] Another aspect of the invention is the use of the compound 5-benzoyl-2,3-dihydro-1-H-pyrrolizine-1-carboxylic acid, an optically active form thereof, the racemic mixture, or a pharmaceutically-acceptable salt thereof, in combination with a local

anesthetic, to prepare a composition for nasal administration to a subject for the treatment of pain or inflammation.

[0014] An important characteristic of all aspects of the invention is that the anesthetic is chosen to be present at a level that does not adversely affect the plasma pharmacokinetics (PK) of ketorolac.

Drawings

[0015] Figure 1 shows the mean linear and semi-logarithmic plasma ketorolac concentration profiles over 24 hours.

[0016] Figure 2 shows the mean linear and semi-logarithmic lidocaine concentration over 24 hours.

Detailed Description of the Invention

[0017] All cited patents and literature are incorporated by reference in their entirety.

[0018] We have now found that it is possible to prepare analgesic/anti-inflammatory formulations containing ketorolac as an active ingredient, for the treatment of pain and/or inflammation in a human subject. The formulations are suitable for intranasal administration of a therapeutically effective amount to a subject so that ketorolac so administered is rapidly and thoroughly absorbed, giving therapeutic effects equivalent to or better than those obtained by the previously described intranasal formulation with reduced stinging experienced by some subjects. The formulation is designed to employ an amount of the anesthetic that reduces the sensation of stinging in those patients that might otherwise experience such a sensation upon nasal administration, while not resulting in a sensation of numbness. Importantly, it appears that the PK of ketorolac are not adversely affected by the presence of the anesthetic. That is, the plasma ketorolac concentration vs. time is not significantly modified in an adverse manner by the presence of the anesthetic. Surprisingly, the presence of the anesthetic, e.g. lidocaine hydrochloride at the preferred level of 5-6% w/v, actually decreases the T_{max} for ketorolac to reach its C_{max} in a subject's plasma.

This provides an unexpected advantage over a nasal formulation of ketorolac without lidocaine hydrochloride, in that a faster time to Cmax generally provides a subject with better pain relief.

[0019] The intranasal formulations of the invention contain ketorolac concentrations ranging from 2.5 to 22.5%, for example 5 % to 20%, preferably about 15% w/v based on the final formulation. Alternatively this can be expressed as 25-225 milligrams (mg) per milliliter (mL), preferably 50-200 mg/mL, and most preferably 150 mg/mL. Of course, the selection of the particular excipients depends on the desired formulation dosage form, i.e., on whether a solution to be used in drops or as a spray (aerosol) is desired or whether a suspension, ointment or gel to be applied directly to the nasal cavity is desired. In any case, the invention enables the preparation of single-dose or multi-dose dosage forms, which ensure application of an optimum quantity of drug. Generally, a subject is administered about 25 to 200 microliters of the sprayable aqueous formulation of this invention, preferably 50 to 100 microliters, in one or both nostrils. For example, 100 μ L of a 15% (pH 7.2) w/v solution of ketorolac into each nostril, would result in up to 30 mg of ketorolac in the subject's plasma. While the composition is usually administered four times a day, under certain circumstances it may be administered less frequently if appropriate. Intranasal administration of a composition according to the invention in amounts ranging between 0.5 milligrams (mg)/kilograms (kg)/day and 4 mg/kg/day will generate plasma levels of ketorolac within the range of 0.3-5 mg/L of plasma, which is generally efficacious in treating moderate to severe pain, whether of a pathological or neuropathic origin, such as trauma-inflicted pain, post-operative pain, migraine, and the like. In general, a subject that is 18 to 65 years old could receive up to 120 mg per day of ketorolac by intranasal administration of 100 microliters per nostril of a 15% w/v ketorolac solution 4 times per day. A subject that is an adolescent or is older than 65 could receive 60 mg per day by intranasal administration of 50 microliters per nostril of a 15% w/v ketorolac formulation 4 times a day. Children 12 and under would receive appropriately less.

[0020] The preferred diluent for the formulations according to the invention is water, and other excipients may be added if desired. The preferred 15% w/v ketorolac formulation is hypertonic, i.e., it exhibits an osmotic pressure that is greater than that of

biological fluids. In cases where the concentration of ketorolac is lower, it may be useful to add an isotonicity agent selected among those commonly used in pharmaceuticals.

Substances used for this purpose are, for instance, sodium chloride and glucose. The quantity of isotonicity agent will depend on the desired osmotic pressure of the formulation (taking into account the osmotic effect of the active ingredient). Generally this will be in the range of about 150 to about 850 milliosmoles (mOsm).

[0021] Should a suspension or gel be desired instead of a solution, appropriate oily or gel vehicles may be used or one or more polymeric materials may be included, which desirably should be capable of conferring bioadhesive characteristics to the vehicle.

[0022] Several polymers are used in pharmaceuticals for the preparation of a gel; the following can be mentioned as nonlimiting examples: hydroxypropyl cellulose (KLUCEL®), hydroxypropyl methyl cellulose (METHOCEL®), hydroxyethyl cellulose (NATROSOL®), sodium carboxymethyl cellulose (BLANOSE®), acrylic polymers (CARBONOL®, POLYCARBOPHIL®), gum xanthan, gum tragacanth, alginates and agar-agar. The parenthetical phrase provides a trade name of a product available on the open market.

[0023] Some of them, such as sodium carboxymethyl cellulose (often abbreviated as sodium CMC) and acrylic polymers, have marked bioadhesive properties and are preferred if bioadhesiveness is desired.

[0024] Other formulations suitable for intranasal administration of ketorolac can be obtained by adding to the aqueous vehicle polymers capable of changing the rheologic behavior of the composition in relation to the temperature.

[0025] These polymers make it possible to obtain low viscosity solutions at room temperature, which can be applied for instance by nasal spray and which increase in viscosity at body temperature, yielding a viscous fluid which increases the likelihood of a longer contact with the nasal mucous membrane. Polymers of this class include without limitation polyoxyethylene-polyoxypropylene block copolymers (POLOXAMER®).

Polyoxyethylene is often abbreviated as POE, while polyoxypropylene is abbreviated as POP.

5 [0026] In addition to aqueous, oil or gel diluents, other diluents which may be used in the compositions according to the invention comprise solvent systems containing ethyl alcohol, isopropyl alcohol, propylene glycol, polyethylene glycol, mixtures thereof or mixtures of one or more of the foregoing with water.

[0027] In any case, a pharmaceutically acceptable buffer should be present in order to create optimum pH conditions for both product stability and tolerance (pH range about 4 to about 8; preferably about 6.0 to 7.5). Suitable buffers include without limitation tri-
10 (tromethamine) buffer, phosphate buffer, etc. Preferably potassium phosphate NF is used to adjust the pH to 7.2.

[0028] Other excipients include chemical enhancers such as absorption promoters. These include fatty acids, bile acid salts and other surfactants, fusidic acid, lysophosphatides, cyclic peptide antibiotics, preservatives, carboxylic acids (ascorbic acid,
15 amino acids), glycynethetic acid, o-acylcarnitine. Preferred promoters are diisopropyladipate, POB(9) lauryl alcohol, sodium glycocholate and lysophosphatidyl-choline which proved to be particularly active.

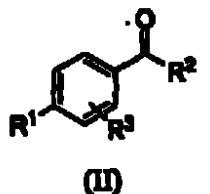
[0029] Another excipient that may be present in a composition of this invention is a chelator, i.e. a substance that binds primarily di- or tri valent metallic ions (e.g. calcium)
20 that might interfere with the stability or activity of the active ingredient. Chelators are known to those of skill in the art by referring to the recent edition of "Remington's Pharmaceutical Sciences." A preferred chelator is sodium ethylenediamine tetraacetic acid (sodium EDTA), USP.

[0030] Finally, the compositions of the invention preferably contain preservatives
25 that ensure the microbiological stability of the active ingredient. Suitable preservatives include without limitation, methyl paraoxybenzoate (methyl paraben), propyl paraoxybenzoate (propyl paraben), sodium benzoate, benzyl alcohol, benzalkonium chloride and chlorobutanol.

[0031] The liquid ketorolac formulations, preferably in the form of solutions, may be administered in the form of drops or spray, using atomizers equipped with a mechanical valve and possibly including a propellant of a type commercially available, such as butane, N₂, Ar, CO₂, nitrous oxide, propane, dimethyl ether, chlorofluorocarbons (e.g., FREON) etc.
 5 Diluents (e.g. a solvent) suitable for spray administration are water, alcohol, glycol, glycerol, and propylene glycol, used alone or in a mixture of two or more. Preferably water is employed as the sole solvent.

[0032] The local anesthetics which can be used according to the invention are known per se and are listed, for example, in Remington's Pharmaceutical Sciences 1990, pp. 1048-1056. Local anesthetics are compounds which reversibly inhibit the excitability of sensory nerve endings or the neuronal conductivity for pain or other sensory stimuli in a limited region of the body without causing permanent harm (cf. J. L. McGuire (editor), Pharmaceuticals, volume 2, Wiley-VCH, Weinheim 2000, pp. 539, et seq.). Local anesthetics within the meaning of the present invention are preferably intended to mean
 10 substances which are listed in the Index Nominum 2000, International Drug Directory, Scientific Publishers Stuttgart 2000 with the therapeutic category "local anesthetic". Depending on the specific anesthetic used and the sensitivity of the patient, the anesthetic is present at a level of 4 to about 10% w/v.

[0033] Local anesthetics preferred according to the present invention are compounds
 20 of the formula (II)



in which

R₁ represents H, NH₂, NH(C₁₋₆ alkyl), O-C₁₋₆ alkyl or CH₂OPh;

25 R₂ represents O-C₁₋₆ alkyl which may optionally have a radical from the group consisting of NH(C₁₋₆ alkyl), N(C₁₋₆ alkyl)₂ or a saturated 5- or six-membered heterocycle

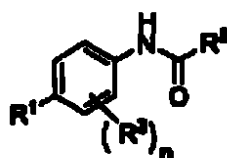
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which contains at least one nitrogen atom and is linked via the latter, and optionally one or two further heteroatoms from the group consisting of N, O, S, and optionally carries one to three further C₁₋₄-alkyl radicals, or

R² represents (CH₂)₁₋₄-Het, where Het represents a saturated 5- or six-membered heterocycle which contains at least one nitrogen atom and is linked via the latter, and optionally one or two further heteroatoms from the group consisting of N, O, S, and optionally carries one to three further C₁₋₄-alkyl radicals; and

R³ represents H, halogen or O-C₁₋₄-alkyl.

[0034] Other useful compounds include those of the formula (III)



(III)

in which

R¹ represents H or OH;

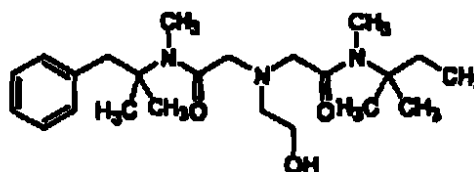
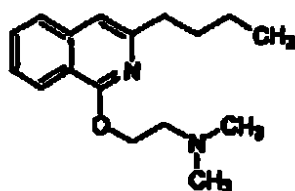
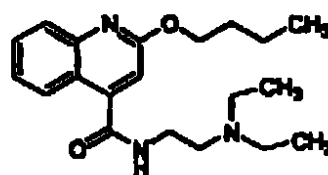
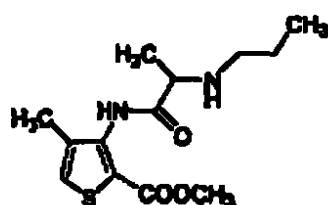
R² represents C₁₋₄-alkyl-N(C₁₋₄-alkyl)₂ where the bridging alkyl chain may optionally carry one or more C₁₋₄-alkyl radicals, or represents a saturated 5- or six-membered heterocycle which contains at least one nitrogen atom and optionally one or two further heteroatoms from the group consisting of N, O, S, and optionally carries one to three further C₁₋₄-alkyl radicals,

R³ represents C₁₋₄-alkyl, halogen or COOC₁₋₄-alkyl; and

n represents 1 or 2.

[0035] Other useful compounds are chosen from the group consisting of

15

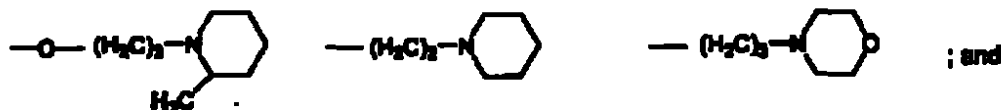


and polidocanol and benoxinate, and physiologically acceptable salts and/or hydrates thereof.

[0036] Particularly preferred local anesthetics according to the invention are those of the formula (II), above, in which

R^1 represents H, NH_2 , $NH-n-C_4H_9$, $O-n-C_3H_7$, $O-n-C_4H_9$ or CH_2OPh ;

R^2 represents OC_2H_5 , $O-n-C_4H_9$, $O-(CH_2)_2N(C_2H_5)_2$, $O(CH_2)_2N(CH_3)_2$, or a radical from the group consisting of



R^3 represents H, Cl, $O-n-C_3H_7$, or $O-n-C_4H_9$.

[0037] Other preferred compounds are those of formula (III), above, in which

R^1 represents H or OH;

R^2 represents $CH_2N(C_2H_5)_2$, $CHCH_3NH-n-C_3H_7$, $CH_2NH-n-C_4H_9$, or a radical from the group consisting of

17



R^3 represents CH_3 , Cl or $COOCH_3$;

n represents 1 or 2;

and benoxinate and physiologically acceptable salts and/or hydrates thereof.

[0038] The local anesthetics that can be particularly preferably employed according to the invention are: benzocaine, butambene, piperocaine, piperocaine hydrochloride, procaine, procaine hydrochloride, chlorprocaine, chlorprocaine hydrochloride, oxybuprocaine, oxybuprocaine hydrochloride, proxymetacaine, proxymetacaine hydrochloride, tetracaine, tetracaine hydrochloride, nirvanin, lidocaine, lidocaine hydrochloride, prilocaine, prilocaine hydrochloride, mepivacaine, mepivacaine hydrochloride, bupivacaine, bupivacaine hydrochloride, ropivacaine, ropivacaine hydrochloride, etidocaine, etidocaine hydrochloride, butamylcaine, butamylcaine hydrochloride, articaine, articaine hydrochloride, cinchocaine, cinchocaine hydrochloride, oxetacaine, oxetacaine hydrochloride, propipocaine, propipocaine hydrochloride, dyclonine, dyclonine hydrochloride, pramocaine, pramocaine hydrochloride, fencocaine, fencocaine hydrochloride, quinisocaine, quinisocaine hydrochloride, benoxinate and polidocanol. These compounds are commercially available or can be prepared in a way known to the skilled person, for example as described in J. L. McGuire (editor), *Pharmaceuticals*, volume 2, Wiley-VCH 2000, pp. 539 et seq.

[0039] Local anesthetics that can preferably be used according to the invention are benoxinate, lidocaine, tetracaine, benoxinate, polidocanol or their pharmaceutically acceptable salts. Lidocaine, lidocaine hydrochloride, and lidocaine methanesulphonate are particularly preferred. The local anesthetic is present according to the invention at a level of 4 to about 10% w/v, preferably about 5-6% w/v. While 4-10% w/v is the general range, adjustments to narrow the range may be useful, e.g. 5-10%, 5-9%, 5-8%, 5-7%, and the like.

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[0040] Illustrative formulations may contain the following ingredients and amounts (w/v) in addition to ketorolac, water, and the anesthetic.

Ingredient	Broad Range (%)	Preferred Range (%)
Chelator (1)	0.001 - 1	0.01 - 0.1
Preservative (2)	0 - 2	0 - 0.25
Absorption promoter (3)	0 - 10	0 - 10
Gelling polymer (4)	0 - 5	0 - 3
Co-solvent (5)	0 - 99	0

(1) E.g., sodium EDTA

5 (2) E.g., methyl paraoxybenzoate or propyl paraoxybenzoate or mixtures thereof

(3) E.g., sodium glycocholate

(4) E.g., sodium CMC

(5) E.g., glycerol

10 [0041] It will be appreciated by those of ordinary skill that ingredients such as sodium CMC and polymers designated as CARBOPOL exist in many types differing in viscosity. Their amounts are to be adjusted accordingly. Different adjustments to each formulation may also be necessary including omission of some optional ingredients and addition of others. It is thus not possible to give an all-encompassing amount range for each
15 ingredient, but the optimization of each preparation according to the invention is within the skill of the art.

[0042] Another alternative for the intranasal administration of the ketorolac-based compositions comprises a suspension of finely micronized ketorolac (generally from 1 to 200 micrometers, preferably from 5 to 100 micrometers) in a propellant or in an oily vehicle
20 or in another vehicle in which the drug is not soluble. The vehicle is mixed or emulsified with the propellant. Vehicles suitable for this alternative are, for instance, vegetable and mineral oils and triglyceride mixtures. Appropriate surfactants, suspending agents and

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5 diluents suitable for use in pharmaceuticals are added to these vehicles. Surfactants include, without limitation, sorbitan sesquioleate, sorbitan monooleate, sorbitan trioleate (amount: between about 0.25 and about 1%); suspending agents include, without limitation, isopropyl myristate (amount: between about 0.5 and about 1%) and colloidal silica (amount: between about 0.1 and about 0.5%); and diluents include, without limitation, zinc stearate (about 0.6 to about 1%).

[0043] Compositions of the invention are administered to a patient in need thereof by contacting the patient's nasal passage, with an amount of the composition sufficient to result in absorption of ketorolac by the patient to reduce the pain and/or inflammation experienced by the patient. This is preferably carried out by spraying a solution, as described herein, into the nasal passage(s) of the patient from a vessel that is equipped with a device (e.g., an atomizer) for producing a spray (e.g. atomized particles). The device produces a mist or suspension of fine liquid particles that are inhaled by the patient into her or his nasal passage(s) from which it is rapidly absorbed into the bloodstream to effect its analgesic and anti-inflammatory action. Appropriate vessels and spray devices are available to one of skill in the art by referring to "Remington's Pharmaceutical Sciences." One source for such vessels is Ing. Erich Pfeiffer GmbH, Radolfzell, Germany. Another source is Valois, 50 avenue de l'Europe, 78164 MARLY-LE-ROI, France.

[0044] The following examples of formulations for the intranasal administration of ketorolac serve to illustrate the invention without limiting its scope.

EXAMPLE 1:

[0045] This example provides a description for making compositions for nasal administration in accordance with the invention. A solution was prepared in accordance with the proportions shown in Table 1. Lidocaine hydrochloride was added to the solution to give the compositions of the invention shown in Table 2.

20

Table 1

Ketorolac tromethamine, USP	15%
Sodium EDTA, NF	0.02%
Potassium phosphate, NF	(q.s. to pH 7.2)
Water for Injection USP (q.s.)	100 g

Table 2.

Ingredients	I	II	III
Ketorolac tromethamine, USP	15%	15%	15%
Sodium EDTA, NF	0.02%	0.02%	0.02%
Potassium phosphate, NF (q.s. to pH 7.2)			
Lidocaine hydrochloride	4%	5%	6%
Water for Injection USP (q.s.)	100 g	100 g	100 g

5

EXAMPLE 1:

[0044] This example provides a description of a phase I clinical study (a double-blind, randomized 4-way crossover) carried out to determine, *i.e.*, if the presence of lidocaine hydrochloride in nasally administered formulations of ketorolac has any adverse effect on the PK profile of ketorolac. The results show that the PK characteristics are improved in the preferred formulations (5-6% w/v) by the presence of the anesthetic lidocaine hydrochloride, and otherwise not adversely affected. In addition, the safety and tolerability data for the formulations were evaluated.

[0045] The clinical study included 16 healthy volunteers who were recruited for the study in which each volunteer received 4 nasally administered spray formulations, three of which are compositions that represent an aspect of the invention. There was a wash-out period of 3-7 days between each dose. The four aqueous spray compositions were prepared as follows:

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	KT(1)	L(2)	NaEDTA(3)	KPO ₄ (4)	Water(5)
A:	15%	0	0.02%	pH 7.2	100g
B:	15%	4%	0.02%	pH 7.2	100g
C:	15%	5%	0.02%	pH 7.2	100g
D:	15%	6%	0.02%	pH 7.2	100g

(1) Ketorolac tromethamine, USP

5 (2) Lidocaine hydrochloride, USP

(3) Sodium EDTA, NF

(4) Potassium phosphate, NF

(5) Water for injection, USP

[0046] Formulation A is known and was included for comparative purposes.

10 Formulations B-D are compositions of the invention with C and D being preferred.

[0047] Blood was drawn from each participant as follows: Pre-dose (time(0) = 0 HR), 0.25, 0.50, 0.75, 1, 1.5, 2, 4, 6, 8, 12, 15, and 24 hours. The blood samples were analyzed for the levels of ketorolac and lidocaine to determine the ketorolac and lidocaine plasma concentrations in nanograms (ng) per milliliter (mL). These values were then

15 combined to obtain the mean concentration time profiles in the participant population. The results for ketorolac are shown in Figures 1 (linear) and 2 (semi-logarithmic), while the results for lidocaine are shown in Figures 3 (linear) and 4 (semi-logarithmic). In each plot "SE" is the standard error. Each subject received a medical screening within 21 days of study drug administration in period 1. Subjects eligible to take part in the study took part in

20 4 periods. The subjects were admitted to the Unit on Day -1 of each period and remained resident until the morning of Day 2. A washout of 3-7 days occurred between each period. A post study medical was performed within 7 days of dosing on the last treatment period.

[0048] It is clear from Figures 1 and 2 that the PK for ketorolac is essentially unaffected by the presence of 4% lidocaine, while the preferred formulation reduced the time to C_{max}.

5 [0049] Each patient was evaluated by a clinician to determine the level of edema, erythema, ulceration, numbness, and stinging of the nasal passages. While the results tended to show that the subjects experienced reduced sensation of stinging, they were not conclusive due to difficulties in the evaluation process.

EXAMPLE 3

10 [0050] This example describes a study for postoperative patients to compare the safety, tolerability, and pharmacokinetics (PK) of 3 formulations of intranasal (IN) ketorolac tromethamine.

[0051] The study is a double-blind, parallel study in postoperative patients. Subjects receive 1 of 3 formulations of IN ketorolac tromethamine 30 mg or placebo. Two
15 of the formulations are preferred formulations according to this invention. The study includes enrolling fifteen subjects in each group for a total of 60 subjects. Each formulation is administered to each subject IN (one spray into each nostril).

[0052] Postoperative patients suitable for the study include patients age 18 through-
20 60 years, with body weight within 20% of ideal body weight as per the MetLife height and weight tables for men and women (version 1999).

[0053] Subjects are randomly assigned to receive either:

- 25 ☐ Treatment A (a composition known in the art) – single IN dose of 30 mg ketorolac tromethamine (one spray into each nostril of 100 μ L of a 15% (pH 7.2) solution).
- ☐ Treatment B (a preferred composition of this invention) – single IN dose of 30 mg ketorolac tromethamine with 5% lidocaine hydrochloride (one spray into each nostril of 100 μ L of a 15% (pH 7.2) solution).

- ☐ Treatment C (a preferred composition of this invention) – single IN dose of 30 mg ketorolac tromethamine with 6% lidocaine hydrochloride (one spray into each nostril of 100 μ L of a 15% (pH 7.2) solution).
- ☐ Treatment D – single IN dose of placebo (one spray into each nostril of 100 μ L of vehicle solution).

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Procedures

Safety assessments	
Clinical laboratory evaluations	Blood and urine samples for clinical laboratory tests are taken at screening. A urine pregnancy test is performed at screening for all women of childbearing potential.
Vital signs measurements and ECG recordings	Supine blood pressure and pulse are measured at screening and at the following timepoints during periods 1-4: predose (within 30 minutes of ketorolac administration), 2 h and 24 h postdose.
Tolerability assessments	Subjects are asked to complete a nasal irritancy questionnaire during all periods at the following timepoints: predose (within 15 minutes of ketorolac administration), 0-5 min, 15 min, 30 min, 1 h, and 24 h postdose.
Physical examination	A physical examination is performed at screening.
Nasal examination	A nasal examination is performed predose (within 30 minutes of ketorolac administration), 15 min, 30 min, 1 h, and 24 h postdose.
Adverse events	Subjects are queried about any adverse events they may have experienced at regular intervals throughout the study.

Data Analysis

- [0054] Nasal irritation scores and adverse event data are tabulated by treatment group, physical findings and laboratory test results are listed by subject.

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APPENDIX OF PRODUCT NAMES AND EXAMPLES OF COMMERCIAL SOURCES

KETOROLAC TROMETHAMINE: Union Quimico Farmaceutico, S.A., Spain

HYDROXYPROPYLCELLULOSE (KLUCEL®) Dow Chemical Co, Midland MI USA

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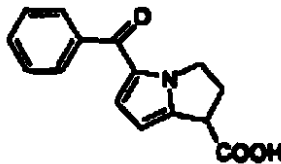
- HYDROXYPROPYLMETHYLCELLULOSE (METHOCEL®) Dow Chem. Co, Midland MI
- HYDROXYETHYLCELLULOSE (NATROSOL®) Hercules Inc, Wilmington DE USA
- SODIUM CARBOXYMETHYLCELLULOSE (BLANOSE®) Hercules Inc, Wilmington DE
- 3 CARBOPOL®: BF Goodrich Chemical Co., Cleveland, OH, USA
- POLYCARBOPHIL: BF Goodrich Chemical Co., Cleveland, OH, USA
- GUM TRAGACANTH: Colony Ip. & Exp. Co., New York, NY, USA
- GUM XANTHAN: Aldrich Chemie, Stanheim, Germany
- 10 SODIUM ALGINATE: Edward Mandell Co., Carmel, New York, USA
- AGAR AGAR: Aldrich Chemie, Stanheim, Germany
- POLOXAMER (LUTROL® f127): BASF Wyndotte Corp., Parsippany, NJ, USA
- ETHYL ALCOHOL: Eastman Chemical Products Inc., Kingsport, TN, USA
- ISOPROPYL ALCOHOL: Baker Chemical Co., New York, NY, USA
- 15 PROPYLENE GLYCOL: Dow Chemical Co., MIDLAND, MI, USA
- POLYETHYLENE GLYCOL: BASF Wyndotte Corp., Parsippany, NJ, USA
- DIISOPROPYLADIPATE: Croda, Gooles, North Humberide, UK
- SODIUM GLYCOCHOLATE: Sigma Chemical Company, St. Louis, MO, USA
- LYSOPHOSPHATIDYLCHOLINE: American Lecithin, Long Island, NY, USA
- 20 METHYLPARAOXYBENZOATE (NIPAGIN): BDH Chemical Ltd, Poole, Dorset, UK
- PROPYLPARAOXYBENZOATE: BDH Chemical Ltd, Poole, Dorset, UK
- SODIUM BENZOATE: Pfizer Inc., New York, NY, USA
- BENZYL ALCOHOL: BDH Chemical Ltd, Poole Dorset, UK
- BENZALCONIUM CHLORIDE: ION Pharmaceuticals, Covina, CA, USA
- 25 CHLORBUTANOL: Eastern Chemical Products, Smithtown, NY USA
- SODIUM EDTA: Grace And Co., London, UK.
- POE(9)LAURYL ALCOHOL: BASF Wyndotte Corp, Parsippany, NJ, USA
- GLYCEROL: Dow Chemical Co., Midland, MI, USA
- SODIUM CHLORIDE: Aldrich Chemie, Stanheim, Germany
- 30 GLUCOSE: Roquette Ltd, Tunbridge Wells, Kent, UK

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THE CLAIMED SUBJECT MATTER OF THE INVENTION IS:

1. A composition for nasal administration to a patient that comprises a therapeutically effective amount of the compound 5-benzoyl-2,3-dihydro-1H-pyrrolizine-1-carboxylic acid, of the formula



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an optically active form thereof, the racemic mixture, or a pharmaceutically acceptable salt thereof, in combination with a pharmaceutically acceptable diluent and 4% w/v to 10% (w/v) of a local anesthetic.

10 2. The composition of claim 1, wherein the compound is ketorolac tromethamine as a racemic mixture.

3. The composition of claim 2 comprising 25 mg - 225 mg of said compound dissolved per mL, wherein the diluent is water and the composition is liquid and sprayable.

15 4. The composition of claim 3 comprising 50-200 mg of said compound per mL.

5. The composition of claim 2 wherein a chelator is present.

6. The composition of claim 1 comprising 2.5-22.5% w/v of said compound dissolved in the diluent, which is water.

7. The composition of claim 6 containing 15% w/v of said compound.

20 8. The composition of claim 1 in a single-dose form for administration to a single patient, wherein the composition is a sprayable liquid and the diluent is water.

9. The composition of claim 1 in a multi-dose formulation, wherein the composition is a sprayable liquid and the diluent is water.

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10. The composition of claim 1 in the form of an aqueous solution.
11. The composition of claim 1, wherein the anesthetic is lidocaine hydrochloride.
12. The composition of claim 11, wherein the anesthetic is present at a level of 5% to 10% w/v, and the diluent is water, and the composition is a sprayable solution.
13. The composition of claim 11, wherein the anesthetic is present at a level of 5% to 6% w/v.
14. The composition of claim 1 contained in a vessel equipped with a device for spraying the composition into the nasal passage of a subject, wherein the composition is an aqueous solution.
15. The composition and vessel of claim 14, wherein the vessel holds about 50 to 2000 microliters (μ L).
16. The composition of claim 1, wherein the pH is 6 to 7.5.
17. A composition suitable for spraying into a human subject's nasal passage that comprises
- (a) water;
 - (b) the compound 5-benzoyl-2,3-dihydro-1H-pyrolizine-1-carboxylic acid, an optically active form thereof, a racemic mixture, or a pharmaceutically acceptable salt, wherein the compound is dissolved in water at a level sufficient to be absorbed by the subject to treat pain or inflammation;
 - (c) a local anesthetic dissolved in the water at a level sufficient to reduce the stinging sensation caused by nasally administering the compound alone to the subject; and
 - (d) optionally other pharmaceutically acceptable excipients.
18. The composition of claim 17, wherein

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- (a) water is the sole diluent,
- (b) the compound is racemic ketorolac tromethamine dissolved at 2.5-22.5% w/v,
- (c) the local anesthetic is lidocaine hydrochloride dissolved at 5-10% w/v, and
- 5 (d) the pH of the composition is adjusted to 7.2 and a chelator is present.

19. The composition of claim 18, wherein the compound is present at a level of 15% w/v, the local anesthetic is present at a level of 5-6% w/v, potassium phosphate is the pH adjuster, and the chelator is sodium EDTA.

10 20. A method for treating pain or inflammation in a subject in need of such treatment, which comprises intranasally administering the composition of any of claims 1-19.

21. The method of claim 20, wherein the method is for treating pain.

22. The method of claim 21, wherein the pain is the result of a trauma inflicted on the subject.

15 23. The method of claim 21, wherein the pain is the result of a medical operation performed on the subject.

24. The method of claim 21, wherein the pain is pathological.

25. The method of claim 21, wherein the pain is neuropathic.

20 26. The method of claim 21, wherein the pain is migraine or other headache pain.

27. The use of the compound 5-benzoyl-2,3-dihydro-1-H-pyrolizine-1-carboxylic acid, the optically active forms thereof, the racemic mixture, or a pharmaceutically salt thereof, in combination with a local anesthetic, to prepare a composition for nasal administration to a subject for the treatment of pain or inflammation.

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28. The use of claim 27, wherein the compound is ketorolac tromethamine, which is present at 2.5-22.5% w/v;

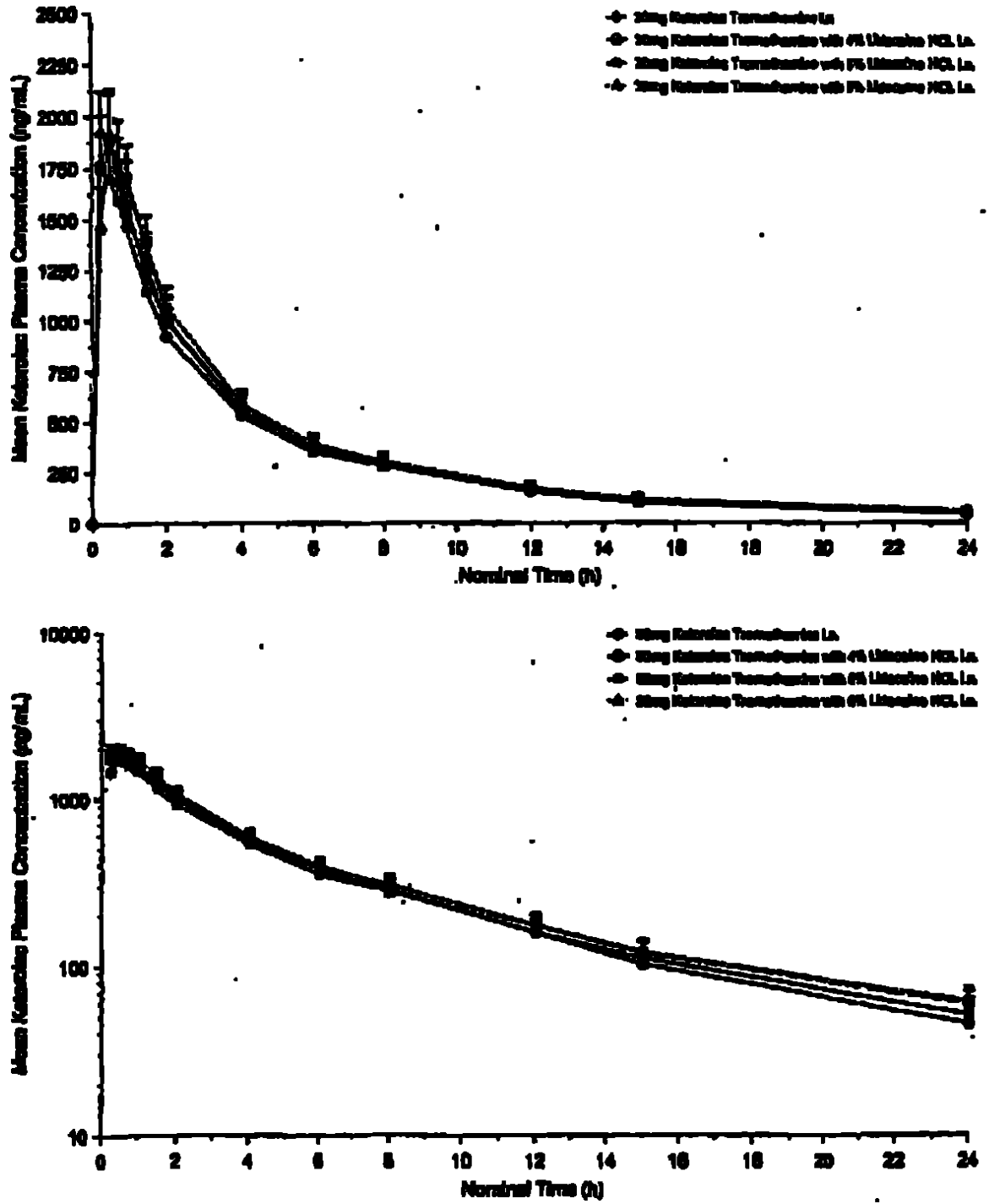
the local anesthetic is lidocaine hydrochloride, which is present at 4-10% w/v; and

the composition is an aqueous, sprayable composition having a pH of 6-8.5.

5 29. The use of claim 28, wherein the compound is present at 15% w/v, the local anesthetic is present at 5-6% w/v, the pH is 7.2, and sodium EDTA is present as a chelator.

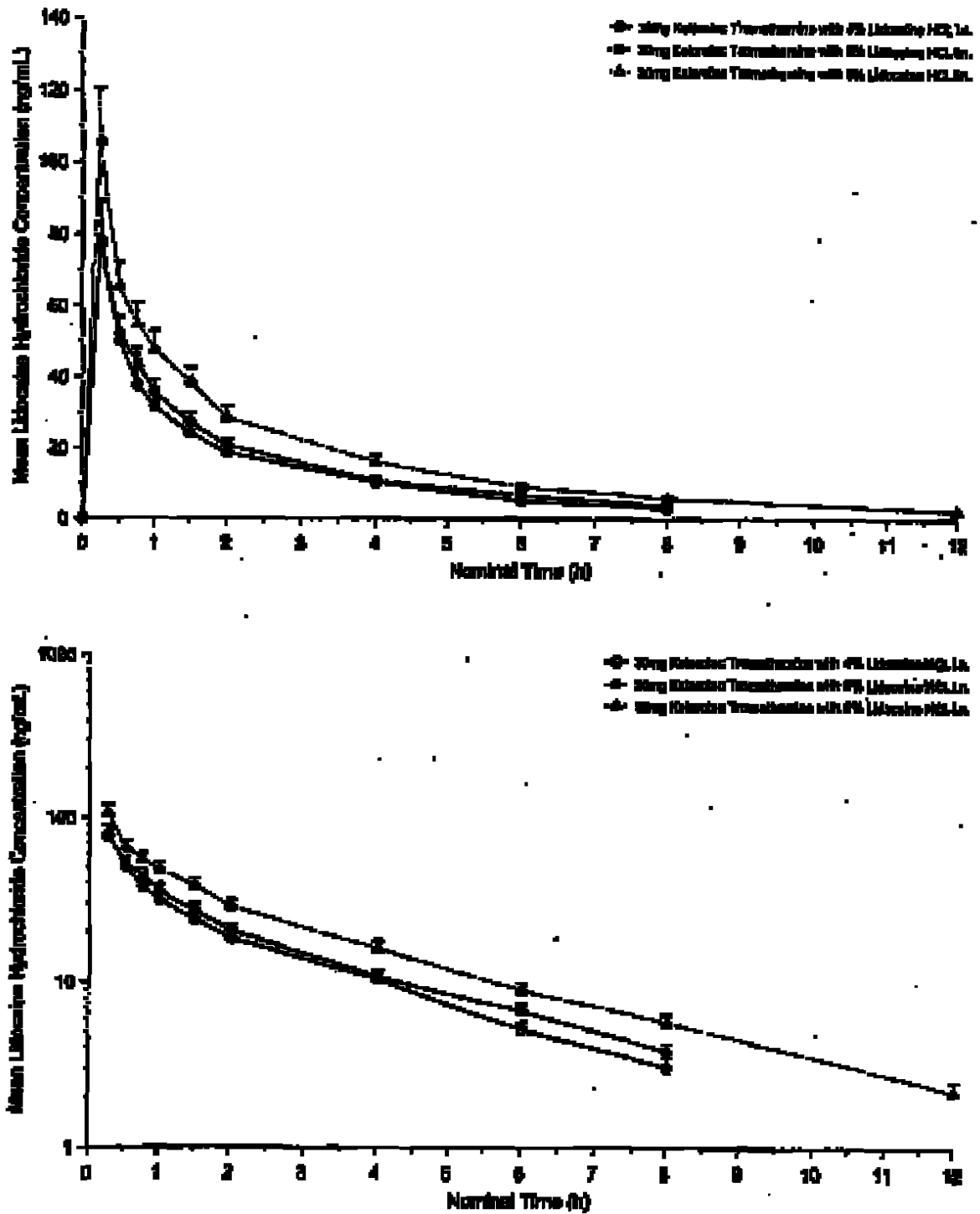
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Figure 1 Mean (+SE) Linear and Semi-logarithmic Plasma Ketorolac Concentration-time Profiles: PK Population



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Figure 2 Mean (+SE) Linear and Semi-logarithmic Plasma Lidocaine Concentration-time Profiles: PK Population



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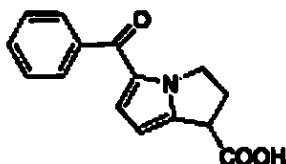
COMPOSICIONES TERAPÉUTICAS PARA LA ADMINISTRACIÓN INTRANASAL DE KETOROLAC

CAMPO DE LA INVENCION

[0001] La presente invención se refiere a composiciones terapéuticas con actividad analgésica y antiinflamatoria, adecuadas para la administración intranasal, que incluyen ketorolac o sus sales adecuadas para uso farmacéutico como principio activo, y un anestésico local para reducir la sensación de ardor y aumentar la eficacia. La presente invención también se refiere a un método terapéutico que describe la administración nasal de la composición a un sujeto para tratar el dolor, donde el sujeto tiene reducida sensación de ardor y la eficacia es mayor en comparación con una composición conocida.

ANTECEDENTES DE LA INVENCION

[0002] Ketorolac o ácido 5-benzoil-2,3-dihidro-1H-pirrolizina-1-carboxílico tiene la siguiente fórmula (I):



Se conoce desde hace varios años (Patente de los Estados Unidos N° 4.089.969) y se usa en terapia humana como analgésico y antiinflamatorio bajo la forma de la sal trometamina. La Patente de los Estados Unidos N° 4.089.969 queda incorporada a la presente mediante referencia.

[0003] Se conocen tanto la forma racémica como el levo y el dextroisómero de este compuesto. También se conocen muchas sales adecuadas para uso farmacéutico, de las cuales la de uso más habitual es la

sal trometamina (2-amino-2-hidroxi-metil-1,3-propanediol). En adelante en la presente, el nombre ketorolac comprende individual o colectivamente la mezcla racémica o cualquiera de los compuestos ópticamente activos y comprende el ácido libre así como la sal trometamina o cualquier otra sal adecuada para uso farmacéutico de cualquiera de los compuestos precedentes.

[0004] Existe una amplia literatura sobre ketorolac (por ejemplo, "Ketorolac - A review of its pharmacodynamic and pharmacokinetic properties and its therapeutic potential", Drugs 39(1): 86-109, 1990). Se la describe como una droga con actividad analgésica considerablemente más elevada que muchas otras drogas antiinflamatorias no esteroideas. Lo más significativo es que tiene actividad analgésica comparable a la de los opiáceos, como la morfina, sin sus muy conocidos efectos secundarios.

[0005] Se conoce que ketorolac se puede formular como composición administrable por vía intranasal. Ver Patente de los Estados Unidos N° 6.333.044 otorgada a Recordati. Sin embargo, se verifica que en algunos sujetos se produce una reacción adversa local en los conductos nasales que tiene como resultado una sensación de ardor o irritación. Si bien la composición nasal de ketorolac posee muchas ventajas descritas en la patente otorgada a Recordati, para ayudar a la aceptación del paciente es necesario minimizar cualquier sensación de ardor, y a la vez no afectar adversamente el perfil farmacocinético de la formulación nasal.

[0006] Se conocen una serie de sustancias como anestésicos locales que se aplican tópicamente en diversas situaciones para adormecer la sensación de dolor. Se conoce que estos anestésicos de modo general no son activos en solución, por lo que generalmente se aplican bajo la forma de

suspensiones o en alguna formulación tópica en la cual el anestésico activo no está disuelto. Notablemente, se descubrió que una solución de un anestésico local se puede usar con ketorolac para minimizar la sensación de ardor en algunas personas que experimentan ardor cuando se les administra ketorolac por vía nasal.

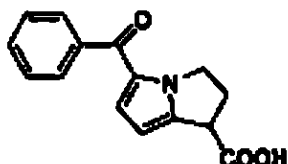
[0007] La Publicación de la Solicitud de Patente de los Estados Unidos N° 2003/0022894 A1 describe una composición que es una combinación de un inhibidor de la cGMP PDE V en combinación con un anestésico local para la administración nasal. Como se trata en esa publicación, al administrar un inhibidor de la PDE V (p. ej., Viagra®) se presentan ciertos problemas. Los inhibidores de la PDE V son vasodilatadores y la administración nasal lleva a la dilatación múltiple de los vasos de la mucosa nasal, efecto que, se afirma, se traduce en picor, ardor, secreción lagrimal u otras irritaciones en ciertos pacientes. La cantidad del anestésico local usada en esa forma farmacéutica generalmente es notoriamente inferior a la necesaria para obtener anestesia tópica. Específicamente, en el párrafo [0072] de la Publicación de la Patente de los Estados Unidos N° 2003/0022894 A1, se indica que "las composiciones... contienen el o los anestésicos locales en concentraciones más bajas que la cantidad estándar en las preparaciones tópicas comerciales para anestesia superficial, es decir en una concentración de menos del 4% (m/v)". En contraste con lo divulgado en dicha publicación de patente de los Estados Unidos, hemos encontrado que el ardor debido a la administración de ketorolac (al no ser ketorolac un vasodilatador) se puede reducir usando una cantidad superior al 4% p/v (es decir, peso volumen, que es intercambiable con masa volumen – m/v y se define como la masa de una sustancia medida en gramos

("g") dividida por el volumen de la solución medido en litros ("l") multiplicado por 100%: % g/l) en la composición como una solución para reducir el problema del ardor que experimentan algunos integrantes de la población.

[0008] La Solicitud de Patente del Reino Unido GB 2315673 A se refiere al tratamiento de la migraña mediante la administración de un anestésico local y un agonista 5-HT_{1D} por vía intranasal. Se basa en la hipótesis de que la absorción del agonista 5-HT_{1D} se verá aumentada por la presencia del anestésico local, que se considera tiene un efecto vasodilatador. Se afirma que el aumento de la absorción debe llevar a acelerar la distribución y el comienzo de la acción del agonista 5HT_{1D}. No se suministran datos en respaldo de esta hipótesis y no se hace mención al tiempo que tarda el 5HT_{1D} en alcanzar la concentración máxima. Notablemente, se encontró ahora que en las formulaciones preferentes de la invención, se acorta el tiempo (T_{máx.}) que tarda el ketorolac en alcanzar su concentración máxima o pico (C_{máx.}), suministrando así mejor analgesia.

RESUMEN DE LA INVENCION

[0009] Un aspecto de la presente invención es una composición para administración por vía nasal que comprende una cantidad eficaz del compuesto ácido 5-benzol-2,3-dihidro-1H-pirrolizina-4-carboxílico, de la fórmula (I)



una forma ópticamente activa del mismo, la mezcla racémica o una sal de los mismos adecuada para uso farmacéutico en combinación con un diluyente adecuado para uso farmacéutico y el 4% - 10% p/v de un anestésico local, p.

ej., clorhidrato de lidocaína. Preferiblemente el compuesto es ketorolac trometamina y está presente en un nivel de aproximadamente el 2,5 – 22,5% (p/v), el anestésico está presente en un nivel del 5% al 10% p/v, y la composición es una solución acuosa que se puede vaporizar.

[0010] Otro aspecto de la presente invención es una composición para vaporizar en el conducto nasal de un sujeto humano, que comprende

- (a) agua;
- (b) el compuesto ácido 5-benzoil-2,3-dihidro-1H-pirrolizina-4-carboxílico, una forma ópticamente activa del mismo, una mezcla racémica, o una sal adecuada para uso farmacéutico (p. ej., trometamina) donde el compuesto está disuelto en agua en un nivel suficiente para ser absorbido por el sujeto para tratar dolor o inflamación;
- (c) un anestésico local (p. ej., clorhidrato de lidocaína) disuelto en agua a un nivel suficiente para reducir toda sensación de ardor causada por la administración por vía nasal al sujeto del compuesto solamente; y
- (d) optativamente otros excipientes adecuados para uso farmacéutico.

[0011] Otro aspecto de la presente invención es un método para tratar el dolor o la inflamación en un sujeto que necesita dicho tratamiento, que comprende la administración intranasal al sujeto de la composición de la presente invención.

[0012] Otro aspecto de la invención es la composición de la invención en un recipiente equipado con un dispositivo para vaporizar la composición en el conducto nasal de un paciente.

[0013] Otro aspecto de la invención el uso del compuesto ácido 5-benzol-2,3-dihidro-1-H-pirrolizina-1-carboxílico, una forma ópticamente activa del mismo, la mezcla racémica, o una sal de los mismos adecuada para uso farmacéutico, en combinación con un anestésico local, para preparar una composición para la administración por vía nasal a un sujeto para el tratamiento del dolor o la inflamación.

[0014] Una característica importante de todos los aspectos de la invención es que el anestésico se elige para que esté presente en dosis de un nivel que no afecten adversamente la farmacocinética (PK) plasmática del ketorolac.

FIGURAS

[0015] La figura 1 muestra los perfiles lineal y semilogarítmico de la media de concentración en plasma de ketorolac a lo largo de 24 horas.

[0016] La figura 2 muestra la concentración lineal media y semilogarítmica de la lidocaína a lo largo de 24 horas.

DESCRIPCIÓN DETALLADA DE LA INVENCION

[0017] Todas las patentes y literatura citadas quedan incorporadas en su totalidad mediante referencia.

[0018] Hemos encontrado ahora que es posible preparar formulaciones analgésicas / antiinflamatorias que contienen ketorolac como principio activo para el tratamiento del dolor y/o la inflamación en un sujeto humano. Las formulaciones son adecuadas para la administración intranasal de una cantidad terapéuticamente eficaz a un sujeto de modo tal que el ketorolac así administrado se absorbe en forma rápida y completa, produciendo efectos terapéuticos equivalentes o superiores a los obtenidos con la formulación

intranasal descrita anteriormente y con reducción del ardor experimentado por ciertos sujetos. La formulación está diseñada para emplear una cantidad del anestésico que reduce la sensación de ardor en aquellos pacientes que de otro modo podrían experimentar dicha sensación con la administración por vía nasal, pero sin provocar sensación de adormecimiento. Es importante señalar que pareciera que la PK del ketorolac no resulta afectada adversamente por la presencia del anestésico. Es decir, la presencia del anestésico no modifica significativamente en forma adversa la concentración plasmática de ketorolac vs. tiempo. Notablemente, la presencia del anestésico, p. ej. clorhidrato de lidocaína en el nivel preferido del 5-6% p/v, en realidad reduce el T_{máx.} del ketorolac hasta alcanzar su C_{máx.} en el plasma de un sujeto. Este hecho ofrece una ventaja inesperada sobre una formulación nasal de ketorolac sin clorhidrato de lidocaína, la cual consiste en que un tiempo más breve hasta alcanzar la C_{máx.} generalmente suministra al sujeto un mejor alivio del dolor.

[0019] Las formulaciones intranasales de la invención contienen concentraciones de ketorolac que van del 2,5 al 22,5%, por ejemplo del 5 % al 20%, preferiblemente aproximadamente el 15% p/v calculado sobre la formulación final. Como alternativa, las mismas se pueden expresar como 25-225 miligramos (mg) por mililitro (ml), preferiblemente 50-200 mg/ml, y más preferiblemente 150 mg/ml. Desde ya, la selección de los excipientes en particular depende de la forma farmacéutica deseada para la formulación, es decir, si se desea utilizar una solución para utilizar en gotas o en vaporizador (aerosol), o si se desea una suspensión, ungüento o gel para aplicar directamente en la cavidad nasal. En cualquier caso, la invención permite la preparación de formas farmacéuticas para dosis únicas o para dosis múltiples.

que aseguran la aplicación de una cantidad óptima de la droga. Generalmente se administra a un sujeto aproximadamente de 25 a 200 microlitros de la formulación acuosa de la presente invención que se puede vaporizar, preferiblemente de 50 a 100 microlitros, en una o ambas fosas nasales. Por ejemplo, 100µl de una solución al 15% p/v (pH 7,2) p/v de ketorolac en cada fosa nasal tendría se traduciría en hasta 30 mg de ketorolac en el plasma del sujeto. Si bien la composición se administra usualmente cuatro veces por día, bajo ciertas circunstancias, si resulta adecuado, se puede administrar con una frecuencia menor. La administración intranasal de una composición de acuerdo con la invención en cantidades que están entre 0,5 miligramos (mg)/kilogramo (kg) / día y 4 mg/kg/día dará niveles plasmáticos de ketorolac que están entre 0,3-5 mg/l de plasma, los cuales resultan generalmente eficaces para tratar el dolor moderado a severo, sea de origen patológico o neuropático, como por ejemplo dolor por traumatismos, dolor posoperatorio, migraña y cuadros similares. En general, un sujeto que tiene entre 18 y 65 años podrá recibir hasta 120 mg por día de ketorolac mediante la administración intranasal de 100 microlitros en cada fosa nasal de una solución al 15% p/v de ketorolac 4 veces por día. Un sujeto adolescente o mayor de 65 años podrá recibir 60 mg por día mediante la administración intranasal de 50 microlitros en cada fosa nasal de una formulación al 15% p/v de ketorolac 4 veces por día. Los niños menores de 12 años recibirán menor cantidad según corresponda.

[0020] El diluyente preferido para las formulaciones de acuerdo con la invención es agua, pudiendo agregarse si se desea otros excipientes. La formulación preferida de ketorolac al 15% p/v es hipertónica, es decir, exhibe una presión osmótica superior a la de los fluidos biológicos. En casos en los

que la concentración de ketorolac es inferior, puede ser de utilidad agregar un agente de isotonia seleccionado entre los de uso habitual en farmacia. Sustancias usadas para este propósito son, por ejemplo, cloruro de sodio y glucosa. La cantidad del agente de isotonia dependerá de la presión osmótica buscada para la formulación (tomando en cuenta el efecto osmótico del principio activo). Por lo general, estará entre aproximadamente 150 hasta aproximadamente 850 miliosmoles (mOsm).

[0021] Si en vez de una solución se desea una suspensión o un gel, se pueden usar vehículos oleosos o en gel adecuados o se pueden incluir uno o más materiales poliméricos que, deseablemente, deben poder conferir características bioadhesivas al vehículo.

[0022] Hay varios polímeros que se usan en farmacia para la preparación de un gel; se pueden mencionar los siguientes a modo de ejemplos no limitativos: hidroxipropil celulosa (KLUCEL®), hidroxipropil metil celulosa (METHOCEL®), hidroxietil celulosa (NATROSOL®), carboximetil celulosa sódica (BLANOSE®), polímeros acrílicos (CARBOPOL®, POLYCARBOPHIL®), goma xantano, goma tragacanto, alginatos y agar-agar. Entre paréntesis figura un nombre comercial de un producto disponible en el mercado público.

[0023] Algunos de ellos, como la carboximetil celulosa sódica (a menudo abreviada como CMC sódica) y los polímeros acrílicos, poseen marcadas propiedades bioadhesivas y son preferibles si se desea bioadhesividad.

[0024] Otras formulaciones adecuadas para la administración intranasal de ketorolac se pueden obtener agregando al vehículo acuoso polímeros con

capacidad de modificar el comportamiento reológico de la composición en relación con la temperatura.

[0025] Estos polímeros hacen posible obtener soluciones de baja viscosidad a temperatura ambiente, que se pueden aplicar, por ejemplo, mediante un vaporizador nasal, y que aumentan su viscosidad a la temperatura del cuerpo, produciendo un líquido viscoso que aumenta las posibilidades de un contacto más prolongado con la membrana mucosa nasal. Polímeros de esta clase incluyen, sin limitación, copolímeros con bloque polioxidileno-polioxipropileno (POLOXAMER®). El polioxidileno se suele abreviar POE, mientras que el polioxipropileno se abrevia POP.

[0026] Además de diluyentes acuosos, oleosos o en gel, otros diluyentes que se pueden usar en las composiciones de acuerdo con la invención comprenden sistemas solventes que contienen alcohol etílico, alcohol isopropílico, propilenglicol, polietilenglicol, mezclas de los mismos o mezclas de uno o más de los compuestos anteriores con agua.

[0027] En cualquier caso es necesario que esté presente una solución amortiguadora adecuada para uso farmacéutico con el fin de crear condiciones óptimas de pH, tanto para favorecer la estabilidad del producto como su tolerancia (pH entre aproximadamente 4 hasta aproximadamente 8; preferiblemente aproximadamente de 6,0 a 7,5). Las soluciones amortiguadoras adecuadas incluyen, sin limitación, solución amortiguadora tris (trometamina), fosfato, etc. Preferiblemente se use fosfato de potasio NF para ajustar el pH a 7,2.

[0028] Otros excipientes incluyen potenciadores químicos, por ejemplo promotores de la absorción. Éstos incluyen ácidos grasos, sales de ácidos

biliares y otros tensioactivos, ácido fusídico, lisofosfátidos, antibióticos peptídicos cíclicos, conservantes, ácidos carboxílicos (ácido ascórbico, aminoácidos), ácido glicirretínico, o-acilcamitina. Promotores preferidos son el diisopropiladipato, POE (9) lauril alcohol, glicocolato sódico y lisofosfatidilcolina, que demostraron resultar particularmente activos.

[0029] Otro excipiente que puede estar presente en una composición de la presente invención es un quelante, es decir, una sustancia que liga principalmente iones metálicos di o trivalentes (p. ej. calcio) que podrían interferir con la estabilidad o la actividad del principio activo. Los quelantes son conocidos por los expertos en el arte mediante referencia a la edición reciente de "Remington's Pharmaceutical Sciences". Un quelante preferido es el ácido etilendiamina tetraacético sódico (EDTA sódico), USP.

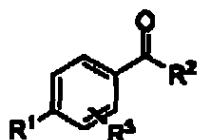
[0030] Por último, las composiciones de la invención preferiblemente contienen conservantes que aseguran la estabilidad microbiológica del principio activo. Los conservantes adecuados incluyen, sin limitación, el metil paraoxibenzoato (metil paraben), propil paraoxibenzoato (propil paraben), benzoato de sodio, alcohol bencílico, cloruro de benzalconio y el clorobutanol.

[0031] Las formulaciones líquidas de ketorolac, preferiblemente bajo la forma de soluciones, se pueden administrar en forma de gotas o con vaporizador, usando atomizadores equipados con una válvula mecánica, con la posibilidad de incluir un propelente de tipo comercial, por ejemplo butano, N₂, Ar, CO₂, óxido nítrico, propano, dimetil éter, clorofluorocarbonos (p. ej., FREON) etc. Disolventes (p. ej. un solvente) adecuados para la administración por vaporización son agua, alcohol, glicol, glicerol, y propilenglicol, usados

solos o en una mezcla de dos o más de los mismos. Preferiblemente se emplea agua como único solvente.

[0032] Los anestésicos locales que se pueden usar de acuerdo con la invención son conocidos per se y figuran, por ejemplo, en Remington's Pharmaceutical Sciences 1990, pp. 1048-1056. Los anestésicos locales son compuestos que inhiben en forma reversible la excitabilidad de las terminaciones nerviosas sensoriales o la conductividad neuronal del dolor u otros estímulos sensoriales en una región limitada del cuerpo sin causar daño permanente (cf. J. L. McGuire (editor), Pharmaceuticals, volume 2, Wiley-VCH, Weinheim 2000, pp. 539, et seq.). Anestésicos locales dentro del significado de la presente invención denotan preferiblemente sustancias que figuran en el Index Nominum 2000, International Drug Directory, Scientific Publishers Stuttgart 2000 en la categoría terapéutica de "anestésico local". De acuerdo con el anestésico específico utilizado y según la sensibilidad del paciente, el anestésico está presente en un nivel del 4 hasta aproximadamente el 10% p/v.

[0033] Los anestésicos locales preferidos de acuerdo con la presente invención son compuestos de la fórmula (II)



(II)

donde

R₁ representa H, NH₂, NH(C₁₋₈ alquil), O-C₁₋₈ alquil o CH₂OPh;

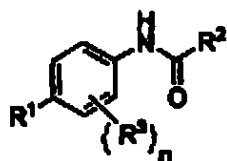
R² representa O-C₁₋₈-alquil que puede tener optativamente un radical del grupo que consiste en NH(C₁₋₈-alquil), N(C₁₋₈-alquil)₂ o un heterociclo saturado

de 5- o seis componentes que contiene al menos un átomo de nitrógeno y está ligado por medio de este último, y optativamente uno o dos heteroátomos del grupo que consiste en N, O, S, y optativamente lleva de uno a tres radicales C_{1-6} -alquilo más, o

R^2 representa $(CH_2)_{1-6}$ -Het, donde Het representa un heterociclo saturado de 5- o seis componentes que contiene al menos un átomo de nitrógeno y está ligado por medio de este último, y optativamente uno o dos heteroátomos del grupo que consiste en N, O, S, y optativamente lleva de uno a tres radicales C_{1-6} -alquilo más; y

R^3 representa H, halógeno o $O-C_{1-6}$ -alquilo.

[0034] Otros componentes útiles incluyen los de la fórmula (III)



(III)

donde

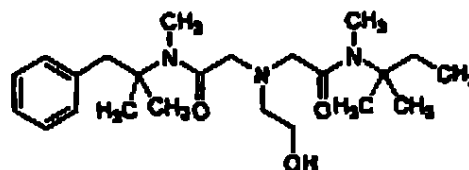
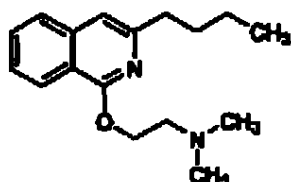
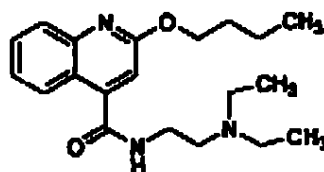
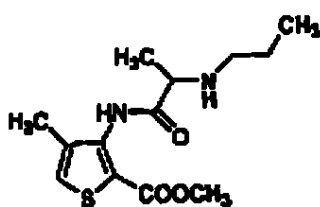
R^1 representa H u OH;

R^2 representa C_{1-6} -alquil- $N(C_{1-6}$ -alquil) $_2$ donde la cadena alquilo puede optativamente llevar uno o más radicales C_{1-6} -alquilo, o representa un heterociclo saturado de 5- o seis componentes que contiene al menos un átomo de nitrógeno y optativamente uno o dos heteroátomos más del grupo que consiste en N, O, S, y optativamente lleva de uno a tres radicales C_{1-6} -alquilo más,

R^3 representa C_{1-6} -alquilo, halógeno o $COOC_{1-6}$ -alquilo; y

n representa 1 o 2.

[0035] Otros compuestos útiles se seleccionan del grupo que consiste en

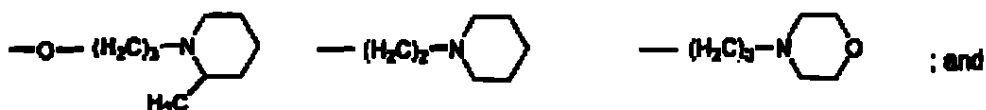


y polidocanol y benoxinato, y las sales y/o hidratos de los mismos adecuados para uso fisiológico.

[0036] Anestésicos locales particularmente preferidos de acuerdo con la invención son los de la fórmula (II) anterior, donde

R^1 representa H, NH_2 , $NH-n-C_4H_9$, $O-n-C_3H_7$, $O-n-C_4H_9$ o CH_2OPh ;

R^2 representa OC_2H_5 , $O-n-C_4H_9$, $O-(CH_2)_2N(C_2H_5)_2$, $O(CH_2)_2N(CH_3)_2$, o un radical del grupo que consiste en



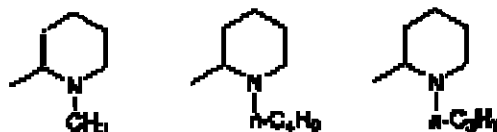
y

R^3 representa H, Cl, $O-n-C_3H_7$ o $O-n-C_4H_9$.

[0037] Otros compuestos preferidos son los de la fórmula (III) anterior, donde

R^1 representa H u OH;

R^2 representa $\text{CH}_2\text{N}(\text{C}_2\text{H}_5)_2$, $\text{CHCH}_3\text{NH-n-C}_3\text{H}_7$, $\text{CH}_2\text{NH-n-C}_4\text{H}_9$ o un radical del grupo que consiste en



R^3 representa CH_3 , Cl o COOCH_3 ;

n representa 1 o 2;

y benoxinato y sales y/o hidratos de los mismos adecuados para uso fisiológico.

[0038] Los anestésicos locales que se pueden emplear en forma particularmente preferida de acuerdo con la invención son: benzocaína, butambeno, piperocaína, clorhidrato de piperocaína, procaina, clorhidrato de procaina, clorprocaína, clorhidrato de clorprocaína, oxibuprocaina, clorhidrato de oxibuprocaina, proximetacaína, clorhidrato de proximetacaína, tetracaína, clorhidrato de tetracaína, nirvanina, lidocaína, clorhidrato de lidocaína, prilocaína, clorhidrato de prilocaína, mepivacaína, clorhidrato de mepivacaína, bupivacaína, clorhidrato de bupivacaína, ropivacaína, clorhidrato de ropivacaína, etidocaína, clorhidrato de etidocaína, butanilicaína, clorhidrato de butanilicaína, articaína, clorhidrato de articaína, cinchocaína, clorhidrato de cinchocaína, oxetacaína, clorhidrato de oxetacaína, propipocaína, clorhidrato de propipocaína, diclonina, clorhidrato de diclonina, pramocaína, clorhidrato de pramocaína, fomocaína, clorhidrato de fomocaína, quiniocaína, clorhidrato de quiniocaína, benoxinato y polidocanol. Estos compuestos se encuentran disponibles comercialmente o se pueden preparar en forma conocida por el

cat

experto en el arte, por ejemplo, según se describe en J. L. McGuire (editor), *Pharmaceuticals*, volume 2, Wiley-VCH 2000, pp. 539 et seq.

[0039] Anestésicos locales que se pueden usar preferiblemente de acuerdo con la invención son benzocaína, lidocaína, tetracaína, benoxinato, polidocanol o sus sales adecuadas para uso farmacéutico. Se prefieren particularmente la lidocaína, el clorhidrato de lidocaína, y el metanosulfonato de lidocaína. El anestésico local está presente de acuerdo con la invención en un nivel desde el 4 hasta aproximadamente 10% p/v, preferiblemente aproximadamente el 5-6% p/v. Si bien el 4-10% p/v es el rango amplitud general, puede ser útil hacer ajustes para limitar la amplitud del mismo, p. ej. 5-10%, 5-9%, 5-8%, 5-7%, y valores similares.

[0040] Formulaciones a título ilustrativo pueden contener los siguientes ingredientes y cantidades (p/v), además de ketorolac, agua y el anestésico.

Ingrediente	Rango amplio	Rango preferido
	(%)	(%)
Quelante (1)	0,001 - 1	0,01 - 0,1
Conservante (2)	0 - 2	0 - 0,25
Promotor de la absorción (3)	0 - 10	0 - 10
Polímero gelificante (4)	0 - 5	0 - 3
Co-solvente (5)	0 - 99	0

(1) P. ej., EDTA sódico

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(2) P. ej., metil paraoxibenzoato o propil paraoxibenzoato o mezclas de los mismos

(3) P. ej., glicocolato sódico

(4) P. ej., CMC sódica

(5) P. ej., glicerol

[0041] El experto podrá apreciar que ingredientes tales como la CMC sódica y los polímeros denominados CARBOPOL existen en muchos tipos con diferentes viscosidades. Sus cantidades deben ajustarse en forma concordante. También puede ser necesario hacer diferentes ajustes en cada formulación, incluyendo la omisión de algunos ingredientes optativos y el agregado de otros. Por lo tanto, no resulta posible dar un rango de cantidades para cada ingrediente que abarque todas las posibilidades; la optimización de cada preparación de acuerdo con la invención está dentro del conocimiento del experto en el arte.

[0042] Otra alternativa para la administración intranasal de las composiciones a base de ketorolac comprende una suspensión de ketorolac finamente micronizado (generalmente de 1 a 200 micrones, preferiblemente de 5 a 100 micrones) en un propelente o en un vehículo oleoso o en otro vehículo en el que la droga no sea soluble. El vehículo se mezcla o se emulsiona con el propelente. Son vehículos adecuados para esta alternativa, por ejemplo aceites vegetales y minerales y mezclas de triglicéridos. A estos vehículos se agregan tensioactivos adecuados, agentes de suspensión y diluyentes adecuados para uso en farmacia. Los tensioactivos incluyen, sin limitación, sorbitan sesquileato, sorbitan monooleato, sorbitan trioleato (cantidad: entre aproximadamente el 0,25 y aproximadamente el 1%); los agentes de

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suspensión incluyen, sin limitación, miristato de isopropilo (cantidad: entre aproximadamente el 0,5 y aproximadamente el 1%) y sílice coloidal (cantidad: entre aproximadamente el 0,1 y aproximadamente el 0,5%) y los diluyentes incluyen, sin limitación, estearato de zinc (entre aproximadamente el 0,6 y aproximadamente el 1%).

[0043] Composiciones de la invención se administran a un paciente que las necesita poniendo en contacto el conducto nasal del paciente con una cantidad de la composición suficiente para permitir la absorción de ketorolac por parte del paciente para reducir el dolor y/o la inflamación experimentados por el paciente. Preferiblemente, esto se lleva a cabo vaporizando una solución, como se describe en la presente, en o los conductos nasales de un paciente contenida en un recipiente equipado con un dispositivo (p. ej., un atomizador) para producir una vaporización (p. ej., partículas atomizadas). El dispositivo produce una niebla o suspensión de finas partículas de líquido que son inhaladas por el paciente hacia su o sus conductos nasales, desde donde se absorbe rápidamente al torrente sanguíneo para producir su acción analgésica y antiinflamatoria. El experto en el arte podrá encontrar recipientes y dispositivos vaporizadores apropiados consultando "Remington's Pharmaceutical Sciences". Una fuente para dichos recipientes es Ing. Erich Pfeiffer GmbH, Radolfzell, Alemania. Otra fuente es Valois, 50 avenue de l'Europe, 78164 MARLY-LE-ROI, Francia.

[0044] Los siguientes ejemplos de formulaciones para la administración intranasal de ketorolac sirven para ilustrar la invención sin limitar su alcance.

EJEMPLO 1:

[0045] Este ejemplo ofrece una descripción para preparar composiciones para administración por vía nasal de acuerdo con la invención. Se preparó una solución según las proporciones que figuran en la Tabla 1. Se agregó clorhidrato de lidocaína a la solución para obtener las composiciones de la invención que se muestran en la Tabla 2.

Tabla 1

Ketorolac trometamina, USP	15%
EDTA sódico, NF	0,02%
Fosfato de potasio, NF	(c.s. para pH 7,2)
Agua para inyección USP (c.s.)	100 g

Tabla 2

Ingredientes	I	II	III
Ketorolac trometamina, USP	15%	15%	15%
EDTA sódico, NF	0,02%	0,02%	0,02%
Fosfato de potasio, NF (c.s. para pH 7,2)			
Clorhidrato de lidocaína	4%	5%	6%
Agua para inyección USP (c.s.)	100 g	100 g	100 g

EJEMPLO 2:

[0046] Este ejemplo ofrece una descripción de un estudio clínico de fase I (doble ciego, randomizado cruzado con 4 brazos) llevado a cabo para determinar, entre otras cosas, si la presencia de clorhidrato de lidocaína en formulaciones de ketorolac administradas por vía nasal tiene algún efecto adverso sobre el perfil PK de ketorolac. Los resultados muestran que las características PK mejoran en las formulaciones preferidas (5-6% p/v) por la presencia del anestésico clorhidrato de lidocaína, sin que haya efectos

negativos. Además, se evaluaron los datos de seguridad y tolerancia de las formulaciones.

[0047] El estudio clínico incluyó a 16 voluntarios sanos que fueron reclutados para el estudio, donde cada voluntario recibió 4 formulaciones administradas por vaporización nasal, tres de las cuales son composiciones que representan un aspecto de la invención. Entre cada administración hubo un período de lavado de 3-7 días. Las cuatro composiciones acuosas para vaporización se prepararon de la siguiente manera:

	KT(1)	L(2)	NaEDTA(3)	KPO ₄ (4)	Agua(5)
A:	15%	0	0,02%	pH 7,2	100g
B:	15%	4%	0,02%	pH 7,2	100g
C:	15%	5%	0,02%	pH 7,2	100g
D:	15%	6%	0,02%	pH 7,2	100g

- (1) Ketorolac trometamina, USP
- (2) Clorhidrato de lidocaína, USP
- (3) EDTA sódico, NF
- (4) Fosfato de potasio, NF
- (5) Agua para inyección, USP

[0048] La formulación A es conocida y se incluyó con fines comparativos. Las formulaciones B-D son composiciones de la invención, siendo preferidas la C y la D.

[0049] Se extrajo sangre de cada participante de la siguiente manera: Antes de la administración (tiempo (t) = 0 h), 0,25; 0,50; 0,75; 1; 1,5; 2; 4; 6; 8; 12; 15; y 24 horas. En las muestras de sangre se analizaron los niveles de

ketorolac y de lidocaína para determinar las concentraciones plasmáticas de ketorolac y lidocaína en nanogramos (ng) por mililitro (ml). Posteriormente, se combinaron estos valores para obtener los perfiles de concentración media – tiempo en la población participante. Los resultados de ketorolac se muestran en las Figuras 1 (lineal) y 2 (semilogarítmica), mientras que los resultados de la lidocaína se muestran en las Figuras 3 (lineal) y 4 (semilogarítmica). En cada trazado, "ES" es el error estándar. Se hizo la selección clínica para cada sujeto dentro de los 21 días de la administración de la droga del estudio en el período 1. Los sujetos elegibles para tomar parte en el estudio lo cumplieron en 4 periodos. Los sujetos fueron admitidos a la Unidad el Día 1 de cada periodo y permanecieron en la misma hasta la mañana del Día 2. Se dejó pasar un periodo de lavado de 3-7 días entre cada periodo. Se realizó una evaluación clínica posterior dentro de los 7 días de la administración en el último periodo de tratamiento.

[0050] Resulta evidente a partir de las Figuras 1 y 2 que la PK del ketorolac permanece esencialmente sin cambios ante la presencia de lidocaína al 4%, en tanto que la formulación preferida redujo el tiempo hasta alcanzar la C_{máx}.

[0051] Cada paciente fue evaluado por un clínico para determinar el nivel de edema, eritema, ulceración, adormecimiento y ardor en los conductos nasales. Si bien los resultados tendieron a mostrar que los sujetos experimentaron sensación reducida de ardor, los mismos no fueron concluyentes debido a dificultades en el proceso de evaluación.

EJEMPLO 3

[0052] En este ejemplo se describe un estudio para pacientes en posoperatorio para comparar la seguridad, tolerancia y las propiedades farmacocinéticas (PK) de 3 formulaciones de ketorolac trometamina intranasal (IN).

[0053] Se trata de un estudio doble ciego con grupos paralelos en pacientes en posoperatorio. Los sujetos reciben 1 de 3 formulaciones de ketorolac trometamina IN 30 mg o placebo. Dos de las formulaciones son formulaciones preferidas de acuerdo con la presente invención. El estudio incluye el enrolamiento de quince sujetos en cada grupo, con un total de 60 sujetos. Cada formulación se administra a cada sujeto por vía IN (una vaporización en cada fosa nasal).

[0054] Los pacientes en posoperatorio adecuados para el estudio incluyen pacientes de 18 a 60 años con un peso dentro del 20% del peso ideal, de acuerdo con las tablas de talla y peso de MetLife para hombres y mujeres (versión 1999).

[0055] Los sujetos son asignados al azar para recibir:

☐ Tratamiento A (una composición conocida en el arte) – dosis única IN de 30 mg de ketorolac trometamina (una vaporización en cada fosa nasal de 100 µl de una solución al 15% (pH 7,2)).

☐ Tratamiento B (una composición preferida de la presente invención) – dosis única IN de 30 mg de ketorolac trometamina con clorhidrato de lidocaína al 5% (una vaporización en cada fosa nasal de 100 µl de una solución al 15% (pH 7,2)).

☐ Tratamiento C (una composición preferida de la presente invención) – dosis única IN de 30 mg de ketorolac trometamina con clorhidrato

de lidocaína al 6% (una vaporización en cada fosa nasal de 100 µl de una solución al 15% (pH 7,2)).

□ Tratamiento D – dosis única IN de placebo (una vaporización en cada fosa nasal de 100 µl de la solución vehículo).

Procedimientos

Evaluaciones de seguridad	
Evaluaciones de laboratorio clínico	En la etapa de selección se toman muestras de sangre y orina para análisis clínicos de laboratorio. En todas las mujeres en edad fértil se realiza una prueba de embarazo en la etapa selección.
Medición de signos vitales y registros del ECG	Se mide la tensión arterial en decúbito y el pulso en la etapa de selección y en los siguientes momentos durante los periodos 1-4: antes de la administración (dentro de los 30 minutos de la administración de ketorolac), 2 h y 24 h después de la administración.
Evaluaciones de tolerancia	Se pide a los sujetos que respondan un cuestionario sobre irritación nasal durante todos los periodos en los siguientes momentos: antes de la administración (dentro de los 15 minutos de la administración de ketorolac), 0-5 min, 15 min, 30 min, 1 h, y 24 h después de la administración.
Examen físico	Se realiza un examen físico en la etapa de selección.
Examen nasal	Se realiza un examen nasal antes de la administración (dentro de los 30 minutos de la administración de

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	ketorolac), 15 min, 30 min, 1 h, y 24 h después de la administración.
Reacciones adversas	A intervalos regulares a lo largo del estudio se interroga a los sujetos sobre cualquier reacción adversa que puedan haber experimentado.

Análisis de los datos

[0056] Los puntajes de irritación nasal y los datos de reacciones adversas se tabulan por grupo de tratamiento, los hallazgos físicos y los resultados de los análisis de laboratorio se consignan por sujeto.

APÉNDICE DE NOMBRES DE PRODUCTOS Y EJEMPLOS DE FUENTES COMERCIALES

KETOROLAC TROMETAMINA: Union Químico Farmaceutico, S.A., Spain

HIDROXIPROPILCELULOSA (KLUCEL®) Dow Chemical Co, Midland MI USA

HIDROXIPROPILMETILCELULOSA (METHOCEL®) Dow Chem. Co, Midland MI

HIDROXIETILCELULOSA (NATROSOLO®) Hercules Inc, Wilmington DE USA

CARBOXIMETILCELULOSA SÓDICA (BLANOSE®) Hercules Inc, Wilmington DE

CARBOPOL®: BF Goodrich Chemical Co., Cleveland, OH, USA

POLICARBOFIL: BF Goodrich Chemical Co., Cleveland, OH, USA

GOMA TRAGACANTO: Colony Ip. & Exp. Co., New York, NY, USA

GOMA XANTANO: Aldrich Chemie, Stanheim, Germany

ALGINATO DE SODIO: Edward Mandell Co., Carmel, New York, USA

AGAR AGAR: Aldrich Chemie, Stanheim, Germany

POLOXAMER (LUTROL® f127): BASF Wyndotte Corp., Parsippany, NJ, USA

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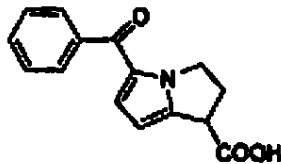
SS

ALCOHOL ETÍLICO: Eastman Chemical Products Inc., Kingsport, TN, USA
ALCOHOL ISOPROPÍLICO: Baker Chemical Co., New York, NY, USA
PROPILENGLICOL: Dow Chemical Co., MIDLAND, MI, USA
POLIETILENGLICOL: BASF Wyndotte Corp., Parsippany, NJ, USA
DIISOPROPILADIPATO: Croda, Goole, North Humerside, UK
GLICOCOLATO SÓDICO: Sigma Chemical Company, St. Louis, MO, USA
LISOFOFATIDILCOLINA: American Lecithin, Long Island, NY, USA
METILPARAOXIBENZOATO (NIPAGIN): BDH Chemical Ltd, Poole, Dorset, UK
PROPILPARAOXIBENZOATO: BDH Chemical Ltd, Poole, Dorset, UK
BENZOATO DE SODIO: Pfizer Inc., New York, NY, USA.
ALCOHOL BENCÍLICO: BDH Chemical Ltd, Poole Dorset, UK
CLORURO DE BENZALCONIO: ION Pharmaceuticals, Covina, CA, USA
CLORBUTANOL: Eastern Chemical Products, Smithtown, NY USA
EDTA SÓDICO: Grace And Co., London, UK
POE(9)LAURIL ÁLCOHOL: BASF Wyndotte Corp, Parsippany, NJ, USA
GLICEROL: Dow Chemical Co., Midland, MI, USA
CLORURO DE SODIO: Aldrich Chemie, Stanheim, Germany
GLUCOSA: Roquette Ltd, Tunbridge Wells, Kent, UK

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REIVINDICACIONES

1. Una composición para administración por vía nasal a un paciente, CARACTERIZADA PORQUE comprende una cantidad terapéuticamente eficaz del compuesto ácido 5-benzoil-2,3-dihidro-1H-pirrolizina-1-carboxílico, de la fórmula



una forma ópticamente activa del mismo, la mezcla racémica, o una sal adecuada para uso farmacéutico de los mismos, en combinación con un diluyente adecuado para uso farmacéutico y del 4% p/v al 10% (p/v) de un anestésico local.

2. La composición de la reivindicación 1, CARACTERIZADA PORQUE el compuesto es ketorolac trometamina como una mezcla racémica.

3. La composición de la reivindicación 2, CARACTERIZADA PORQUE comprende 25 mg - 225 mg de dicho compuesto disueltos por ml, donde el diluyente es agua y la composición es líquida y que se puede vaporizar.

4. La composición de la reivindicación 3, CARACTERIZADA PORQUE comprende 50-200 mg de dicho compuesto por ml.

5. La composición de la reivindicación 2, CARACTERIZADA PORQUE está presente un quelante.

6. La composición de la reivindicación 1, CARACTERIZADA PORQUE comprende el 2,5-22,5% p/v de dicho compuesto disuelto en el diluyente, que es agua.

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7. La composición de la reivindicación 6, CARACTERIZADA PORQUE contiene el 15% p/v de dicho compuesto.

8. La composición de la reivindicación 1 en una forma farmacéutica de dosis única para administrar a un único paciente, CARACTERIZADA PORQUE la composición es un líquido que se puede vaporizar y el diluyente es agua.

9. La composición de la reivindicación 1 en una formulación para dosis múltiples, CARACTERIZADA PORQUE la composición es un líquido que se puede vaporizar y el diluyente es agua.

10. La composición de la reivindicación 1, CARACTERIZADA PORQUE está bajo la forma de una solución acuosa.

11. La composición de la reivindicación 1, CARACTERIZADA PORQUE el anestésico es clorhidrato de lidocaína.

12. La composición de la reivindicación 11, CARACTERIZADA PORQUE el anestésico está presente en un nivel del 5% al 10% p/v, y el diluyente es agua, y la composición es una solución que se puede vaporizar.

13. La composición de la reivindicación 11, CARACTERIZADA PORQUE el anestésico está presente en un nivel del 5% al 6% p/v.

14. La composición de la reivindicación 1, CARACTERIZADA PORQUE está contenida en un recipiente equipado con un dispositivo para vaporizar la composición en el conducto nasal de un sujeto, donde la composición es una solución acuosa.

15. La composición y el recipiente de la reivindicación 14, CARACTERIZADA PORQUE el recipiente tiene capacidad de aproximadamente 50 a 2000 microlitros (μ l).

5x

16. La composición de la reivindicación 1, CARACTERIZADA PORQUE el pH es de 6 a 7,5.

17. Una composición adecuada para vaporizar en el conducto nasal de un sujeto humano, CARACTERIZADA PORQUE comprende

(a) agua;

(b) el compuesto ácido 5-benzoil-2,3-dihidro-1H-pirrolizina-1-carboxílico, una forma ópticamente activa del mismo, una mezcla racémica, o una sal adecuada para uso farmacéutico, donde el compuesto está disuelto en agua en un nivel suficiente para ser absorbido por el sujeto para tratar dolor o inflamación;

(c) un anestésico local disuelto en agua en un nivel suficiente para reducir la sensación de ardor causada por la administración por vía nasal del compuesto solo al sujeto; y

(d) optativamente, otros excipientes adecuados para uso farmacéutico.

18. La composición de la reivindicación 17, CARACTERIZADA PORQUE

(a) el agua es el único diluyente,

(b) el compuesto es ketorolac trometamina racémico disuelto al 2,5-22,5% p/v,

(c) el anestésico local es clorhidrato de lidocaína disuelto al 5-10% p/v, y

(d) el pH de la composición se ajusta a 7,2 y está presente un quelante.

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19. La composición de la reivindicación 18, CARACTERIZADA PORQUE el compuesto está presente en un nivel del 15% p/v, el anestésico local está presente en un nivel del 5-6% p/v, el regulador del pH es fosfato de potasio y el quelante es EDTA sódico.

20. Un método para tratar el dolor o la inflamación en un sujeto que necesita dicho tratamiento, CARACTERIZADO PORQUE comprende la administración intranasal de la composición de cualquiera de las reivindicaciones 1-19.

21. El método de la reivindicación 20, CARACTERIZADO PORQUE el método es para tratar el dolor.

22. El método de la reivindicación 21, CARACTERIZADO PORQUE el dolor es el resultado de un traumatismo infligido al sujeto.

23. El método de la reivindicación 21, CARACTERIZADO PORQUE el dolor es el resultado de una operación médica practicada en el sujeto.

24. El método de la reivindicación 21, CARACTERIZADO PORQUE el dolor es patológico.

25. El método de la reivindicación 21, CARACTERIZADO PORQUE el dolor es neuropático.

26. El método de la reivindicación 21, CARACTERIZADO PORQUE el dolor es migraña u otro tipo de dolor de cabeza.

27. El uso del compuesto ácido 5-benzoil-2,3-dihidro-1-H-pirrolizina-1-carboxílico, las formas ópticamente activas del mismo, la mezcla racémica, o una sal de los mismos adecuada para uso farmacéutico, en combinación con un anestésico local, CARACTERIZADO PORQUE es para preparar una

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composición para la administración por vía nasal a un sujeto para el tratamiento del dolor o la inflamación.

28. El uso de la reivindicación 27, CARACTERIZADO PORQUE el compuesto es ketorolac trometamina, que está presente al 2,5-22,5% p/v;

el anestésico local es clorhidrato de lidocaína, que está presente al 4-10% p/v; y

la composición es una composición acuosa que se puede vaporizar que tiene un pH de 6-8,5.

29. El uso de la reivindicación 28, CARACTERIZADO PORQUE el compuesto está presente al 15% p/v, el anestésico local está presente al 5-6% p/v, el pH es 7,2, y el EDTA sódico está presente como un quelante.

COMPOSICIONES TERAPÉUTICAS PARA LA ADMINISTRACIÓN INTRANASAL DE KETOROLAC

Resumen

Composiciones terapéuticas, particularmente composiciones acuosas que se pueden vaporizar, que comprenden ketorolac o una sal adecuada para uso farmacéutico, en combinación con un anestésico local, por ejemplo, clorhidrato de lidocaína. Las composiciones se administran por vía nasal a un sujeto que lo necesita para tratar el dolor o la inflamación y tiene el beneficio de una reducción del ardor y una mayor eficacia en comparación con composiciones conocidas administradas por vía nasal.

Fig.	Inglés	Español
1	Figure 1: Mean (+SE) linear and semi-logarithmic Plasma Ketorolac Concentration-time Profiles: PK population 30 mg Ketorolac Tromethamine i.n. 30 mg Ketorolac Tromethamine with 4% Lidocaine i.n. 30 mg Ketorolac Tromethamine with 5% Lidocaine i.n. 30 mg Ketorolac Tromethamine with 6% Lidocaine i.n. Mean Ketorolac Plasma Concentration (mg/mL) Nominal Time (h)	Figura 1: Perfiles lineales y semilogarítmicos de la media (+ES) de concentración plasmática-tiempo de Ketorolac: Población PK 30 mg Ketorolac Trometamina i.n. 30 mg Ketorolac Trometamina con 4% de lidocaína i.n. 30 mg Ketorolac Trometamina con 5% de lidocaína i.n. 30 mg Ketorolac Trometamina con 6% de lidocaína i.n. Media de concentración plasmática de Ketorolac (mg/ml) tiempo nominal (h)
2	Figure 1: Mean (+SE) linear and semi-logarithmic Plasma Lidocaine Concentration-time Profiles: PK population	Figura 2: Perfiles lineales y semilogarítmicos de la media (+ES) de concentración plasmática-tiempo de lidocaína: Población PK

	30 mg Ketorolac Tromethamine with 4% Lidocaine i.n.	30 mg Ketorolac Trometamina con 4% de lidocaína i.n.
	30 mg Ketorolac Tromethamine with 5% Lidocaine i.n.	30 mg Ketorolac Trometamina con 5% de lidocaína i.n.
	30 mg Ketorolac Tromethamine with 6% Lidocaine i.n.	30 mg Ketorolac Trometamina con 6% de lidocaína i.n.
	Mean Lidocaine Hydrochloride Concentration (mg/mL)	Media de concentración de clorhidrato de lidocaína (mg/ml)
	Nominal Time (h)	tiempo nominal (h)

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

FLICK, Karen, E.
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ETATS-UNIS D'AMERIQUE

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NOTIFICATION OF TRANSMITTAL OF
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REPORT ON PATENTABILITY
(PCT Rule 71.1)

Date of mailing
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Applicant's or agent's file reference
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IMPORTANT NOTIFICATION

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Priority date (day/month/year)
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Applicant
ROXRO PHARMA, INC. et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary report on patentability and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary report on patentability. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed invention is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

30 mo. = 4/23/07

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 056369-1460		FOR FURTHER ACTION		See Form PCT/PEA/416
International application No. PCT/US2005/045883		International filing date (day/month/year) 15.12.2005		Priority date (day/month/year) 23.12.2004
International Patent Classification (IPC) or national classification and IPC INV. A61K31/407 A61K31/167 A61K9/08 A61P25/06 A61P29/00				
Applicant ROXRO PHARMA, INC. et al.				
1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36. 2. This REPORT consists of a total of 7 sheets, including this cover sheet. 3. This report is also accompanied by ANNEXES, comprising: a. ☐ sent to the applicant and to the International Bureau a total of sheets, as follows: ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 807 of the Administrative Instructions). ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box. b. ☐ (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).				
4. This report contains indications relating to the following items: ☒ Box No. I Basis of the report ☐ Box No. II Priority ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability ☐ Box No. IV Lack of unity of invention ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement ☐ Box No. VI Certain documents cited ☒ Box No. VII Certain defects in the international application ☒ Box No. VIII Certain observations on the international application				
Date of submission of the demand 13.09.2006		Date of completion of this report 09.03.2007		
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80299 Munich Tel. +49 89 2369 - 0 Te: 523696 apmu d Fax: +49 89 2369 - 4466		Authorized officer Zimmer, Barbara Telephone No. +49 89 2369-6600 		

**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/US2005/045883

Box No. I Basis of the report

1. With regard to the language, this report is based on
 - ☒ the international application in the language in which it was filed
 - ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of:
 - ☐ international search (under Rules 12.3(a) and 23.1(b))
 - ☐ publication of the international application (under Rule 12.4(a))
 - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))
2. With regard to the elements' of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report):*

Description, Pages

1-19 as originally filed

Claims, Numbers

1-29 as originally filed

Drawings, Sheets

12, 22 as originally filed

- ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing
3. ☐ The amendments have resulted in the cancellation of:
 - ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (specify):
 - ☐ any table(s) related to sequence listing (specify):
 4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
 - ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (specify):
 - ☐ any table(s) related to sequence listing (specify):

" If item 4 applies, some or all of these sheets may be marked "superseded."

**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/US2005/045883

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application,
- ☒ claims Nos. 20-26 with regard to industrial applicability

because:

- ☒ the said international application, or the said claims Nos. 20-26 with regard to industrial applicability relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet
- ☐ the description, claims or drawings (indicate particular elements below) or said claims Nos. are so unclear that no meaningful opinion could be formed (specify):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed (specify):
- ☐ no international search report has been established for the said claims Nos.
- ☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:
 - ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.
 - ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.
 - ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13ter.1(a) or (b) and 13ter.2.
- ☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-bis of the Administrative Instructions, and such tables were not available to the International Preliminary Examining Authority in a form and manner acceptable to it.
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.
- ☐ See separate sheet for further details

**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**International application No.
PCT/US2005/045883

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-16,18,19,24,26,28,29
	No: Claims	17,20-23,25,27
Inventive step (IS)	Yes: Claims	
	No: Claims	1-29
Industrial applicability (IA)	Yes: Claims	1-19,27-29
	No: Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

**INTERNATIONAL PRELIMINARY
REPORT ON PATENTABILITY
(SEPARATE SHEET)**

International application No.

PCT/US2005/045883

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 20-26 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Art. 34(4)(a)(i) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Reference is made to the following documents:

D1: XP008024919
D2: US-A-6 333 044
D3: US-A-6 090 368
D4: US-A-2003/ 0022894
D5: GB-A-2 315 673

2. Novelty

Prior art document D1 discloses an aqueous analgetic composition comprising 0.5% lidocaine and ketorolac; although used for intravenous regional anaesthesia, said solutions are suitable for nasal administration (p. 458, left col., para. 3). D1, therefore, seems to be novelty destroying for the subject-matter of independent claims 17, 20-23, 25 and 27 of the present application (Art. 33(2) PCT).

3. Inventive Step

3.1 Apart from the fact that the subject-matter of the present application is not novel it

does not involve an inventive step for the following reasons:

Prior art documents D2 and D3 both disclose analgesic/ anti-inflammatory pharmaceutical compositions for intranasal administration comprising ketorolac: they differ from the subject-matter of the present application in the lack of an anaesthetic (D2: claims and D3: claims).

The technical problem in view of D2, which is regarded as closest prior art, is the provision of an improved pharmaceutical intranasal composition comprising ketorolac for the treatment of pain and migraine.

It is known from D4 that the addition of lidocaine in a concentration of less than 4% to pharmaceutical intranasal composition for migraine treatment overcomes the problem of itching and stinging ([0010], [0011] and [0072]); the mechanism by which the stinging is caused, is of no relevance.

Notwithstanding the argumentation of the applicant, the combination of D2 with D4 is obvious for a person skilled in the art as both prior art documents relate to the same technical problem.

Prior art document D5 further discloses the use of 4 and 8 % intranasal lidocaine in combination with a 5-HT_{1D} agonist for the treatment of migraine (examples 11-14)

Therefore, the subject-matter of independent claims 1, 17, 20 and 27 of the present application, apart from partly being not novel, does not seem to involve an inventive step (Art.33(3) PCT).

3.2 The dependent claims do not appear to contain any additional features which involve an inventive step when combined with the subject-matter of any claim to which they refer, in particular in view of prior art document D5. Dependent claims are only allowable when related to a patentable independent claim (Rule 6.4 PCT).

3.3 As a result, the subject-matter of claims 1-29 does not seem to involve an inventive step (Art. 33(3) PCT).

4. For the assessment of the present claims 20-26 on the question whether they are

**INTERNATIONAL PRELIMINARY
REPORT ON PATENTABILITY
(SEPARATE SHEET)**

International application No.

PCT/US2005/045883

industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VII

Certain defects in the international application

1. As the expression "hereby incorporated by reference" ([0002] and [0017]) is not deleted in the description the requirements of Rules 5 and 9.1 PCT are not met.
2. The tabulated data mentioned under [0054] are missing.

Re Item VIII

Certain observations on the international application

Independent claim 17 as well as claims 18 and 19 depending thereupon do not meet the requirements of Art. 6 PCT in that the matter for which protection is sought is not clearly defined. The claim attempts to define the subject-matter in terms of the result to be achieved, which merely amounts to a statement of the underlying problem, without providing the technical features necessary for achieving this result.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



INTERNATIONAL PATENT COOPERATION TREATY (PCT)

(43) International Publication Date
6 July 2006 (06.07.2006)

PCT

(10) International Publication Number
WO 2006/071601 A3

(51) International Patent Classification

A61K 31/407 (2006.01) A61P 25/06 (2006.01)
A61K 31/167 (2006.01) A61P 29/00 (2006.01)
A61K 9/08 (2006.01)

(13)US: 697 N. San Antonio Rd., Los Altos, California 94022 (US); THIRUCOTE, Ramchandran (US/US); 2021 Rockport Ave., Redwood Shores, California 94065 (US).

(21) International Application Number:

PCT/US2005/045863

(74) Agent: MORAN, Tom M.; KOLEY & LARDNER LLP, 1530 Page Mill Road, Palo Alto, California 94304-1125 (US).

(22) International Filing Date:

15 December 2005 (15.12.2005)

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AT, AU, AL, AM, AR, AT, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, FI, GB, GR, GU, HK, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SI, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

60639,022 23 December 2004 (23.12.2004) US

(71) Applicant (for all designated States except US): ROXERO PHARMA, INC. (US/US); 535 Middlefield Road, Suite 240, Menlo Park, California 94025-3444 (US).

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),

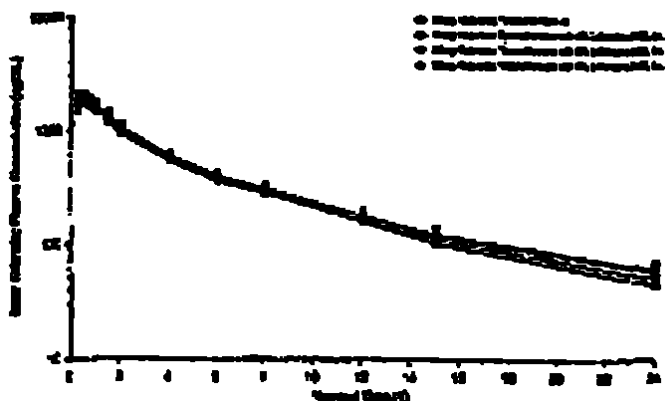
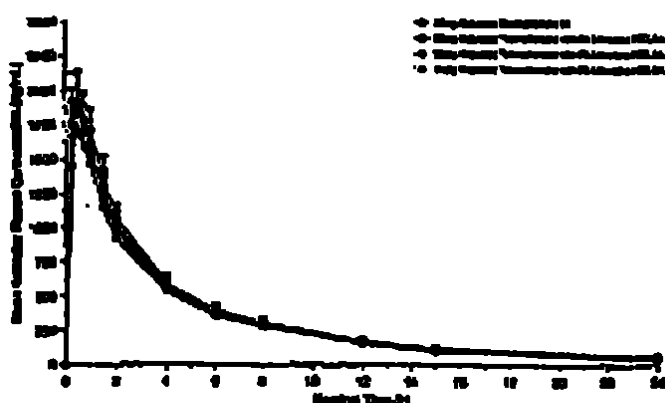
(72) Inventors; and

(75) Inventors/Applicants (for US only): WHITING, Roger

(Continued on next page)

(54) Title: THERAPEUTIC COMPOSITIONS FOR INTRANASAL ADMINISTRATION OF KETOROLAC

Mean ($\pm$ SE) Linear and Semi-logarithmic Plots Ketorolac Concentration-time Profiles PK Population



(57) Abstract: Therapeutic compositions, particularly sprayable aqueous compositions, comprise ketorolac or a pharmaceutically acceptable salt, in combination with a local anesthetic, such as lidocaine hydrochloride. The compositions are nasally administered to a subject in need thereof to treat pain or inflammation and have the benefit of reduced stinging and improved efficacy, compared to known orally administered compositions.

WO 2006/071601 A3

(iii) Date of publication of the international search report:
17 August 2006

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2005/045883

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/407 A61K31/167 A61K9/08 A61P25/06 A61P29/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Character of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	REUBEN S S ET AL: "AN EVALUATION OF THE ANALGESIC EFFICACY OF INTRAVENOUS REGIONAL ANESTHESIA WITH LIDOCAINE AND KETOROLAC USING A FOREARM VERSUS UPPER ARM TOURNIQUET" ANESTHESIA AND ANALGESIA, WILLIAMS AND WILKINS, BALTIMORE, MD, US, vol. 95, no. 2, 2002, pages 457-460, XP008024919 ISSN: 0003-2999 page 458, left-hand column, paragraph 3	1,9,10, 12,13, 17, 20-23, 25,27
Y	US 6 333 044 B1 (SANTUS GIANCARLO ET AL) 25 December 2001 (2001-12-25) cited in the application the whole document	1-29
-/-		

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the position date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is considered with one or more other such documents, such combinations being obvious to a person skilled in the art
- *Z* document member of the same patent family

Date of the actual completion of the international search

29 May 2006

Date of mailing of the international search report

03/07/2006

Name and mailing address of the ISA/

European Patent Office, P.O. Box 5010, Patentstr. 2
NL - 2280 HV The Hague
Tel. (+31-70) 340-2040, Tx. 31 651 apo nl,
Fax (+31-70) 340-3016

Authorized officer

Zimmer, B

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2005/045883

C(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 6 090 368 A (ZIA ET AL) 18 July 2000 (2000-07-18) claims	1-29
Y	US 2003/022894 A1 (SERNO PETER ET AL) 30 January 2003 (2003-01-30) cited in the application paragraphs [0010], [0011]	1-29
Y	GB 2 315 673 A (* MERCK & CO INC) 11 February 1998 (1998-02-11) cited in the application claims	1-29

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2005/045883

Box II Observations where certain claims were found unsearchable (Continuation of Item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 20-26 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition. Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 64(a).

Box III Observations where unity of invention is lacking (Continuation of Item 3 of first sheet)

This International Searching Authority found multiple inventions in this International Application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2005/045883

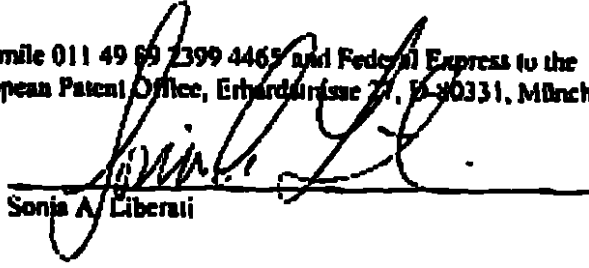
Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 6333044	B1	25-12-2001	NONE
US 6090368	A	18-07-2000	NONE
US 2003022894	A1	30-01-2003	BG 108245 A 31-01-2005 BR 0208813 A 09-03-2004 CA 2443639 A1 24-10-2002 CN 1537004 A 13-10-2004 CZ 20032752 A3 14-01-2004 DE 10118306 A1 17-10-2002 EE 200300501 A 15-12-2003 WO 02083674 A2 24-10-2002 EP 1381368 A2 21-01-2004 HU 0303877 A2 29-03-2004 JP 2004525968 T 26-08-2004 MX PA03009314 A 10-03-2004 NO 20034556 A 10-12-2003 PL 363033 A1 15-11-2004 SK 12682003 A3 02-03-2004
GB 2315673	A	11-02-1998	NONE

Federal Express Tracking Number: 790067773697

Date of Deposit: 12 September 2006

I hereby certify that this paper is being sent via Facsimile 011 49 69 2399 4465 and Federal Express to the International Preliminary Examining Authority, European Patent Office, Erhardstrasse 27, D-80331, München, Germany.

By:


Sonja A. Liberati

**IN THE EUROPEAN PATENT OFFICE
INTERNATIONAL PRELIMINARY EXAMINATION AUTHORITY**

In re application of **ROXRO PHARMA, INC.**

Serial No.: **PCT/US2005/045883**

Filed: **15 December 2005 (15.12.05)**

For: **THERAPEUTIC COMPOSITIONS FOR INTRANASAL
ADMINISTRATION OF KETOROLAC**

International Preliminary Examining Authority
European Patent Office
Erhardstrasse 27
D-80331 München, Germany

TRANSMITTAL

In reference to the above-mentioned PCT application, transmitted herewith, are the following documents:

1. Chapter II Demand for Preliminary Examination (3 pp.);
2. Fee Calculation Sheet (1 pp);
3. Letter Responsive to Written Opinion (6 pp);
4. Copy of PCT General Powers of Attorney (3 pp); and
5. EPO Form 1010 (1 pp).

Respectfully submitted,
FOLEY & LARDNER LLP

Foley & Lardner LLP
1530 Page Mill Road
Palo Alto, CA 94304-2155
Phone: (650) 856-3700
Fax: (650) 856-3710

By:


Karen E. FLICK (Reg. No. 44,111)

The demand must be filed directly with the competent International Preliminary Examining Authority or, if two or more Authorities are competent, with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line below:
IPEA/EP

**PCT
DEMAND**

CHAPTER II

under Article 31 of the Patent Cooperation Treaty:
The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation.

For International Preliminary Examining Authority use only

Identification of IPEA		Date of receipt of DEMAND	
Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION		Applicant's or agent's file reference 056369-1460	
International application No. PC/US2005/045883	International filing date (day/month/year) 15 December 2005 (15.12.2005)	(Earliest) Priority date (day/month/year) 23 December 2004 (23.12.2004)	
Title of invention THERAPEUTIC COMPOSITIONS FOR INTRANASAL ADMINISTRATION OF KETOROLAC			
Box No. II APPLICANT(S)			
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) ROXRO PHARMA, INC. 535 Middlefield Road, Suite 240 Menlo Park, California 94025-3444 United States of America		Telephone No.: 650-322-4554	
		Facsimile No.: 650-322-4514	
		Teleprinter No.:	
		Applicant's registration No. with the Office:	
State (that is, country) of nationality: US		State (that is, country) of residence: US	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) WHITTING, Roger 697 N. San Antonio Rd. Los Altos, California 94022 United States of America			
State (that is, country) of nationality: US		State (that is, country) of residence: US	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) THIRUCOTE, Ramachandran 2021 Rockport Ave. Redwood Shores, California 94065 United States of America			
State (that is, country) of nationality: US		State (that is, country) of residence: US	
☐ Further applicants are indicated on a continuation sheet.			

Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCEThe following person is ☒ agent ☐ common representativeand ☒ has been appointed earlier and represents the applicant(s) also for international preliminary examination.☐ is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.☐ is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*FLICK, Karen E.
FOLEY & LARDNER, LLP
1530 Page Mill Road
Palo Alto, California 94304
United States of AmericaTelephone No.:
(650) 856-3700Facsimile No.:
(650) 856-3710

Teleprinter No.:

Agent's registration No. with the Office:
44,111☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.**Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION****Statement concerning amendments:***

1. The applicant wishes the international preliminary examination to start on the basis of:

☒ the international application as originally filedthe description ☒ as originally filed☐ as amended under Article 34the claims ☒ as originally filed☐ as amended under Article 19 (together with any accompanying statement)☐ as amended under Article 34the drawings ☒ as originally filed☐ as amended under Article 342. ☐ The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.3. ☐ The applicant wishes the start of the international preliminary examination to be postponed until the expiration of the applicable time limit under Rule 69.1(d).4. ☐ The applicant wishes the international preliminary examination to start earlier than at the expiration of the applicable time limit under Rule 54bis.1(a).

* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Language for the purposes of international preliminary examination: English.....

☒ which is the language in which the international application was filed.☐ which is the language of a translation furnished for the purposes of international search.☐ which is the language of publication of the international application.☐ which is the language of the translation (to be) furnished for the purposes of international preliminary examination.**Box No. V ELECTION OF STATES**

The filing of this demand constitutes the election of all Contracting States which are designated and are bound by Chapter II of the PCT.

Box No. VI CHECK LIST

The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purposes of international preliminary examination:

- | | | |
|--|---|----------|
| 1. translation of international application | : | sheets |
| 2. amendments under Article 34 | : | sheets |
| 3. copy (or, where required, translation) of amendments under Article 19 | : | sheets |
| 4. copy (or, where required, translation) of statement under Article 19 | : | sheets |
| 5. letter together with arguments | : | 6 sheets |
| 6. other (specify): | | |

For International Preliminary Examining Authority use only

received	not received
☐	☐
☐	☐
☐	☐
☐	☐
☐	☐
☐	☐

The demand is also accompanied by the item(s) marked below:

- | | |
|---|--|
| 1. ☒ fee calculation sheet | 3. ☐ statement explaining lack of signature |
| 2. ☐ original separate power of attorney | 6. ☐ sequence listing in computer readable form |
| 3. ☐ original general power of attorney | 7. ☐ tables in computer readable form related to a sequence listing |
| 4. ☒ copy of general power of attorney, reference number, if any. | 8. ☒ other (specify): Transmittal Letter |

Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).


Karen E. FLICK
Attorney for Applicant (Reg. No. 44,111)

For International Preliminary Examining Authority use only

- | | |
|---|---|
| 1. Date of actual receipt of DEMAND: | |
| 2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b): | |
| 3. ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply. | 6. ☐ The date of receipt of the demand is AFTER the expiration of the time limit under Rule 54bis.1(a) and item 7 or 8, below, does not apply. |
| 4. ☐ The date of receipt of the demand is WITHIN the time limit of 19 months from the priority date as extended by virtue of Rule 50.1. | 7. ☐ The date of receipt of the demand is WITHIN the time limit under Rule 54bis.1(a) as extended by virtue of Rule 50.1. |
| 5. ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCLUDED pursuant to Rule 82. | 8. ☐ Although the date of receipt of the demand is after the expiration of the time limit under Rule 54bis.1(a), the delay in arrival is EXCLUDED pursuant to Rule 82. |

For International Bureau use only

Demand received from IPEA on:

PCT

FEE CALCULATION SHEET

Annex to the Demand

International application No. PCT/US2005/045883		For International Preliminary Examining Authority use only	
Applicant's or agent's file reference 056369-1460		Date stamp of the IPEA	
Applicant ROXRO PHARMA, INC.			
CALCULATION OF PRESCRIBED FEES			
1. Preliminary examination fee		EUR 1,595.00	P
2. Handling fee (Applicants from certain States are entitled to a reduction of 75% of the handling fee. Where the applicant is (or all applicants are) so entitled, the amount to be entered at H is 25% of the handling fee.)		EUR 129.00	H
3. Total of prescribed fees Add the amounts entered at P and H and enter total in the TOTAL box		EUR 1,724.00	
		TOTAL	
Mode of Payment			
☒ authorization to charge deposit account with the IPEA (see below)	☐ cash		
☐ cheque	☐ revenue stamps		
☐ postal money order	☐ coupons		
☐ bank draft	☐ other (specify):		
AUTHORIZATION TO CHARGE (OR CREDIT) DEPOSIT ACCOUNT (this mode of payment may not be available at all IPEAs)			
☒ Authorization to charge the total fees indicated above		IPEA/EP	
☒ (this check-box may be marked only if the conditions for deposit accounts of the IPEA so permit) Authorization to charge any deficiency or credit any overpayment in the total fees indicated above.		Deposit Account No: 28308572	
		Date: 12 September 2006	
		Name: Karen E. FLICK (Res. No. 44.111)	
		Signature: [Signature]	

PCT

GENERAL POWER OF ATTORNEY

(for several international applications filed under the Patent Cooperation Treaty)

(PCT Rule 90.5)

The undersigned person(s)
(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

ROXBO PHARMA, Inc.
535 Middlefield Road, Suite 240
Menlo Park, California 94025-3444
United States of America

hereby appoints (appoint) the following person(s) as: ☒ agent ☐ common representative

Name and address
(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

BENZ, William H., Reg. No. 25,952; ENG, Hugo M., Reg. No. 50,840; FLICK, Karen E., Reg. No. 44,111; KONSKI, Antoinette F., Reg. No. 34,202; MORAN, Tom M., Reg. No. 26,314; ROFF, Traci H., Reg. No. 44,307; SACHDEV, Gurjeet K., Reg. No. 37,434; SWISS, Gerald F., Reg. No. 30,113; TANNER, Lorna L., Reg. No. 50,782;

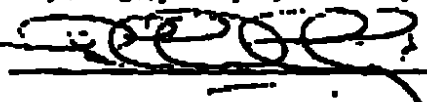
VOLEY & LARDNER LLP
1530 Page Mill Road
Palo Alto, California 94304-1125
United States of America

to represent the undersigned before

- ☒ all the competent International Authorities
- ☐ the International Searching Authority only
- ☐ the International Preliminary Examining Authority only

In connection with any and all international applications filed with the following Office:
US as receiving Office and to make or receive payments on behalf of the undersigned.

Signatures of the applicant(s) *(where there are several persons, each of them must sign, next to each signature, indicate the name of the person signing and the capacity in which the person signs, if such capacity is not obvious from reading the power);*

Date: Dec. 27, 2005 By: 
Name: Roger Whiting
Title: President

PCT
GENERAL POWER OF ATTORNEY
(for several international applications filed under the Patent Cooperation Treaty)
(PCT Rule 90.5)

The undersigned person(s)

(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

WHITING, Roger
697 W. San Antonio Road
Los Altos, California 94022
United States of America

hereby appoints (appoint) the following person(s) as: ☒ agent ☐ common representative

Name and address

(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

BENZ, William H., Reg. No. 25,552; ENG, Hugo M., Reg. No. 50,640; FLICK, Karen E.,
Reg. No. 44,111; MORAN, Tom M., Reg. No. 26,314; SWISS, Gerald F., Reg. No.
30,113; TANNER, Lorna L., Reg. No. 50,782; TODD, Stephan, Reg. No. 47,139.

FOLEY & LARDNER LLP
1530 Page Mill Road
Palo Alto, California 94304-1125
United States of America

to represent the undersigned before

- ☒ all the competent International Authorities
☐ the International Searching Authority only
☐ the International Preliminary Examining Authority only

in connection with any and all international applications filed with the following Office:

US as receiving Office and to make or receive payments on behalf of the undersigned.

Signatures of the applicant(s) *(where there are several persons, each of them must sign, next to each signature, indicate the name of the person signing and the capacity in which the person signs. If such capacity is not obvious from reading this power)*

Date: 26th July 2005 By: 

Name: Roger WHITING

Title: Applicant / Inventor

PCT

GENERAL POWER OF ATTORNEY

(for several international applications filed under the Patent Cooperation Treaty)

(PCT Rule 90.5)

The undersigned person(s)

(Print: name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

THIRUCOTE, Ramachandran
2021 Rockport Ave.
Redwood Shores, California 94065
United States of America

hereby appoints (appoint) the following person(s) as: ☒ agent ☐ common representative

Name and address

(Print: name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

BENI, William H., Reg. No. 25,952; ENG, Hugo M., Reg. No. 50,840; FLICK, Karen E., Reg. No. 44,111; KORSKI, Antoinette E., Reg. No. 34,202; MORAN, Tom M., Reg. No. 26,114; ROFF, Traci E., Reg. No. 44,307; SACHDEV, Gurjeet K., Reg. No. 37,434; WHISS, Gerald P., Reg. No. 30,113; TANNER, Lorna L., Reg. No. 50,782;

POLEY & LARDNER LLP
1530 Fegen Mill Road
Palo Alto, California 94304-1125
United States of America

to represent the undersigned before

- ☒ all the competent International Authorities
☐ the International Searching Authority only
☐ the International Preliminary Examining Authority only

in connection with any and all international applications filed with the following Office:

US as receiving Office and to make or receive payments on behalf of the undersigned.

Signatures of the applicant(s) (where there are several persons, each of them must sign, next to each signature, indicate the name of the person signing and the capacity in which the person signs. (If such capacity is not obvious from reading this power);

Date: Dec 27th 2005

By: [Signature]

Name: Ramachandran THIRUCOTE
Title: Applicant / Inventor



Payment of fees and costs

European Patent Office
Treasury and Accounts Directorate
D-80298 München
Fax: (+49-89) 2399-2528

Please complete in typescript only

01 Name of payer
FOLEY & LARDNER LLP

02 Address
1530 Page Mill Road
Palo Alto, California 94304-1125
United States of America

Payer's reference
056369-1460

Mode of payment
☐ Bank/Giro transfer¹

☐ Enclosed Cheque No.

☒ Debit from deposit account with the EPO is requested²

Beneficiary Office

Deposit account No.
28300572

Patent application / Patent No. (A separate form is required for each application)

03 EP

PCT **PCT/US2005/045883**

03

	Code		Currency	Amount
04	001	Filing fee	EUR	
05	002	Search fee	EUR	
06	006	Designation fee(s) ³	EUR	
07	015	Claims fee(s) (Rule 31(1) EPC)	EUR	
08	055	Additional copy	EUR	
09	008	Examination fee	EUR	1,595.00
10	007	Fee for grant including fee for printing (up to 35 pages)	EUR	
11	008	Additional fee for printing (more than 35 pages)	EUR	
12	033	Renewal fee for the 2nd year	EUR	
13	034	Renewal fee for the 4th year	EUR	
14	035	Renewal fee for the 5th year	EUR	
15		Extension fee(s) for ⁴ :	EUR	
16	224	Handling Fee	EUR	129.00
17			EUR	
18			EUR	
19			EUR	
20			EUR	
21			EUR	
22		Total	EUR	1,724.00

Signature

EPO Form K10 31 02

Expiry date 1.4.2006 onwards

Palo Alto California, USA; 12 September 2006
Place, Date

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PATENT COOPERATION TREATY

Applicant: Roxro Pharma, Inc.
Title: THERAPEUTIC COMPOSITIONS FOR
INTRANASAL ADMINISTRATION OF
KETOROLAC
Appl. No.: PCT/US2005/045883
Filing Date: 15 December 2005

LETTER RESPONSIVE TO WRITTEN OPINION

International Preliminary Examining Authority
European Patent Office
Erhardstrasse 27
D-80331 München, Germany

Sir:

This communication is responsive to the Written Opinion of the International
Searching Authority dated 3 July 2006, concerning the above-referenced international patent
application.

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REMARKS

Applicant respectfully requests reconsideration of the present application in view of the comments that follow.

Applicant gratefully acknowledges the Authority's determination that claims 2-8, 11, 14-16, 18, 19, 24, 26, 28, and 29 are novel and that claims 1-19 and 27-29 have industrial applicability. Applicant notes that no opinion relating to the industrial applicability of claims 20-26 was formed, because the Authority considers the subject matter of these claims to be covered by the searching provisions of Rule 67.1(iv) PCT regarding treatment of a human by therapy.

The Authority cites 5 documents in forming its opinions relating to novelty and inventive step:

- D1: XP008024919 (Reuben, et al. *Anesth Analg* 2002;95-457-90)
- D2: US Patent No. 6,333,044 to Santus et al.
- D3: US Patent No. 6,090,368 to Zia et al.
- D4: US Patent Publ. No. 2003/0022894 by Semo, et al.
- D5: GB 2 315 673

Novelty

The Authority states that prior art document D1 discloses an aqueous analgetic composition comprising 5% lidocaine and ketorolac suitable for nasal administration. This reference discloses administration of 20 mL of solution containing 100 mg lidocaine and 10 mg ketorolac to a patient after installation of a forearm tourniquet. The reference also discloses the administration of 40 mL of solution containing 200 mg lidocaine and 20 mg ketorolac to a patient after installation of an upper arm tourniquet. Applicant submits that, in each case, the solution administered to the patient contains 0.5% lidocaine¹, not 5% as asserted by the Authority. Claim 1, the broadest composition claim, requires that the

¹ Assuming that the density of the solution is approximately equivalent to water:

$$\frac{100 \text{ mg lidocaine}}{20 \text{ mL solution}} \times \frac{1 \text{ mL solution}}{1 \text{ g}} \times \frac{1 \text{ g}}{1000 \text{ mg}} \times 100\% = 0.5\% \text{ (w/v)}$$

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composition contain 4% w/v to 10% w/v of a local anesthetic, such as lidocaine. Since 0.5% does not fall within the recited range, Applicant submits that reference D1 does not negate the novelty any of the currently pending claims.

In addition, nothing in this reference indicates that the disclosed composition would be suitable for nasal administration. Indeed, this reference highlights one benefit of using a forearm tourniquet as requiring a decreased amount of analgesic, *i.e.* 20 mL rather than 40 mL of solution. Applicant submits that 20 mL of solution is not "suitable for nasal administration." Further, nothing in the reference even suggests the solution of D1 would provide an therapeutically effective amount of ketorolac if it were administered in a quantity suitable for nasal administration (e.g. approximately 200 μ l as described in Example 3 of the present specification). If one were to follow the protocols described in the present specification using the solution described in document D1 to be applied nasally, only 0.1 mg of ketorolac would be administered to the patient. Therefore, again, reference D1 does not disclose the invention as claimed in the present application and therefore does not negate the novelty of any of the claims.

Inventive Step

Applicant admits that each of prior art documents D2 and D3 disclose compositions suitable for nasal administration comprising a therapeutically effective amount of ketorolac. However, neither of these references disclose the inclusion of a local anesthetic or even the desirability of an agent to decrease stinging and irritation. Neither document identifies a problem, nor a solution to the problem.

The Authority refers to document D4 as disclosing "that the addition of 4% lidocaine to pharmaceutical intranasal composition for migraine treatment overcomes the problem of itching and stinging." First, the active ingredient of document D4, *i.e.*, an imidazotriazinone, is structurally and functionally distinct from ketorolac. The Authority provides no evidence or analysis supporting the implicit assumption that imidatriazinones and ketorolac are equivalently stinging, that the stinging is caused by the same mechanism, or that the same amount of local anesthetic would reduce or eliminate undesirable itching or stinging. It would not have been obvious to a person skilled in the art that the undesirable side effects of

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structurally unrelated molecules could be diminished or overcome using exactly the same method.

Further, this document does not disclose the addition of 4% lidocaine, but rather the inclusion of less than 4% lidocaine in the pharmaceutical intranasal compositions. See paragraph [0072]. Indeed, document D4, explicitly teaches away from using 4% lidocaine, the standard amount in commercially available topical preparations for surface analgesia (lines 3-5 of paragraph [0072]). Document D4 states that

It has been found, surprisingly, that only a small amount of a local anaesthetic needs to be added to the imidazotriazinone-containing compositions, to overcome the disadvantages described above. The doses of local anaesthetic necessary for this purpose are generally distinctly less than those necessary for surface anaesthesia. A feeling of local numbness, as occurs after blockade of nerves conducting irritation, by, for example, a local anaesthetic, can therefore be avoided on use of the compositions according to the invention.

The claims of the present invention require that the local anesthetic be included in an amount of 4% to 10%, well above that described as desirable in document D4. One of ordinary skill would not look to D4 to modify D2 or D3. Even if one of ordinary skill would attempt to combine D4 with D2 or D3, the combination would not result in a composition as it is claimed in the present application. Therefore references D2, D3, and D4 do not establish the lack of inventive step.

The Authority also asserts that prior art document D5 "discloses the use of 4% and 6% intranasal lidocaine in combination with a 5-HT-1D agonist for the treatment of migraines." First, the active ingredient of document D5, i.e., a 5-HT-1D agonist, is structurally and functionally distinct from ketorolac. See page 4, lines 10-18. Note the exemplary 5-HT-1D compounds listed: rizatriptan, sumatriptan, naratriptan, and zolmitriptan. The Authority provides no evidence or analysis supporting the implicit assumption that any 5-HT-1D agonist and ketorolac are somehow equivalent or are equivalently stinging, or the stinging is caused by the same mechanism, or the same amount of local anesthetic would reduce or eliminate undesirable itching or stinging. There is no evidence that a person skilled in the art

would find that the undesirable side effects of structurally unrelated molecules could be diminished or overcome using exactly the same method.

In support of the assertion that D5 discloses the "use of 4% and 6% intranasal lidocaine," the Authority points to the claims of D5. However, none of the claims of D5 specify a 5-HT-1D-containing composition suitable for nasal administration having 4% or 6% lidocaine. Indeed, only one claim, claim 11, recites an explicit amount of lidocaine. Claim 11 recites a intranasal formulation

Which comprises from about 1 to about 35 mg of rizatripan and from about 1 to about 3 mg of lidocaine in a pharmaceutically acceptable intranasal carrier which ranges in volume from about 0.1 mL to about 1.0 mL.

The claim appears to be missing a decimal between zero and one in the first volume of the range. For the purposes of this analysis, Applicant assumes the range of claim 11 is meant to be from about 0.1 mL to about 1.0 mL. A composition according to claim 11, having the maximum of lidocaine (3 mg in 0.1 mL solution) would contain only 3% lidocaine, not the 4% or 6% asserted by the Authority. Thus the claims of D5 do not suggest the 4% to 10% range claimed in the present invention. It is possible that the Authority meant to refer to Examples 11 to 14 of prior art document D5. These examples disclose intranasal formulations containing 4 mg or 6 mg of lidocaine in a 1 mL solution. However, these solutions contain 0.4% and 0.6% lidocaine, not 4% and 6% as asserted by the Authority. Nothing in document D5 discloses the desirability of including 4% to 10% local anesthetic in an intranasal ketorolac formulation.

From the reasoning presented above, Applicant submits that an inventive step was involved in the claimed invention when documents D2, D3, D4, and D5 are read as one of ordinary skill would read them. Applicant believes that the invention claimed in the present application is both novel and inventive.

Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

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The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 50-0872. Should no proper payment be enclosed herewith, as by a check or credit card payment form being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 50-0872. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 50-0872.

Respectfully submitted,

Date 12 September 2006

By Karen E. Flick

FOLEY & LARDNER LLP
1530 Page Mill Road
Palo Alto, California 94304-1125
Telephone: (650) 251-1115
Facsimile: (650) 856-3710

Karen E. Flick
Attorney for Applicant
Registration No. 44,111

92

PATENT COOPERATION TREATY

KEF 93

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

POLEY & LARDNER LLP
Attn: Moran, Tom M.
1530 Page Mill Road
Palo Alto, CA 94304-1125
UNITED STATES OF AMERICA

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT AND
THE WRITTEN OPINION OF THE INTERNATIONAL
SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Applicant's or agent's file reference 056269-2460	Date of mailing (day/month/year) 03/07/2005
International application No. PCT/US2005/045853	International filing date (day/month/year) 15/12/2003
Applicant ROXEO PHARMA, INC.	

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes
1211 Geneva 20, Switzerland, Facsimile No.: (41-22) 338.52.70

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.
3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that
- ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.
- ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. Reminders

Shortly after the expiration of 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of each comment to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

Within 18 months from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later); otherwise, the applicant must, within 30 months from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

In respect of other designated Offices, the time limit of 30 months (or later) will apply even if no demand is filed within 18 months.

See the Annex to Form PCT/IS/A/501 and, for details about the applicable time limits, Office by Office, see the PCT Applicant's Guide, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the International Searching Authority  European Patent Office, P.O. Box 1 Patentstrasse 2 NL-2200 HV Rijswijk Tel: +31-70 340-2040, Tx: 31 651 600 01 Fax: +31-70 340-2010	Authorized officer Natalia Moranchio Alcaine
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These Notes are intended to give the basic instructions concerning the filing of amendments under Article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and these requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report and the written opinion of the International Searching Authority, an opportunity to enter the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g., the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only (see PCT Applicant's Guide, Volume I-A, Annexes B1 and B2).

The attention of the applicant is drawn to the fact that amendments to the claims under Article 19 are not allowed where the International Searching Authority has declared, under Article 17(2), that no international search report would be established (see PCT Applicant's Guide, Volume I-A, paragraph 238).

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 9 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

When a claim for international preliminary examination has been filed, see below.

How?

Enter by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, as a result of an amendment or cancellations, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Section 206(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

PCT

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INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 056369-1460	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/US2005/045883	International filing date (day/month/year) 15/12/2005	(Earliest) Priority Date (day/month/year) 23/12/2004
Applicant ROXRO PHARMA, INC.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 5 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the language, the international search was carried out on the basis of:

- ☒ the international application is the language in which it was filed
☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))

b. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, see Box No. I.

2. ☒ Certain claims were found unsearchable (See Box No. II)

3. ☐ Unity of invention is lacking (see Box No. III)

4. With regard to the title,

- ☒ the text is approved as submitted by the applicant
☐ the text has been established by this Authority to read as follows:

5. With regard to the abstract,

- ☒ the text is approved as submitted by the applicant
☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the drawings,

- a. the figure of the drawings to be published with the abstract is Figure No. 1
☒ as suggested by the applicant
☐ as selected by this Authority, because the applicant failed to suggest a figure
☐ as selected by this Authority, because this figure better characterizes the invention
 b. ☐ none of the figures is to be published with the abstract

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2005/045883

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A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K31/407 A61K31/167 A61K9/08 A61P25/06 A61P29/00

According to International Patent Classification (IPC) and/or national classification and/or

B. FIELD(S) SEARCHED

Alphabetical documentation (symbolic) (classification systems followed) (or classification symbols)

A61K A61P

Unclassified documents searched other than minimum recommendations to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search term used)

EPO-Internal, WPI Data, PAJ, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevance to claim No.
X	REUBEN S S ET AL: "AN EVALUATION OF THE ANALGESIC EFFICACY OF INTRAVENOUS REGIONAL ANESTHESIA WITH LIDOCAINE AND KETOROLAC USING A FOREARM VERSUS UPPER ARM TOURNIQUET" ANESTHESIA AND ANALGESIA, WILLIAMS AND WILKINS, BALTIMORE, MD, US, vol. 95, no. 2, 2002, pages 457-460, XP008024919 ISSN: 0003-2999 page 458, left-hand column, paragraph 3	1,9,10, 12,13, 17, 20-23, 25,27.
Y	US 6 333 044 B1 (SANTUS GIANCARLO ET AL) 25 December 2001 (2001-12-25) cited in the application the whole document	1-29

-/-

☒ Further documents are cited in the continuation of this fi.

☒ See patent family issues.

Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document not published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" documents relating to an oral disclosure, use, exhibition or other means
- "P" documents published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in relation with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, each combination being obvious to a person skilled in the art
- "Z" document member of the same patent family

Date of the actual completion of the international search

29 May 2006

Date of mailing of the international search report

03/07/2006

Name and mailing address of the ISA/

European Patent Office, P.O. Box, Patentweg 2
Munich - 80589 Germany
Tel: +49 89 3 59 340-2040, Telex: 521 051 eppo d
Fax: +49 89 3 59 340-3010

Authorized officer

Zimmer, B

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INTERNATIONAL SEARCH REPORT

International Application No.
PCT/US2005/045883

97

(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 6 090 368 A (ZIA ET AL) 18 July 2000 (2000-07-18) claims	1-29
Y	US 2003/022894 A1 (SERNO PETER ET AL) 30 January 2003 (2003-01-30) cited in the application paragraphs [0010], [0011]	1-29
Y	GB 2 315 673 A (* MERCK & CO INC) 11 February 1998 (1998-02-11) cited in the application claims	1-29

INTERNATIONAL SEARCH REPORT

international application No. 98
PCT/US2005/045883

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ **Claim Nos.:**
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 20-26 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition. Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy
2. ☐ **Claim Nos.:**
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ **Claim Nos.:**
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this International Application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not require payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claim Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2005/045883

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 6333044	B1	25-12-2001	NONE
US 6090368	A	18-07-2000	NONE
US 2003022894	A1	30-01-2003	BG 108245 A 31-01-2005 BR 0208813 A 09-03-2004 CA 2443639 A1 24-10-2002 CN 1537004 A 13-10-2004 CZ 20032752 A3 14-01-2004 DE 10118306 A1 17-10-2002 EE 200300501 A 15-12-2003 WO 02083674 A2 24-10-2002 EP 1381368 A2 21-01-2004 HU 0303877 A2 29-03-2004 JP 2004525968 T 26-08-2004 MX PA03009314 A 10-03-2004 NO 20034556 A 10-12-2003 PL 363033 A1 15-11-2004 SK 12682003 A3 02-03-2004
GB 2315673	A	11-02-1998	NONE

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From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43b/s.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/J52005/045883

International filing date (day/month/year)
15.12.2005

Priority date (day/month/year)
23.12.2004

International Patent Classification (IPC) or both national classification and IPC
INV. A61K31/07 A61K31/167 A61K9/08 A61P25/06 A61P29/00

Applicant
ROXRO PHARMA, INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☒ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 65.1 bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



European Patent Office
D-60288 Munich
Tel. +49 89 2369-0 Telex 523650 epmu d
Fax +49 89 2369-4485

Date of completion of
this opinion

see form
PCT/ISA/210

Authorised Officer

Zimmer, B

Telephone No. +49 89 2369-4600



**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2005/045883

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Box No. I Basis of the opinion

1. With regard to the language, this opinion has been established on the basis of:
 - ☒ the international application in the language in which it was filed
 - ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).
2. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☐ on paper
 - ☐ in electronic form
 - c. time of filing/furnishing:
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in electronic form.
 - ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2005/045883

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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

- ☐ the entire international application
- ☒ claims Nos. 20-26 with regard to industrial applicability

because:

- ☒ the said international application, or the said claims Nos. 20-26 with regard to industrial applicability relate to the following subject matter which does not require an international search (specify):

see separate sheet

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed (*specify*):
- ☐ no international search report has been established for the whole application or for said claims Nos.
- ☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:
 - ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
 - ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
 - ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13ter.1(a) or (b).
- ☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-bis of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.
- ☐ See Supplemental Box for further details

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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2005/045883

Box No. V Reasoned statement under Rule 43bis 1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	2-8,11,14-16,18,19,24,26,28,29
	No: Claims	1,9,10,12,13,17,20-23,25,27
Inventive step (IS)	Yes: Claims	
	No: Claims	1-29
Industrial applicability (IA)	Yes: Claims	1-19,27-29
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 20-26 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Art. 34(4)(a)(i) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Reference is made to the following documents:

D1: XP008024919
D2: US-A-6 333 044
D3: US-A-6 090 368
D4: US-A-2003/ 0022894
D5: GB-A-2 315 673

2. Novelty

Prior art document D1 discloses an aqueous analgetic composition comprising 5% lidocaine and ketorolac suitable for nasal administration (p. 458, left col., para. 3). It is thus novelty destroying for the subject-matter of claims 1, 9, 10, 12, 13, 17, 20-23, 25 and 27 of the present application (Art. 33(2) PCT).

3. Inventive Step

3.1 Apart from the fact that the subject-matter of the present application is not novel it does not involve an inventive step for the following reasons:

Prior art documents D2 and D3 both disclose analgesic/ anti-inflammatory pharmaceutical compositions for intranasal administration comprising ketorolac; they differ from the subject-matter of the present application in the lack of an anesthetic (D2: claims and D3: claims).

The technical problem in view of D2, which is regarded as closest prior art, is the provision of an improved pharmaceutical intranasal composition comprising ketorolac for the treatment of pain and migraine.

It is known from D4 that the addition of 4% lidocaine to pharmaceutical intranasal composition for migraine treatment overcomes the problem of itching and stinging ([0010] and [0011]).

The combination of D2 with D4 is obvious for a person skilled in the art as both prior art documents relate to the same technical problem.

Prior art document D5 further discloses the use of 4 and 6 % intranasal lidocaine in combination with a 5-HT_{1D} agonist for the treatment of migraine (claims).

Therefore, the subject-matter of independent claims 1, 17, 20 and 27 of the present application does not seem to involve an inventive step (Art.33(3) PCT).

3.2 The dependent claims do not appear to contain any additional features which involve an inventive step when combined with the subject-matter of any claim to which they refer, in particular in view of prior art document D5. Dependent claims are only allowable when related to a patentable independent claim (Rule 6.4 PCT).

3.3 As a result, the subject-matter of claims 1-29 does not seem to involve an inventive step (Art. 33(3) PCT).

4. For the assessment of the present claims 20-26 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound

for the manufacture of a medicament for a new medical treatment.

Re Item VII

Certain defects in the international application

1. Claim 17 comprises all the features of claim 1 and is therefore not appropriately formulated as a claim dependent on the latter (Rule 6.4 PCT).
2. As the expression "hereby incorporated by reference" ([0002] and [0017]) is not deleted in the description the requirements of Rules 5 and 9.1 PCT are not met.
3. The tabulated data mentioned under [0054] are missing.

Re Item VIII

Certain observations on the international application

Independent claim 17 as well as claims 18 and 19 depending thereupon do not meet the requirements of Art. 6 PCT in that the matter for which protection is sought is not clearly defined. The claim attempts to define the subject-matter in terms of the result to be achieved, which merely amounts to a statement of the underlying problem, without providing the technical features necessary for achieving this result.

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PCT REQUEST

Original (for SUBMISSION)

0	For receiving Office use only	
0-1	International Application No.	
0-2	International Filing Date	
0-3	Name of receiving Office and PCT International Applicant	
0-4	Form PCT/IBQ/101 PCT Request Prepared Using	PCT-SAFE [EASY mode] Version 3.50 (Build 0002,175)
0-5	Pelldan The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty	
0-6	Receiving Office (specified by the applicant)	United States Patent and Trademark Office (USPTO) (NO/US)
0-7	Applicant's or agent's file reference	058389-1460
I	Title of invention	THERAPEUTIC COMPOSITIONS FOR INTRANASAL ADMINISTRATION OF KETOROLAC
II	Applicant	
II-1	This person is	applicant only
II-2	Applicant for	all designated States except US
II-4	Name	ROXEO PHARMA, INC.
II-5	Address	818 Middlefield Road, Suite 260 Menlo Park, California 94025-1444 United States of America
II-6	State of nationality	US
II-7	State of residence	US
II-8	Telephone No.	(650) 322-4554
II-9	Facsimile No.	(650) 322-4514
III	Applicant and/or inventor	
III-1-1	This person is	applicant and inventor
III-1-2	Applicant for	US only
III-1-4	Name (LAST, First)	WHITING, Roger
III-1-5	Address	657 W. San Antonio Rd. Los Altos, California 94022 United States of America
III-1-6	State of nationality	US
III-1-7	State of residence	US

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PCT REQUEST

Original (for SUBMISSION)

II-2	Applicant and/or inventor	applicant and inventor US only THIRUCOTE, Ramachandran 2021 Rockport Ave. Redwood Shores, California 94065 United States of America
II-2-1	This person is	
II-2-2	Applicant for	
II-2-3	Name (LAST, First)	
II-2-4	Address	
II-2-5	State of nationality	
II-2-7	State of residence	
IV-1	Agent of choice representative or address for correspondence The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as	Agent
IV-1-1	Name (LAST, First)	MORAN, Tom M.
IV-1-2	Address	FOLEY & LARDNER LLP 1530 Page Mill Road Palo Alto, California 94304-1125 United States of America
IV-1-3	Telephone No.	(650) 856-2700
IV-1-4	Facsimile No.	(650) 856-3710
IV-1-5	e-mail	tmoran@foley.com
IV-1-6	Agent's registration No.	26,314
V	DESIGNATIONS	
V-1	The filing of this request constitutes under Rule 4.8(a), the designation of all Contracting States bound by the PCT on the international filing date, for the grant of every kind of protection available and, where applicable, for the grant of both regional and national patents.	
VI-1	Priority claim of earlier national application	23 December 2004 (23.12.2004) 60/619,022 US
VI-1-1	Filing date	
VI-1-2	Number	
VI-1-3	Country	
VI-2	Priority document request The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as base(s):	VI-1
VI-3	International Searching Authority chosen	European Patent Office (EPO) (ISA/EP)

PCT REQUEST

Original (for SUBMISSION)

VIII	Declarations	Number of declarations	
VIII-1	Declaration as to the identity of the inventor	-	
VIII-2	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	-	
VIII-3	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	-	
VIII-4	Declaration of inventorship (only for the purpose of the designation of the United States of America)	-	
VIII-5	Declaration as to non-prejudicial disclosure or exceptions to lack of novelty	-	
IX	Check list	number of sheets	electronic file(s) attached
IX-1	Request (including declaration sheets)	4	✓
IX-2	Description	19	-
IX-3	Claims	4	-
IX-4	Abstract	1	✓
IX-5	Drawings	2	-
IX-7	TOTAL	30	
	Accompanying items	paper document(s) attached	electronic file(s) attached
IX-6	Fee calculation sheet	✓	-
IX-17	PCT-SAFE physical media	-	✓
IX-18	other	Transmittal Letter w/ Express Mail mailing no. NY 576 633 179 US	
IX-18	other	Return Postcard	
IX-18	other	Check No. 1483 in the amount of \$3,220	
IX-19	Figure of the drawings which should accompany the abstract	1	
IX-20	Language of filing of the international application	English	
X-1	Signature of applicant, agent or authorized representative		
X-4-1	Name (LAST, First)	MORAN, Tom N.	
X-4-2	Name of signatory	Attorney for Applicant	
X-4-3	Capacity		

PCT REQUEST

Original (for SUBMISSION)

FOR RECEIVING OFFICE USE ONLY

10-1	Date of actual receipt of the purported international application	
10-2	Drafting of	
10-2-1	Received	
10-2-2	Not received	
10-3	Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application	
10-4	Date of timely receipt of the required corrections under PCT Article 11(2)	
10-5	International Searching Authority	ISA/EP
10-6	Transmittal of search copy delayed until search fee is paid	

FOR INTERNATIONAL BUREAU USE ONLY

11-1	Date of receipt of the search copy by the International Bureau	
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PCT (ANNEX - FEE CALCULATION SHEET)

Original (for SUBMISSION)
(This sheet is not part of and does not count as a sheet of the international application)

D		For receiving Office use only	
D-1	International Application No.		
D-2	Date stamp of the receiving Office		
D-4	Form PCT/RO/ON (Annex) PCT Fee Calculation Sheet Prepared Using	PCT-SAFE [EASY mode] Version 3.50 (Build 0002.175)	
D-4-1	Applicant's or agent's file reference	056369-1460	
E	Applicant	ROXRO PHARMA, INC.	
12	Calculation of prescribed fees	Fee amount/multiplier	Total amount (USD)
12-1	Transmittal fee Y	0	300
12-2-1	Search fee B	0	1877
12-2-2	International search to be carried out by	IS	
12-3	International filing fee (first 30 sheets) H	1102	
12-4	Remaining sheets	0	
12-5	Additional amount	0	
12-6	Total additional amount	0	
12-7	H + I =	1102	
12-12	EASY Filing reduction R	-79	
12-13	Total international filing fee (I-R)	1023	
12-14	Fee for priority document		
	Number of priority documents requested	1	
12-15	Fee per document (Q)	20	
12-16	Total priority document fee P	20	
12-17	TOTAL FEES PAYABLE (T+G+H+Q)		3220
12-18	Mode of payment	cheque	
12-20	Deposit account instructions	The Receiving Office United States Patent and Trademark Office (USPTO) (RO/US)	
12-20-2	Authorization to charge any deficiency or credit any overpayment in the total fees indicated above	✓	
12-21	Deposit account No.	50-0873	
12-22	Date	15 December 2005 (15.12.2005)	
12-23	Name and signature	MORAN, Tom M. 	

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PCT

Original (for SUBMISSION)

13-3-7	Validation messages Certainty	Yellow! The power of attorney or a copy of the general power of attorney will need to be furnished unless all applicants sign the request form.
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Therapeutic compositions, particularly sprayable aqueous compositions, comprise ketorolac or a pharmaceutically acceptable salt, in combination with a local anesthetic, such as lidocaine hydrochloride. The compositions are nasally administered to a subject in need thereof to treat pain or inflammation and have the benefit of reduced stinging and improved efficacy, compared to known nasally administered compositions.

PATENT COOPERATION TREATY

056369-1460

KEF 114

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF RECEIPT OF
RECORD COPY

(PCT Rule 24.2(a))

To:

MORAN, Tom M.
FOLEY & LARDNER LLP
1830 Page Mill Road
Palo Alto, California 94304-1125
United States of America

Date of mailing (day/month/year) 24 April 2006 (24.04.2006)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference 056369-1460	International application No. PCT/US2005/045883

The applicant is hereby notified that the International Bureau has received the record copy of the international application as detailed below.

Name(s) of the applicant(s) and State(s) for which they are applicants:

ROXRO PHARMA, INC. (for all designated States except US)
WHITING, Roger et al (for US)

International filing date : 15 December 2005 (15.12.2005)
Priority date(s) claimed : 23 December 2004 (23.12.2004)
Date of receipt of the record copy
by the International Bureau : 10 March 2006 (10.03.2006)
List of designated Offices :

AP : BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW
EA : AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
EP : AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR
OA : BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
National : AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

19 7 -23-02 30 6-23-07
20 8 -23-06

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 28, Switzerland	Authorized officer: V. Galliard (Fax 338-71-30)
Facsimile No. (41-22) 338-71-30	Telephone No. (41-22) 338 8810

114

Continuation of Form PCT/IB/301

NOTIFICATION OF RECEIPT OF RECORD COPY

115

Date of mailing (day/month/year) 24 April 2006 (24.04.2006)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference 056369-1460	International application No. PCT/US2006/045883
ATTENTION The applicant should carefully check the data appearing in this Notification. In case of any discrepancy between these data and the indications in the international application, the applicant should immediately inform the International Bureau. In addition, the applicant's attention is drawn to the information contained in the Annex, relating to: - time limits for entry into the national phase - see updated important information (as of April 2002) - requirements regarding priority documents (if applicable) A copy of this Notification is being sent to the receiving Office and to the International Searching Authority.	

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INFORMATION ON TIME LIMITS FOR ENTERING THE NATIONAL PHASE 176

The applicant is reminded that the "national phase" must be entered before each of the designated Offices indicated on the cover sheet of this Notification by paying national fees and furnishing translations, as prescribed by Articles 22 and 38 and the applicable national laws. In addition, the applicant may also have to comply with other special requirements applicable in certain Offices. It is the applicant's responsibility to ensure the necessary steps to enter the national phase are taken in a timely fashion. Most Offices do not issue reminders to applicants in connection with the entry into the national phase.

The applicable time limit for entering the national phase will, subject to what is said in the following paragraph, be 30 MONTHS from the priority date, not only in respect of any elected Office if a demand for international preliminary examination is filed before the expiration of 18 months from the priority date (see Article 39(1)), but also in respect of any designated Office, in the absence of filing of such demand, where Article 22(1) as modified with effect from 1 April 2002 applies in respect of that designated Office. For further details, see PCT Gazette No. 44/2001 of 1 November 2001, pages 1992ff, 19932 and 19934, as well as the PCT Newsletter, October and November 2001 and February 2002 issues.

In practice, time limits other than the 30-month time limit will continue to apply, for various periods of time, in respect of certain designated or elected Offices. For regular updates on the applicable time limits (20, 21, 30 or 31 months, or other time limit), Office by Office, refer to the PCT Gazette ("Section IV" part published on a weekly basis), to the PCT Newsletter (on a monthly basis) and to the relevant National Chapters in Volume II of the PCT Applicant's Guide (the paper version of which is updated usually twice a year and the Internet version of which is updated usually on a weekly basis). Finally, a cumulative table of all applicable time limits for entering the national phase is available from WIPO's Internet site, via links from various pages the site indexing those of the Gazette, Newsletter and Guide, at <http://www.wipo.int/pct/en/index.html>.

Information about the requirements for filing a demand for international preliminary examination is set out in the PCT Applicant's Guide, Volume IA, Chapter DC. Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination (at present, all PCT Contracting States are bound by Chapter II).

REQUIREMENTS REGARDING PRIORITY DOCUMENTS

For applicants who have not yet complied with the requirements regarding priority documents, the following is recalled.

Where the priority of an earlier national, regional or international application is claimed, the applicant must submit a copy of the said earlier application, certified by the authority with which it was filed ("the priority document") to the receiving Office (which will transmit it to the International Bureau) or directly to the International Bureau, before the expiration of 18 months from the priority date, provided that any such priority document may still be submitted to the International Bureau before that date of international publication of the international application, in which case that document will be considered to have been received by the International Bureau on the last day of the 18-month time limit (Rule 17.1(a)).

Where the priority document is issued by the receiving Office, the applicant may, instead of submitting the priority document, request the receiving Office to prepare and transmit the priority document to the International Bureau. Such request must be made before the expiration of the 18-month time limit and may be subjected by the receiving Office to the payment of a fee (Rule 17.1(b)).

If the priority document concerned is not submitted to the International Bureau or if the request to the receiving Office to prepare and transmit the priority document has not been made (and the corresponding fee, if any, paid) within the applicable time limit indicated under the preceding paragraphs, any designated State may disregard the priority claim, provided that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within the time limit which is reasonable under the circumstances (Rule 17.1(c)).

Where several priorities are claimed, the priority date to be considered for the purposes of computing the 18-month time limit (and all other PCT time limits) is the filing date of the earliest application whose priority is claimed (Article 21(2)(b)).

From the INTERNATIONAL BUREAU

056369-1460

PCT**SECOND AND SUPPLEMENTARY NOTICE
INFORMING THE APPLICANT OF THE
COMMUNICATION OF THE INTERNATIONAL
APPLICATION (TO DESIGNATED OFFICES
WHICH APPLY THE 30 MONTH TIME
LIMIT UNDER ARTICLE 22(1))**

(PCT Rule 47.1(c))

To:

RECEIVED

112

MAY 09 2007

MORAN, Tom M.
FOLEY & LARDNER LLP
1530 Page Mill Road
Palo Alto, California 94304-1125
ETATS-UNIS D'AMERIQUE

FOLEY & LARDNER LLP

Date of mailing (day/month/year)
28 April 2007 (26.04.2007)Applicant's or agent's file reference
056369-1460**IMPORTANT NOTICE**International application No.
PCT/US2005/045883International filing date (day/month/year)
15 December 2005 (15.12.2005)Priority date (day/month/year)
23 December 2004 (23.12.2004)

Applicant

ROXRO PHARMA, INC. et al

1. **ATTENTION:** For any designated Office(s), for which the time limit under Article 22(1), as in force from 1 April 2002 (30 months from the priority date), does not apply, please see Form PCT/IB/308(First Notice) issued previously.
2. Notice is hereby given that the following designated Office(s), for which the time limit under Article 22(1), as in force from 1 April 2002, does apply, have requested that the communication of the international application, as provided for in Article 20, be effected under Rule 93bis.1. The International Bureau has effected that communication on the date indicated below:
06 July 2006 (06.07.2006)

AU, AZ, BY, CN, CO, DZ, EP, HU, KG, KP, KR, MD, MK, MZ, NA, NG, PG, RU, SY, TM, US

In accordance with Rule 47.1(c-bis)(i), these Offices will accept the present notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant in the designated Office(s).

3. The following designated Offices, for which the time limit under Article 22(1), as in force from 1 April 2002, does apply, have not requested, as at the time of mailing of the present notice, that the communication of the international application be effected under Rule 93bis.1:

AE, AG, AL, AM, AP, AT, BA, BB, BG, BR, BW, BZ, CA, CR, CU, CZ, DE, DK, DM, EA, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GR, ID, IL, IN, IS, JP, KE, KM, KN, KZ, LG, LK, LR, LS, LT, LV, LY, MA, MG, MN, MW, MX, NI, NO, NZ, OA, OM, PH, PL, PT, RO, SC, SD, SG, SK, SL, SM, TJ, TN, TR, TT, UA, UZ, VC, VN, YU, ZA, ZM, ZW

In accordance with Rule 47.1(c-bis)(ii), these Offices accept the present notice as conclusive evidence that the Contracting State for which that Office acts as a designated Office does not require the furnishing, under Article 22, by the applicant of a copy of the international application.

4. **TIME LIMITS** for entry into the national phase

For the designated or elected Office(s) listed above, the applicable time limit for entering the national phase will, subject to what is said in the following paragraph, be 30 MONTHS from the priority date.

In practice, time limits other than the 30-month time limit will continue to apply, for various periods of time, in respect of certain of the designated or elected Office(s) listed above. For regular updates on the applicable time limits (30 or 31 months, or other time limit), Office by Office, refer to the *PCT Gazette*, the *PCT Newsletter* and the *PCT Applicant's Guide*, Volume II, National Chapters, all available from WIPO's Internet site, at <http://www.wipo.int/pct/en/index.html>.

It is the applicant's sole responsibility to monitor all these time limits.

PREVIOUSLY
DOCKETED
30 MON - 6.23.07

The International Bureau of WIPO
34, chemin des Colombettes
CH-1211 Geneva 20, Switzerland

Authorized officer

Simin Baharlou

Facsimile No. +41 22 338 82 70

e-mail: pct@wipo.ch

056369-1460

KEF 118

From the INTERNATIONAL BUREAU:

PCT

NOTIFICATION CONCERNING
SUBMISSION OR TRANSMITTAL
OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

MORAN, Tom M.
FOLEY & LARDNER LLP
1530 Page Mill Road
Palo Alto, California 94304-1125
ETATS-UNIS D'AMERIQUE

Date of mailing (day/month/year) 27 April 2006 (27.04.2006)	
Applicant's or agent's file reference 056369-1460	IMPORTANT NOTIFICATION
International application No. PCT/US2005/045883	International filing date (day/month/year) 15 December 2005 (15.12.2005)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 23 December 2004 (23.12.2004)
Applicant ROXRO PHARMA, INC. et al	

1. By means of this form, which replaces any previously issued notification concerning submission or transmittal of priority documents, the applicant is hereby notified of the date of receipt by the International Bureau of the priority document(s) relating to all earlier application(s) whose priority is claimed. Unless otherwise indicated by the letters "NR" in the right-hand column or by an asterisk appearing next to a date of receipt, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).

2. *If applicable* The letters "NR" appearing in the right-hand column denote a priority document which, on the date of mailing of this form, had not yet been received by the International Bureau under Rule 17.1(a) or (b). Where, under Rule 17.1(a), the priority document must be submitted by the applicant to the receiving Office or the International Bureau, but the applicant fails to submit the priority document within the applicable time limit under that Rule, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned having given the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

3. *If applicable* An asterisk (*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b) (the priority document was received after the time limit prescribed in Rule 17.1(a) or the request to prepare and transmit the priority document was submitted to the receiving Office after the applicable time limit under Rule 17.1(b)). Even though the priority document was not furnished in compliance with Rule 17.1(a) or (b), the International Bureau will nevertheless transmit a copy of the document to the designated Offices, for their consideration. In case such a copy is not accepted by the designated Office as the priority document, Rule 17.1(c) provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
23 December 2004 (23.12.2004)	✓ 80/030,022	US	20 March 2006 (20.03.2006)

197350 203 3062327

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Authorized officer

Gijbertus Beijer

Facsimile No. +41 22 338 82 70

Facsimile No. +41 22 338 82 70

Form PCT/IB/314 (October 2005)

Telephone No. +41 22 338 95 61

CTWSRDP



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UNITED STATES PATENT AND TRADEMARK OFFICE

United States Department of Commerce
Office of the United States Patent and Trademark Office

NOVEMBER 23, 2005

PTAS

TOM M. MORAN/TOLEY & LAMIMER LLP
1590 PAGE MILL ROAD
PALO ALTO, CA 94304-1125

500062083A

500062083A

UNITED STATES PATENT AND TRADEMARK OFFICE
NOTICE OF RECORDED ASSIGNMENT DOCUMENT

THE ENCLOSED DOCUMENT HAS BEEN RECORDED BY THE ASSIGNMENT DIVISION OF THE U.S. PATENT AND TRADEMARK OFFICE. A COMPLETE MICROFILM COPY IS AVAILABLE AT THE ASSIGNMENT SEARCH ROOM ON THE REEL AND FRAME NUMBER REFERENCED BELOW.

PLEASE REVIEW ALL INFORMATION CONTAINED ON THIS NOTICE. THE INFORMATION CONTAINED ON THIS RECORDED NOTICE REFLECTS THE DATA PRESENT IN THE PATENT AND TRADEMARK ASSIGNMENT SYSTEM. IF YOU SHOULD FIND ANY ERRORS OR HAVE QUESTIONS CONCERNING THIS NOTICE, YOU MAY CONTACT THE EMPLOYEE WHOSE NAME APPEARS ON THIS NOTICE AT 571-272-3350. PLEASE SEND REQUEST FOR CORRECTION TO: U.S. PATENT AND TRADEMARK OFFICE, MAIL STOP: ASSIGNMENT SERVICES DIVISION, P.O. BOX 1450, ALEXANDRIA, VA 22313.

RECORDATION DATE: 11/23/2005

REEL/FRAME: 016012/0592
NUMBER OF PAGES: 6BRIEF: ASSIGNMENT OF ASSIGNOR'S INTEREST (SEE DOCUMENT FOR DETAILS).
DOCKET NUMBER: 056369-1450ASSIGNOR:
WHITING, ROGER

DOC DATE: 02/15/2005

ASSIGNOR:
THIRUGOTI, RAMCHANDRAN

DOC DATE: 02/15/2005

ASSIGNEE:
ROKNO PEARNA LLC
595 MIDDLEFIELD ROAD
SUITE 240
MENLO PARK, CALIFORNIA 94025-3444

119

120

016812/0592 PAGE 2

SERIAL NUMBER: 60639022

FILING DATE: 12/23/2004

PATENT NUMBER:

ISSUE DATE:

TITLE: THERAPEUTIC COMPOSITIONS FOR INTRAMUSCULAR ADMINISTRATION OF KETOROLAC

ASSIGNMENT DIVISION

OFFICE OF PUBLIC RECORDS

120

PATENT ASSIGNMENT

Electronic Version v1.1
Stylesheet Version v1.1

11/23/2005
500062083

121

SUBMISSION TYPE:	NEW ASSIGNMENT												
NATURE OF CONVEYANCE:	ASSIGNMENT												
CONVEYING PARTY DATA													
<table border="1"><thead><tr><th>Name:</th><th>Execution Date</th></tr></thead><tbody><tr><td>Roger Whiting</td><td>02/16/2005</td></tr><tr><td>Rameshchandra Thirucota</td><td>02/16/2005</td></tr></tbody></table>		Name:	Execution Date	Roger Whiting	02/16/2005	Rameshchandra Thirucota	02/16/2005						
Name:	Execution Date												
Roger Whiting	02/16/2005												
Rameshchandra Thirucota	02/16/2005												
RECEIVING PARTY DATA													
<table border="1"><tbody><tr><td>Name:</td><td>Roero Pharma LLC</td></tr><tr><td>Street Address:</td><td>535 Middlefield Road</td></tr><tr><td>Internal Address:</td><td>Suite 240</td></tr><tr><td>City:</td><td>Menlo Park</td></tr><tr><td>State/Country:</td><td>CALIFORNIA</td></tr><tr><td>Postal Code:</td><td>94025-3444</td></tr></tbody></table>		Name:	Roero Pharma LLC	Street Address:	535 Middlefield Road	Internal Address:	Suite 240	City:	Menlo Park	State/Country:	CALIFORNIA	Postal Code:	94025-3444
Name:	Roero Pharma LLC												
Street Address:	535 Middlefield Road												
Internal Address:	Suite 240												
City:	Menlo Park												
State/Country:	CALIFORNIA												
Postal Code:	94025-3444												
PROPERTY NUMBERS Total: 1													
<table border="1"><thead><tr><th>Property Type</th><th>Number</th></tr></thead><tbody><tr><td>Application Number:</td><td>50539022</td></tr></tbody></table>		Property Type	Number	Application Number:	50539022								
Property Type	Number												
Application Number:	50539022												
CORRESPONDENCE DATA													
Fax Number: (888)856-3710 <i>Correspondence will be sent via US Mail when the fax attempt is unsuccessful</i>													
Email: lcummings@olexy.com													
Correspondent Name: Tom M. Moren-Poley & Lander LLP													
Address Line 1: 1530 Page Mill Road													
Address Line 4: Palo Alto, CALIFORNIA 94304-1125													
ATTORNEY DOCKET NUMBER:	055355-1450												
NAME OF SUBMITTER:	Tom M. Moren												
Total Attachments: 4 source=Roero assignment/page1.tif source=Roero assignment/page2.tif source=Roero assignment/page3.tif													

11/23/05 3:28 FAX 500062083

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source=Form assignment page 4.5

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FORM PTO-1593 (modified)

U.S. DEPARTMENT OF COMMERCE

(Rev. 6-93)

RECORDATION FORM COVER SHEET PATENTS ONLY

Patent and Trademark Office

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To the Director of the United States Patent and Trademark Office: Please record the attached original documents or copies thereof.

1. Name of conveying party(ies): Roger WHITING Ramachandran THIRUCOTE		2. Name and address of receiving party(ies): RoxRo Pharma, LLC 638 Middlefield Rd., S 240 Menlo Park, CA 94028	
Additional conveying party(ies) NO		Additional name(s) & address(es) attached? NO	
3. Nature of conveyance: ASSIGNMENT Execution Date: 02/18/2004			
4. Application number(s) or patent number(s): If this is being filed together with a new application, the execution date of the application is:			
A. Patent Application Number(s): 60/639,022		B. Patent Number(s): 	
Additional numbers attached? NO			
5. Name and address of party to whom correspondence concerning document should be mailed: Tom M. Moran FOLEY & LARDNER LLP 1530 Page Mill Road Palo Alto, California 94304-1125		6. Total number of applications/patents involved: 1 7. Total fee (37 C.F.R. § 3.41): \$40.00 Check Enclosed ☒ Charge to deposit account 8. Deposit account number: 60-0872	
DO NOT USE THIS SPACE			
9. Statement and signature: <i>To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document. The Commissioner is hereby authorized to charge any additional recordation fees which may be required in this matter to the above-identified deposit account.</i>			
Tom M. Moran, Reg. No. 25,314			
Name of person signing		Signature	
		Date	
		22 Nov 2005	
Total number of pages including cover sheet, attachments, and document: 4			

**ASSIGNMENT
(Joint)**

124

WHITING, Roger, residing at 697 N. San Antonio Rd., Los Altos, California
94022

THIRUCOTE, Ramachandran, residing at 2021 Rockport Ave., Redwood
Shores, California 94065

(each referred to as "Assignor") have made an invention(s) (the "Invention(s)") set forth in an application for patent of the United States, entitled **THERAPEUTIC COMPOSITIONS FOR INTRANASAL ADMINISTRATION OF KETOROLAC**, and which is:

- (1) ☒ provisional application
- (a) ☐ to be filed herewith; or
- (b) ☒ bearing Application No. 60/639,077, and filed on December 23, 2004; or
- (2) ☐ non-provisional application
- (a) ☐ to be filed herewith; or
- (b) ☐ bearing Application No. , and filed on .

WHEREAS, **Roxco Pharma LLC**, a corporation duly organized under and pursuant to the laws of California, and having its principal place of business at 335 Middlefield Road, Suite 240, Menlo Park, CA 94025-3444 (the "Assignee"), is desirous of acquiring the entire right, title, and interest in: the Invention(s); the application for patent identified in paragraph (1) or (2); the right to file applications for patent of the United States or other countries on the Invention(s); any application(s) for patent of the United States or other countries claiming priority to these application(s); any provisional or other right to recover damages, including royalties, for prior infringements of these applications; and any patent(s) of the United States or other countries that may be granted therefor or thereon.

NOW, THEREFORE, for good and sufficient consideration, the receipt of which is hereby acknowledged, and to the extent that the Assignor has not done so already via a prior agreement with the Assignee, or if the Assignor has already done so via a prior agreement with the Assignee then in confirmation of any obligation to do so in said prior agreement, the Assignor has sold, assigned, transferred, and set over, and by these presents does sell, assign, transfer, and set over, unto the Assignee, its successors, legal representatives, and assigns, the Assignor's entire right, title, and interest in:

- (a) the Invention(s);
- (b) the application for patent identified in paragraph (1) or (2);

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(c) the right to file applications for patent of the United States or other countries on the Invention(s), including all rights under the Paris Convention for the Protection of Industrial Property and under the Patent Cooperation Treaty;

(d) any application(s) for patent of the United States or other countries claiming the Invention(s);

(e) any application(s) for patent of the United States or other countries claiming priority to the application for patent identified in paragraph (1) or (2) or any application(s) for patent claiming the Invention(s), including any division(s), continuation(s), and continuation(s)-in-part; and

(f) any provisional or other right to recover damages, including royalties, for prior infringements of any application for patent identified in the preceding paragraphs (b)-(e); and

(g) any patent(s) of the United States or other countries that may be granted for or on any application for patent identified in the preceding paragraphs (b) - (e), including any reissue(s) and extension(s) of said patent(s).

The above-granted rights, titles, and interests are to be held and enjoyed by the Assignee, for its own use and behalf and the use and behalf of its successors, legal representatives, and assigns, as fully and entirely as the same would have been held and enjoyed by the Assignor had this sale and assignment not been made.

The Assignor hereby represents to the Assignee, its successors, legal representatives, and assigns, that, at the time of execution and delivery of these presents, or if applicable, at such time said prior agreement was executed, the Assignor is a lawful owner of an undivided interest in the entire right, title, and interest in and to the Invention(s), that the Invention(s) are unencumbered, except, if applicable, by obligation assign in accordance with said prior agreement, and that the Assignor has good and full right and lawful authority to sell and convey the same in the manner set forth herein.

The Assignor hereby covenants and agrees to and with the Assignee, its successors, legal representatives, and assigns, that the Assignor will sign all papers and documents, take all lawful oaths, and do all acts necessary or required to be done in connection with any and all proceedings for the procurement, maintenance, enforcement and defense of the Invention(s), said applications, and said patents, including interference proceedings, without charge to the Assignee, its successors, legal representatives, and assigns, but at the cost and expense of the Assignee, its successors, legal representatives, and assigns.

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The Assignor hereby authorizes and requests the attorneys of COOLEY GODWARD L.L.P. to insert in the spaces provided above the filing date, the application number, and the attorney docket number of the application identified in paragraph (1) or (2) when known.

The Assignor hereby requests the Commissioner of Patents to issue said patents of the United States to the Assignee for the sole use and behalf of the Assignee, its successors, legal representatives, and assigns.

Date: Feb. 15th 2005

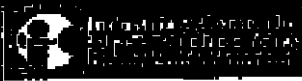
By:


WHITING, RogerDate: Feb. 15th 2005

By:


THIRUCOTE, Ramachandran

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		FORMATO DE DIGITALIZACION RELACION DE ANEXOS				Formato digitalizado por el Centro de Digitalización del Archivo Nacional de Cuba	
Expediente No				07-52072		No de Folia	
Item				No de unidades		No de Folia	
1	CD						
2	DVD						
3	REVISTA						
4	LIBRO						
5	PERIODICO						
6	DISQUETES						
7	SOBRE DE MANILA	X		1			✓
8	SOBRE BLANCO TAMAÑO CARTA						
9	SOBRE BLANCO TAMAÑO OFICIO						
10	OTROS						
Observaciones ART. FINAL							



No. 07-052072-00000-0000

Fecha: 2007-05-24 10:05:17 Dep. 2020 NUECREACION
Tm. 11 PATENTE/VI Ene: 379 FASENACIONAL/II
Act. 411 PRESENTACION Folios: 127



Industria y Comercio
SUPERINTENDENCIA

**REQUISITOS MINIMOS PARA ADMISION A TRAMITE
PCT**

PATENTE DE INVENCION

☒

MODELO DE UTILIDAD ☐

- ◆ Indicación de que se solicita la concesión de una patente ☒
- ◆ Datos de identificación del solicitante o de la persona que presenta la solicitud ☒
- ◆ Descripción de la invención ☒
- ◆ Dibujos de ser estos pertinentes ☒
- ◆ Comprobante de pago de las tasas establecidas ☒

COMPLETA ☐

INCOMPLETA ☐

DISEÑO INDUSTRIAL ☐

- ◆ Indicación de que se solicita el registro de Diseño Industrial ☐
- ◆ Datos de identificación del solicitante o de la persona que presenta la solicitud ☐
- ◆ Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño ☐
- ◆ Comprobante de pago de las tasas establecidas ☐

COMPLETA ☐

INCOMPLETA ☐

ESQUEMA DE TRAZADO ☐

- ◆ Indicación de que se solicita el registro de un Esquema de Trazado ☐
- ◆ Datos de identificación del solicitante o de la persona que presenta la solicitud ☐
- ◆ Representación gráfica del esquema trazado ☐
- ◆ Comprobante de pago de las tasas establecidas ☐

COMPLETA ☐

INCOMPLETA ☐

Firma Responsable

24 MAYO 2007

Fecha

Carrera 13 No. 27-00 Piso 5, 7 y 10
Commutador: 3 82 08 40
Fax: 350 62 20
E-mail: info@sic.gov.co
www.sic.gov.co
Bogotá, D.C., Colombia

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FORMULARIO ÚNICO DE SOLICITUD PCT

ENTRADA EN FASE NACIONAL

SOLICITUD DE:

☒ Patente de invención

☐ Modelo de Utilidad

☐ Capítulo I.

☒ Capítulo II.

2) SOLICITANTE (71)

Nombre: ROXRO PHARMA, INC.

Dirección: 535 Middlefield Road, Suite 240, Menlo Park, California 94025-3444 USA

Nacionalidad o domicilio: Menlo Park, California USA

Lugar de constitución: California USA

Teléfono: Fax:

E. Mail:

IDENTIFICACIÓN

C.C. ☐ NIT: ☐

C.E. ☐ OTRO ☐

NÚMERO: Cual:

3) REPRESENTANTE O APODERADO

Nombre: DILIA MARIA RODRIGUEZ D'ALEMAN

Dirección: Carrera 11 N°. 86-53 Piso 6 Bogotá D.C.

Teléfono: 6181088 Fax: 6350824

E. Mail: info@clarkemodet.com.co

IDENTIFICACIÓN

C.C. ☒ NIT: ☐

C.E. ☐ OTR ☐

NÚMERO: 41.854.882

TP: 20824 CSJ

4) INVENTOR (ES) (72)

Nombre: 1. WHITING, Roger; 2. THIRUCOTE, Ramachandran

Dirección: 1. 697 n. San Antonio Rd., Los Altos, California 94022 USA; 2. Rockport Ave., Redwood Shores, California 94065 USA

Nacionalidad o Domicilio: Todos los anteriores, estadounidenses

5) PCT (86)

Solicitud Internacional No. PCT/US2005/045883 Fecha: Dic. 15, 2005

Publicación Internacional No. WO2006/071601 A2 Fecha: Julio 6, 2006

6) Título (54) COMPOSICIONES TERAPÉUTICAS PARA LA ADMINISTRACIÓN INTRANASAL DE KETAROLAC

7) Clasificación Internacional: A61K 31/407 A61K 31/167 A61K 9/08 A61P 25/08 A61P 29/00

8) PRIORIDAD

SI ☒ NO ☐

33) País de Origen

Estados Unidos

(32) Fecha

Dic. 23, 2004

(31) Número de Solicitud

60/639,022

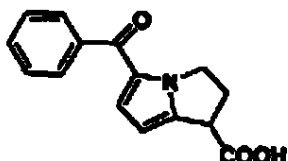
9) Comprobante de pago N°:

Instrucciones para el diligenciamiento del presente formulario. Ver reverso de esta página

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REIVINDICACIONES

1. Una composición para administración por vía nasal a un paciente, **CARACTERIZADA PORQUE** comprende una cantidad terapéuticamente eficaz del compuesto ácido 5-benzoi-2,3-dihidro-1H-pirrolizina-1-carboxílico, de la fórmula



una forma ópticamente activa del mismo, la mezcla racémica, o una sal adecuada para uso farmacéutico de los mismos, en combinación con un diluyente adecuado para uso farmacéutico y del 4% p/v al 10% (p/v) de un anestésico local.

2. La composición de la reivindicación 1, **CARACTERIZADA PORQUE** el compuesto es ketorolac trometamina como una mezcla racémica.

3. La composición de la reivindicación 2, **CARACTERIZADA PORQUE** comprende 25 mg - 225 mg de dicho compuesto disueltos por ml, donde el diluyente es agua y la composición es líquida y que se puede vaporizar.

4. La composición de la reivindicación 3, **CARACTERIZADA PORQUE** comprende 50-200 mg de dicho compuesto por ml.

5. La composición de la reivindicación 2, **CARACTERIZADA PORQUE** está presente un quelante.

6. La composición de la reivindicación 1, **CARACTERIZADA PORQUE** comprende el 2,5-22,5% p/v de dicho compuesto disuelto en el diluyente, que es agua.

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REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá,
2020

Doctor(a)
RODRIGUEZ DELIA MARIA

REFERENCIA	Radicación No.	7 52072
	Solicitud internacional	PCT/US2005/045883
	Fecha inicio fase nacional	23/07/2007
	Trámite	11
	Evento	379
	Actuación	430
	Oficio No.	8902

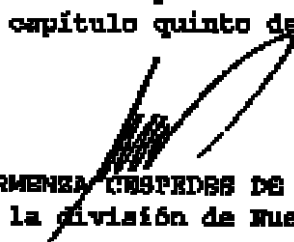
Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante. (Art. 26-k) Decisión 486. Cuando se trate de documentos otorgados en el extranjero, deben legalizarse de conformidad con lo dispuesto por los artículos 259 y 260 del Código de Procedimiento Civil.

2. La solicitud no contiene el poder debidamente otorgado, con el lleno de los requisitos exigidos por los artículos 63 y subsiguientes del Código de Procedimiento Civil. Adicionalmente, deberá presentar el documento que acredita la existencia y representación legal de la sociedad solicitante, cuando ésta fuere persona jurídica.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal a), del capítulo quinto del título primero de la Circular Única No.10 de 2001.


ALIX CARMENA CUSTODIOS DE VENGEL
Jefe de la División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de fecha 27 JUL 2007
adpall