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(54) Title: STABLE PHARMACEUTICAL COMPOSITIONS OF KETOROLAC OR SALTS THEREOF

(57) Abstract: Pharmaceutical compositions of ketorolac or salts thereof, having improved storage stability as compared to known compositions. The process of manufacturing thereof is also provided. The compositions are particularly suitable for topical administration into the nose in the treatment of pain or inflammation.

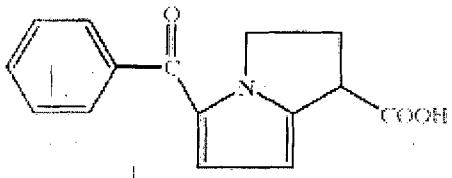
STABLE PHARMACEUTICAL COMPOSITIONS OF KETOROLAC OR SALTS THEREOF

FIELD OF THE INVENTION

The present invention relates to stable pharmaceutical compositions of ketorolac or salts thereof. In particular, the present invention relates to storage stable pharmaceutical compositions of ketorolac or salts thereof and processes of manufacturing such compositions. The composition is particularly suitable for topical administration into the nose for the treatment of pain or inflammation.

BACKGROUND OF THE INVENTION

Ketorolac is a nonsteroidal agent with potent analgesic and moderate antiinflammatory activity. Chemically it is 5-benzoyl-2, 3-dihydro-1H-pyrrolizine-1-carboxylic acid and the formula of which is:



Ketorolac has been known for several years, for example in U.S. Patent No. 4,089,969, and is used in human therapy as an analgesic and an anti-inflammatory.

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.

Ample literature is available on ketorolac, for example "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.

Due to its bioactivity, a commercially available ketorolac contained pharmaceutical preparation for topical (mucosal) or systemic diseases is preferred.

Suitable formulations of ketorolac that can be formulated as a nasally administrable composition are disclosed for example in U.S. Patent No. 6,333,044.

U.S. Patent Publication No. 2009/0042968 discloses a composition that is a combination of ketorolac and a local anesthetic for nasal administration to reduce the stinging sensation.

International (PCT) Publication No. WO 2009/152369 discloses a unit dose formulation for nasal administration to one or two nostrils comprising:
(a) greater than 12 to about 38 mg of ketorolac per nostril at a concentration of greater than 22.5 % w/v; and (b) a pharmaceutically acceptable carrier; wherein said unit dose has a volume of 100 microliters or less per nostril.

U.S. Patent No. 6,090,368 discloses a pharmaceutical nasal spray consisting of an effective amount of ketorolac based analgesic admixed with a phospholipid or a bioadhesive polymer selected from the group consisting of polyacrylics, cellulosics, gums, cyclodextrins, chitosans, hyaluronates and albumins said spray when administered intranasally having a therapeutic blood level compared to that of the same spray when injected.

U.S. Patent Publication No. US 20110021595 discloses a topical aqueous ophthalmic solution comprising ketorolac, a combination of medium and high molecular weight carboxymethyl cellulose and containing no preservative, wherein the carboxymethyl cellulose is present in the amount of about 0.5 percent by weight and ketorolac is present in a concentration of about 0.40 to about 0.45 percent by w/v.

Currently, nasal spray product of ketorolac is marketed in the US in the form of a nasal spray under the trade name Sprix® by Roxro Pharmaceuticals Inc.

Since aqueous and ethanolic solutions of ketorolac or salts thereof are susceptible to degradation when subjected to long term storage under room temperature (without subjecting to cold chain storage), the recommended storage condition for commercially available product requires cold chain storage, an uninterrupted series of storage and distribution activities so as to maintain a temperature range, particularly within 36°F and 46°F (2°C and 8°C) and also ought to be protected from light. This specialty storage requirement thus leads to increase in the final product cost when it reaches to the end consumer.

Hence, there exists a need to devise a storage stable formulation of ketorolac which exhibits improved shelf-life over the storage period.

SUMMARY OF THE INVENTION

In one general aspect there is provided a storage stable pharmaceutical composition comprising ketorolac or salts thereof with one or more pharmaceutically acceptable excipients, wherein the composition retains at least 80% of the potency of ketorolac or salts thereof in the pharmaceutical composition after storage for at least four months at room temperature.

In another general aspect there is provided a storage stable pharmaceutical composition comprising ketorolac or salts thereof, at least one stabilizing agent and one or more pharmaceutically acceptable excipients.

In another general aspect there is provided a storage stable pharmaceutical composition comprising ketorolac or salts thereof, at least one stabilizing agent and one or more pharmaceutically acceptable excipients, wherein when said composition is stored to 25°C in closed vials for four months, the total amount of related substances does not increase more than 0.4%.

In another general aspect there is provided a storage stable pharmaceutical composition comprising ketorolac or salts thereof, at least one stabilizing agent and one or more pharmaceutically acceptable excipients, wherein when said composition is stored to 25°C in closed vials for four months, the total amount of ketorolac-1-keto impurity does not increase more than 0.2%.

In another general aspect there is provided a storage stable pharmaceutical composition comprising ketorolac or salts thereof, at least one stabilizing agent, wherein the ratio of the amount of ketorolac or salt thereof to the amount of stabilizing agent is in the range of from about 1:0.1 to about 1:0.5.

In another general aspect there is provided a storage stable pharmaceutical composition comprising ketorolac or salts thereof and at least one stabilizing agent, wherein the amount of stabilizing agent is from about 10% to about 50% by weight of the ketorolac or salts thereof.

In another general aspect there is provided a storage stable aqueous nasal spray composition comprising ketorolac or salts thereof, at least one stabilizing agent and one or more pharmaceutically acceptable excipients.

In another general aspect there is provided a storage stable pharmaceutical composition comprising ketorolac or salts thereof, at least one polyhydroxy alcohol and one or more pharmaceutically acceptable excipients.

In another general aspect there is provided a storage stable pharmaceutical composition comprising ketorolac or salts thereof, at least one stabilizing agent, at least one buffer, at least one preservative, at least one taste masking agent, at least one antioxidant, at least one pH adjusting agent, and optionally one or more pharmaceutically acceptable excipients.

Embodiments of the storage stable pharmaceutical composition may include one or more of the following features. For example, the pharmaceutical composition may include one or more pharmaceutically acceptable excipients selected from surfactant, preservatives, chelating agents, tonicity adjusting agent, absorption promoters, viscosifier, pH adjusting agents, sweetener/taste masking agents and the like.

In another general aspect there is provided a process of preparing a storage stable pharmaceutical composition comprising ketorolac or salts thereof comprises steps of:

(a) preparing a solution comprising one or more stabilizing agent, one or more buffer, one or more chelating agent, one or more antioxidant, one or more preservative and optionally one or more other pharmaceutical excipients in purified water;

(b) adding ketorolac or a salt thereof to the solution of step (a) and adjusting the pH of the solution using one or more pH adjusting agents;

(c) making the final volume with purified water; and

(d) filling the solution of step (c) into suitable containers.

Embodiments of the storage stable pharmaceutical composition may include one or more of the following features. For example, the pharmaceutical composition may include one or more pharmaceutically acceptable excipients selected from surfactant, preservatives, chelating agents, absorption promoters, viscosifier, pH adjusting agents, one or more tonicity adjusting agent, sweetener/taste masking agents and the like.

In another general aspect there is provided use of a stabilizing agent for preparing a storage stable pharmaceutical composition comprising ketorolac or salts thereof with one or more pharmaceutically acceptable excipients for use in preparation of medicament for treatment of pain or inflammation comprising administering the said composition to the patient in need thereof.

In another general aspect there is provided a method of treating moderate to moderately severe pain that requires analgesia at the opioid level in a subject in need thereof, comprising nasally administering to the subject a storage stable pharmaceutical composition comprising ketorolac or salt thereof with one or more pharmaceutically acceptable excipients.

The details of one or more embodiments of the invention are set forth in the description below. Other features, objects and advantages of the invention will be apparent from the description.

DETAILED DESCRIPTION OF THE INVENTION

The inventors of the present invention have surprisingly found that it is possible to develop a storage stable pharmaceutical composition of ketorolac using judicial combination of pharmaceutically acceptable excipients.

In particular, the present inventors have found that a stable pharmaceutical composition of ketorolac may be obtained by using pharmaceutically acceptable excipients comprising one or more stabilizing agents. Further, the inventors of the present invention have found that that the resulting pharmaceutical composition of ketorolac may remain stable when subjected to the stability condition. The composition can be stored at room temperature over the storage period and does not require cold chain storage and/or protection from light.

It will be appreciated that ketorolac, for the purpose of the present invention, the term '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.

The term "stable" or "storage stable" indicates that when the composition is stored at room temperature (25°C) for extended period of time such as four months, there is no significant change in dissolution profile and/or therapeutically effective amount and/or total impurities percentages do not exceed 5% by weight to the ketorolac or salt thereof.

Particularly, the invention relates to a stable pharmaceutical composition comprising ketorolac or salts thereof, wherein when said composition is stored to 25°C in closed vials for four months, the total amount of related substances does not increase more than 0.4%.

Additionally, the invention relates to a stable pharmaceutical composition comprising ketorolac or salts thereof, wherein when said composition is stored to 25°C in closed vials for four months, the total amount of ketorolac-1-keto impurity does not increase more than 0.2%.

The term "stabilizing agent" refers to a pharmaceutically acceptable excipient that enhances the chemical or physical stability of the active ingredient in the formulation.

The inventors of the present invention believe that use of judicial combination of pharmaceutical excipients including one or more stabilizing agents, for example polymer/s may contribute in improving the stability of liquid compositions of ketorolac.

Accordingly the present invention relates to a stable pharmaceutical composition for nasal administration comprising, ketorolac or salt thereof, together with a stabilizing agent. The composition further may comprise one or more physiologically compatible buffer in a suitable amount for the pH of the composition to remain in the range of from 3.5 to 8.0.

Such composition is able to guarantee long stability and may provide good absorption of the active ingredient, thereby may restrain the use of irritant absorption enhancing agents/promoters or complicated preparation and delivery techniques.

In an embodiment, the stabilizing agent present in the pharmaceutical composition of ketorolac or a salt thereof comprises at least one polymer. The polymer can be selected from water soluble polymers and water insoluble polymers or mixtures thereof.

Examples of suitable polymers which can be employed in the stable pharmaceutical composition of ketorolac may be selected from, but not limited to polyhydroxy alcohols such as glycerin, polyethylene glycol, propylene glycol, diethylene glycol, triethylene glycol, tetraethylene glycol, 2-methyl-2,4-pentanediol, 1,2,6-hexanetriol and thioglycol, alginic acid, polyoxyethylene polyoxypropylene glycol, low methoxyl pectin, cellulose derivatives such as- methyl cellulose, carboxymethyl cellulose sodium, xanthan gum, hydroxypropyl cellulose, hydroxypropyl methyl cellulose or mixtures thereof.

The amount of stabilizing agent in the composition may range from about 10% to about 50% by weight of the ketorolac or salts thereof.

In an embodiment, the ratio of the amount of ketorolac or salt thereof to the amount of stabilizing agent in the composition is in the range of from about 1:0.1 to about 1:0.5.

The present invention further provides a stable pharmaceutical composition comprising ketorolac or salts thereof which retains at least therapeutic effective concentration of ketorolac after subjecting to the stability condition.

In an embodiment, the stable pharmaceutical composition comprising ketorolac or salts thereof retains at least 80% of the potency of ketorolac or salts thereof in the pharmaceutical composition after storage for three months at room temperature.

In a further embodiment, the stable pharmaceutical composition comprising ketorolac or salts thereof retains at least therapeutic effective concentration of ketorolac after subjecting to the stressed stability conditions for at least 1 month.

In a further embodiment, the stable pharmaceutical composition comprising ketorolac or salts thereof retains at least therapeutic effective concentration of ketorolac after subjecting to the storage at room temperature for at least 1 year.

In a further embodiment, the invention provides use of a stabilizing agent for preparing a storage stable pharmaceutical composition comprising ketorolac or salts thereof.

The invention further provides a process of preparing the stable pharmaceutical composition of ketorolac or salt thereof.

In an embodiment, the process of preparing the stable pharmaceutical composition of ketorolac or salt thereof comprises preparing the solution of ketorolac or its salts thereof with one or more pharmaceutically acceptable excipients.

In a further embodiment, there is provided the process of preparing the stable pharmaceutical composition of ketorolac or salt thereof comprises steps of-

(a) preparing a solution comprising one or more stabilizing agent, one or more buffer, one or more chelating agent, one or more antioxidant, one or more preservative and optionally one or more other pharmaceutical excipients in purified water;

(b) adding ketorolac or salt thereof, to the solution of step (a); (b) adjusting the pH of solution of step (b) using one or more pH adjusting agents;

(c) making the final volume with purified water; and

(d) filling the solution of step (c) into suitable containers.

The composition can be filled in to commercially available bottles and fit with metered dose pumps for nasal delivery of the drug products.

Preferably, the composition of the present invention is manufactured under an inert gas (e.g. nitrogen) atmosphere. In an embodiment, the composition is packed in the container by purging inert gas in the headspace of the container.

The composition can, for nasal administration, be applied in all medicament forms which are suitable for nasal administration, such as, for example, nasal drops or nasal sprays, by means of dispensing devices suitable for this purpose, such as bottles with drop device or nasal spray pumps.

The stable pharmaceutical composition of ketorolac or salt thereof comprise one or more pharmaceutically acceptable excipients selected from vehicles, surfactants, chelating agents, preservative, pH adjusting agents, absorption promoters, viscosifiers, sweetener/taste masking agents.

Suitable vehicles for the composition according to the invention include aqueous based vehicles suitable for topical administration. In addition to aqueous (purified water), oil or gel vehicles, other vehicles 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.

Preferably, the purified water used to prepare the storage stable composition of the invention is, preferably, has oxygen content of less than 8%.

Examples of suitable surfactants which can be employed in the stable pharmaceutical composition of ketorolac may be selected from, but not limited to polysorbates, their ether ethoxylates, produced by reaction of sorbitan esters with ethylene oxide, polyoxyethylene alkyl phenol, polyoxyethylene cetyl ether, polyoxyethylene alkyl-aryl ether, polyoxyethylene monolaurate, polyoxyethylene vegetable oil, polyoxyethylene sorbitan monolaurate, polyoxyethylene esters or mixed fatty and resin acids, polyoxyethylene sorbitol lanolin derivative, polyoxyethylene tridecylether, polyoxyethylene sorbitan esters of mixed fatty and resin acids, polyoxyethylene sorbitan monostearate, polyoxyethylene sorbitan monooleate, polyoxyethylene monostearate, polyoxyethylene stearyl ether, polyoxyethylene oleyl ether, polyoxyethylene tridecyl ether, polyoxyethylene fatty alcohol, polyoxyethylene alkyl amine, polyoxyethylene glycol monopalmitate, polyoxyethylene sorbitan monopalmitate, polyoxyethylene cetyl ether, polyoxyethylene oxypropylene stearate,

polyoxyethylene lauryl ether, polyoxyethylene lanolin derivative, sodium oleate, quaternary ammonium derivative, potassium oleate, N-cetyl N-ethyl morpholinium ethosulfate, sodium lauryl sulfate or mixtures thereof.

In order to improve the ability of the composition to be tolerated on administration to the nasal mucous membrane, it is advantageous to formulate it as isotonic composition. The osmolality can be set by variation of the amounts of the dissolved substances present in the composition besides ketorolac and any further substances present, and/or by addition of an isotonicity agent, preferably a physiologically tolerated salt, such as, for example, sodium chloride or potassium chloride, or a physiologically tolerated polyol, such as, for example, a sugar alcohol, in particular sorbitol or glycerol, in the concentration necessary for rendering isotonic.

Examples suitable of the preservatives which can be employed in the stable pharmaceutical composition of ketorolac may be selected from, but not limited to benzyl alcohol, quaternary ammonium halides, phenylcarbinol, thimerosal, disodium edetate. Quaternary ammonium halide preservatives are preferred. Suitable quaternary ammonium halide preservatives include polyquaternium-1 and benzalkonium halides. The amount of the preservative present in the pharmaceutical composition may range from about 0.005 to about 0.5% w/w relative to the total weight of the composition.

Examples of suitable antioxidants which can be employed in the stable pharmaceutical composition of ketorolac may be selected from, but not limited to ascorbic acid, alpha-tocopherol (vitamin-E), butylated hydroxyanisole, butylated hydroxytoluene, glutathione and the like. The amount of the antioxidant present in the pharmaceutical composition may ranges from about 0.0002 to about 0.5% w/w relative to the total weight of the composition.

Examples of suitable chelating agents which can be employed in the stable pharmaceutical composition of ketorolac may be selected from, but not limited to edetate disodium (EDTA); edetate trisodium; edetate tetrasodium; and diethyleneamine pentaacetate, preferably EDTA. The amount of the chelating agent present in the aqueous pharmaceutical composition may range from about 0.0001-1% w/w relative to the total weight of the composition.

Examples of viscosifiers which can be employed in the stable pharmaceutical composition of ketorolac may be selected from, but not limited to water insoluble polymers, acrylic polymers, polyoxyethylene-polyoxypropylene block copolymers, xanthan gum, tragacanth gum, alginates, agar-agar.

Examples of suitable pH adjusting agents which can be employed in the stable pharmaceutical composition of ketorolac may be selected from, but not limited to sodium hydroxide, hydrochloric acid, citric acid, acetic acid, fumaric acid, hydrochloric acid, malic acid, nitric acid, phosphoric acid, propionic acid, sulfuric acid, tartaric acid, or combinations thereof.

The composition of the present invention comprises an amount of a pH adjusting agent sufficient to adjust the pH of the composition to from about 3.5 to about 8.0.

Examples of suitable buffers may include one or more of borate buffers, tartarate buffers, lactate buffers, citrate buffers, phosphate buffers (e.g. potassium phosphate monobasic), citric acid/phosphate buffers, carbonate/carbonic acid buffers, succinate/succinic acid buffers, and tris(hydroxymethyl)aminomethane /hydrochloric acid buffers and the like. The amount of aqueous solvent and co-solvent may range from about 0.005% w/w to about 1% w/w of the composition.

Examples of suitable sweetener/taste masking agents which can be employed in the stable pharmaceutical composition of ketorolac may be selected from, but not limited to sucralose, thaumatin (e.g., Talin®) sucrose, saccharin (including the salt forms: sodium, calcium, etc.), fructose, glucose, dextrose, corn syrup, aspartame, acesulfame-K, xylitol, sorbitol, erythritol, ammonium glycyrrhizinate, thaumatin, neotame, mannitol, eucalyptus oil, camphor, and natural or artificial flavors or flavoring agents (for example menthol, mints, vanilla, orange, etc.), or combinations of two or more of such agents.

It will also be appreciated to the skilled artisan that in order to improve the physical properties, appearances, or smells of the composition of the present invention, one or more further pharmaceutically acceptable excipients may be added as desired.

The stable pharmaceutical composition of ketorolac may comprise one or more additional pharmaceutical active agent/s selected from the therapeutic category of, but not limited to, corticosteroids, non- steroidal anti-inflammatory agents, antihistaminic agents, decongestants, antiallergic agents and the like.

The pharmaceutical composition of the present invention can be administered as a nasal spray, drop, suspension or solution. The composition may also be administered using a nasal tampon or a nasal sponge.

In an embodiment, the aqueous pharmaceutical composition is provided in the form of nasal spray.

Other means for delivering the nasal spray, such as inhalation via a metered dose inhaler (MDI), may also be used. Several types of MDIs are regularly used for administration by inhalation. These types of devices can include breath-actuated MDI, spacer/holding chambers in combination with MDI, and nebulizers. The term "MDI" as used herein refers to an inhalation delivery system comprising, for example, a canister containing mixture of active agent and a propellant optionally with one or more excipients, a metered dose valve, an actuator, and a mouthpiece. The canister is usually filled with a solution of an active agent, such as the nasal spray composition, and a propellant, such as one or more hydrofluoroalkanes [e.g. 1,1,1,2-tetrafluoroethane (HFA-134a) and 1,1,1,2,3,3,3-heptafluoropropane (HFA-227)]; chlorofluorocarbons; and alcohols such as ethanol, isopropanol, butanol, propanol or mixtures thereof. When the actuator is depressed a metered dose of the solution is aerosolized for inhalation. Particles comprising the active agent are propelled toward the mouthpiece where they may then be inhaled by a subject.

It will be appreciated that the above dosing regime should be tailored according to the individual patient's age, body weight and/or symptom severity.

In another general aspect, there is provided a method of treating moderate to moderately severe pain that requires analgesia at the opioid level in a subject in need thereof, comprising: nasally administering to the subject a storage stable pharmaceutical composition comprising ketorolac or salt thereof with one or more pharmaceutically acceptable excipients.

The invention is further illustrated by the following examples which are provided to be exemplary of the invention and do not limit the scope of the invention. While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

Example 1

Table 1

Sr. No.	Ingredients	Qty (%w/w)
1	Ketorolac tromethamine	15.750
2	Sodium Edetate	0.020
3	Potassium Phosphate Monobasic	0.680

4	Propylene Glycol	5.000
5	Methyl Paraben	0.100
6	Propyl Paraben	0.010
7	Ascorbic acid	0.050
8	Sodium Hydroxide	q.s.to pH
9	Nitrogen	-
10	Purified Water	q.s.to 100 %

Procedure:

A solution of sodium edetate, potassium phosphate monobasic, and ascorbic acid, were prepared in purified water. Methyl paraben and propyl paraben were dissolved separately in propylene glycol. The propylene glycol solution was then added to previously prepared aqueous solution. To this add ketorolac tromethamine withn continuous stirring.. Finally pH of the solution was maintained at pH 7.2 using 2M sodium hydroxide. The final preparartion was filtered through 0.45 micron PVDF filter. The solution was distributed in type I glass bottles previously purged with nitrogen gas. The whole process was carried out using purified water having dissolved oxygen content less than 8%.

Example 2: Stability study

Stability study of the nasal spray composition of ketorolac tromethamine prepared in accordance with the present invention and marketed product was carried out. The composition of the present invention in closed vials was stored at room temperature over four months. Marketed product was stored in labeled storage condition (at 2-8°C). The amount (potency) of ketorolac tomethamine, relative substances and impurities were determined in both the formulation.

The result indicates that the composition of the present invention remains stable and retains at least 80% potency of ketorolac tromethamine over the storage period.

The results also indicated that composition of the present invention possesses excellent storage stability over marketed composition, and also does not require cold chain storage (2-8°C).

Table 2

Test	Results	
	Example 1	Marketed

				product
pH	7.05	7.03	7.12	7.05
% Assay	97.6	98.7	96.4	95.0%
Related substances				
Ketoralac 1-keto analog	0.05	0.06	0.10	0.30
0.54 RRT Impurity	0.08	0.08	0.08	ND
Maximum unknown	0.13	0.11	0.10	0.12
Total Impurity	0.26	0.27	0.30	0.42

While, the invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the invention.

We Claim:

1. A storage stable pharmaceutical composition comprising ketorolac or salts thereof, at least one stabilizing agent and one or more pharmaceutically acceptable excipients, wherein the composition retains at least 80% of the potency of ketorolac or salts thereof in the pharmaceutical composition after storage for at least four months at room temperature.

2. The storage stable pharmaceutical composition as claimed in claim 1, wherein the composition when stored at 25°C in closed vials for four months, the total amount of related substances does not increase more than 5% by weight to the ketorolac or salts thereof.

3. The storage stable pharmaceutical composition as claimed in claim 1, wherein the composition when stored at 25°C in closed vials for four months, the total amount of related substances does not increase more than 0.4%.

4. The storage stable pharmaceutical composition as claimed in claim 1, wherein the composition when stored at 25°C in closed vials for four months, the total amount of ketorolac-1-keto impurity does not increase more than 0.2%.

5. The storage stable pharmaceutical composition as claimed in claim 1, wherein the stabilizing agent comprises one or more of polyhydroxy alcohols, alginic acid, low methoxyl pectin, and xanthan gum.

6. The storage stable pharmaceutical composition as claimed in claim 1, wherein the polyhydroxy alcohols comprises one or more of glycerin, polyethylene glycol, propylene glycol, diethylene glycol, triethylene glycol, tetraethylene glycol, 2-methyl-2,4-pentanediol, 1,2,6-hexanetriol, thioglycol, and polyoxyethylene polyoxypropylene glycol.

7. The storage stable pharmaceutical composition as claimed in claim 1, wherein the ratio of the amount of ketorolac or a salt thereof to the amount of the stabilizing agent is in the range of from about 1:0.1 to about 1:0.5.

8. The storage stable pharmaceutical composition as claimed in claim 1, wherein the amount of stabilizing agent comprises from about 10% to about 50% by weight of the ketorolac or salts thereof.

9. The storage stable pharmaceutical composition as claimed in claim 1, wherein pH of the composition ranges from about 3.5 to about 8.0.

10. The storage stable pharmaceutical composition as claimed in claim 1, wherein the composition is in the form of a nasal spray, drops, a solution, a suspension, or a tampon.

11. The storage stable pharmaceutical composition as claimed in claim 1, wherein the pharmaceutically acceptable excipients comprises one or more of buffers, tonicity adjusting agents, taste masking agents, antioxidants, preservatives, and pH adjusting agents.

12. A stable aqueous nasal spray solution for topical administration comprising:
(a) ketorolac, or pharmaceutically acceptable salts thereof;
(b) about 1% to about 10% w/w of propylene glycol;
(c) about 0.005% to about 0.15% w/w of at least one paraben;
(d) about 0.005% to about 1% w/w of ascorbic acid;
(e) about 0.0002% to about 1% w/w of sodium edetate;
(f) about 0.005% to about 1% w/w of potassium phosphate monobasic;
(g) sodium hydroxide; and
(h) purified water in quantity sufficient to make volume.

13. A process for the preparation of a storage stable pharmaceutical composition of ketorolac or salts thereof, the process comprising:
(a) preparing a solution comprising one or more stabilizing agent, one or more buffer, one or more chelating agent, one or more antioxidant, one or more preservative and optionally one or more other pharmaceutical excipients in purified water;
(b) adding ketorolac or salt thereof to the solution of step (a) and adjusting the pH of the solution using one or more pH adjusting agents;

(c) making the final volume with purified water; and

(d) filling the solution of step (c) into suitable containers.

14. A method of treating moderate to moderately severe pain that requires analgesia at the opioid level in a subject in need thereof comprising nasally administering to the subject, a storage stable pharmaceutical composition comprising ketorolac or salts thereof, at least one stabilizing agent and one or more pharmaceutically acceptable excipients, wherein the composition retains at least 80% of the potency of ketorolac or salts thereof in the pharmaceutical composition after storage for four months at room temperature.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IN2012/000152

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/00 A61K9/08 A61K47/10 A61K31/00
ADD.

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

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 practicable, search terms used)
EPO-Internal, CHEM ABS Data, EMBASE, WPI Data, BIOSIS, FSTA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 333 044 B1 (SANTUS GIANCARLO [IT] ET AL) 25 December 2001 (2001-12-25) cited in the application	1-11,13, 14
Y	examples	1-14

X	WO 2009/152369 A1 (ROXRO PHARMA INC [US]; WHITING ROGER [US]; THIRUCOTE RAMACHANDRAN [US]) 17 December 2009 (2009-12-17) cited in the application	1-11,13, 14
Y	paragraph [0082] - paragraph [0088]	1-14

X	WO 94/10987 A1 (PHARMETRIX CORP [US]) 26 May 1994 (1994-05-26)	1-11,13, 14
Y	page 27, line 17 - line 29 page 28, line 24 - page 32, line 20	1-14

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[X] Further documents are listed in the continuation of Box C.

[X] 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 application or patent 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 publication 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 combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 September 2012	10/09/2012

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Schüle, Stefanie

INTERNATIONAL SEARCH REPORT

International application No
PCT/IN2012/000152

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	US 2009/246273 A1 (AL-GHANANEEM ABEER M [US]) 1 October 2009 (2009-10-01) examples claims 1-31	1-11,13, 14 1-14

X Y	US 2004/151774 A1 (PAULETTI GIOVANNI M [US] ET AL) 5 August 2004 (2004-08-05) examples	1-5, 7-11,14 1-14

A	"Ketorolac - A review of its pharmacodynamic and pharmacokinetic properties and its therapeutic potential", DRUGS, vol. 39, no. 1, 1990, pages 86-109, XP008123320, cited in the application the whole document	1-14

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IN2012/000152

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