Abstract:
The present invention relates to a liquid pharmaceutical composition for treating a patient having moderate to severe pain. The liquid pharmaceutical composition comprises an effective amount of ketorolac or ketorolac tromethamine, and an effective amount of tramadol or its pharmaceutically acceptable salt. The liquid pharmaceutical composition is effective in reducing pain score from 8-9 to 5.3 or less.
LIQUID PHARMACEUTICAL FORMULATION CONTAINING KETOROLAC AND TRAMADOL

TECHNICAL FIELD

This application relates to a liquid pharmaceutical formulation comprising ketorolac and tramadol. This application also relates to the use of the pharmaceutical formulation in treating moderate to moderately severe pain such as postoperative pain (e.g., after cesarean delivery or other surgeries), cancer pain, visceral pain, and trauma pain.

BACKGROUND OF THE INVENTION

Based on the physical causes, pain can be divided into three types: nociceptive, neuropathic, and mix-type.

Nociceptive pain is usually caused by noxious stimulation such as heat and cut that directly results in damage or injury to the body or tissue. Based on the initiation site of the pain, nociceptive pain can be further divided into two types: somatic and visceral pain. Somatic pain arises from bone, joint, muscle, skin, or connective tissues that directly in contact with the external noxious stimuli. Visceral pain arises from compression, extension, and injury of the internal organs. Most people describe the symptoms as achy, sharp, stinging, and throbbing. Nociceptive pain is usually short in duration and end when the damage recovers. Examples of nociceptive pain include postoperative pain, sprains, bone fractures, burns, bumps, bruises, and inflammatory pain (with the exception of inflammation caused by arthritis).

Neuropathic pain is originated from spontaneous ectopic neuron discharge in the nervous system either in central or in peripheral. Due to the underlying etiologies are usually irreversible, most of neuropathic pain are chronic pain. Most people describe neuropathic pain as shooting, burning, tingling, lancinating, electric shock qualities, numbness, and persistent allodynia. The nomenclature of neuropathic pain is based on the site of initiating nervous system with the etiology; for examples, central post-stroke pain, diabetes peripheral neuropathy, post-herpetic (or post-shingles) neuralgia, terminal cancer pain, phantom limb pain.

Mix-type pain is featured by the coexistence of both nociceptive and neuropathic pain. For example, muscle pain trigger central or peripheral neuron sensitization leading to chronic low back pain, migraine, and myofacial pain.
Clinically pain intensity is rated on a scale of 0 to 10; with 0 is no pain, 1-3 is mild pain, 4-6 is moderate pain, and 7-10 is severe pain. For example, 8-9 is designated for moderately severe pain.

WHO “3-Step” Guideline provides the guideline for managing pain. The “3-Step” is determined by the pain intensity and the analgesia activity of drugs.

(a) 1st Step mild pain: Acetaminophen, NSAIDs, or combination of both. Common used NSAIDs including aspirin, diclofenac, indomethacin, sulindac, ketoprofen, etodolac, ketorolac.

(b) 2nd Step moderate pain: NSAIDs plus opiate, including aspirin or acetaminophen with codein, oxycodon, dihydrocodein, hydrocodon, tramadol

(c) 3rd Step severe pain: Strong opiate including morphine, hydromorphine, methadol, levorphanol, fentanyl, oxycodon

It is well recognized that acetaminophen, NSAIDs, and opioids all have their inherent drawbacks. Acetaminophen and NSAIDs often exhibit ceiling effect (upper limit of pain relief). Once that upper limit is reached, taking additional medication provides no further pain relief. In addition, NSAIDs has end organ toxicities in heart, liver, GI tract, and kidney at the regular doses. Opioids usually cause intolerable adverse effects such as constipation, respiratory depression, physical dependence and abuse problems. Primarily, NSAIDs provide peripheral anti-nociception and opioids provide central anti-nociception.

Ketorolac (molecular weight 255.27), or ketorolac tromethamine is a non-steroidal anti-inflammatory drug (NSAID) in the family of heterocyclic acetic acid derivative, often used as an analgesic. Ketorolac acts by inhibiting the bodily synthesis of prostaglandins. Ketorolac in its oral (tablet or capsule) and intramuscular (injected) preparations is a racemic mixture of both (S)-(-)-ketorolac, the active isomer, and (R)-(+) -ketorolac. This drug is administered to treat moderate pain or, combined with reduced opioid doses, for severe pain.

Tramadol (molecular weight 263.4), (IR,2R)-rel-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexanol, is in a class of opiate agonists. Tramadol is classified as a central nervous system drug usually marketed as the hydrochloride salt (tramadol hydrochloride). Tramadol hydrochloride is a centrally acting weak opioid analgesic with no anti-inflammatory activity, used in treating moderate to severe pain. The drug has a wide range of applications, including treatment for restless leg syndrome and fibromyalgia.
SUMMARY OF THE INVENTION

The present invention is directed to a liquid pharmaceutical composition for treating a patient having moderate to severe pain. The pharmaceutical composition comprises an effective amount of ketorolac or ketorolac tromethamine, and an effective amount of tramadol or its pharmaceutically acceptable salt, in a liquid formulation.

In one embodiment, the effective amount of ketorolac or ketorolac tromethamine is 42-52.5 mg, and the effective amount of tramadol or its pharmaceutically acceptable salt is 28-35 mg.

In another embodiment, the effective amount of ketorolac or ketorolac tromethamine is 21-26.25 mg, and the effective amount of tramadol or its pharmaceutically acceptable salt is 70-87.5 mg.

BRIEF DESCRIPTION OF THE FIGURES

FIG. 1 is a scatter plot of visual analogue scale vs. time from first injection of the liquid pharmaceutical composition. K₆₀= Ketorolac 60 mg, K₆₀+T₄₀= Ketorolac 60 mg + tramadol 40 mg, K₄₅+T₇₅= Ketorolac 45 mg + tramadol 75 mg, K₃₀+T₁₀₀= Ketorolac 30 mg + tramadol 100 mg, T₁₀₀= tramadol 100 mg.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to a liquid pharmaceutical formulation comprising (a) ketorolac or ketorolac tromethamine (collectively referred to as ketorolac in this application) and (b) tramadol or their pharmaceutically acceptable salt thereof (collectively referred to as tramadol in this application), in an aqueous solution. The liquid ketorolac-tramadol formulation is suitable for injection, for example, intravenous injection or intramuscular injection. The liquid ketorolac-tramadol formulation is also suitable for oral administration. The liquid ketorolac-tramadol formulation is stable for at least 1 day, preferably 3 days, more preferably 7 days at room temperature (about 22-28 °C). "Stable," as used herein, refers that both drug maintains at least 80%, preferably 90%, of their initial amounts in the solution, and the solution does not show visible precipitation.

The liquid ketorolac-tramadol formulation provides combined benefits of the two individual drugs of ketorolac and tramadol. The advantages of combined ketorolac-tramadol formulation include: (a) providing shorter analgesia onset and prolonged duration, (b) providing both central and peripheral analgesic effect by complementary mechanisms of actions, and (c) reducing the dose of each drug and thus minimizing side effects. Further,
since NSAIDs can only manage mild to moderate pain due to a ceiling effect, ketorolac-tramadol formulation is superior to one single drug, because the addition of tramadol eliminates the ceiling effect of ketorolac. Thus, ketorolac-tramadol formulation can be used to treat pain with moderately severe intensity. These improvements offer more treatment options to patients.

The liquid ketorolac-tramadol solution is preferably a clear solution, but it may also be a suspension form and emulsion form.

The effective dosage of the liquid ketorolac-tramadol formulation in general is about 7.5-60 mg of ketorolac and 10-100 mg of tramadol.

Effective amounts of ketorolac and tramadol may also be 42-59 mg of ketorolac and 14-71 mg of tramadol; preferably 42-52.5 mg of ketorolac, and 28-35 mg of tramadol; or 45-52.5 mg of ketorolac, and 30-35 mg of tramadol.

Effective amounts of ketorolac and tramadol may also be 9-42 mg ketorolac and 71-99 mg of tramadol; preferably 18.75-26.25 mg of ketorolac, and 62.5-87.5 mg of tramadol; or 21-26.25 mg of ketorolac, and 70-87.5 mg of tramadol.

The dosage is typically formulated in 1-20 ml for intravenous injection and 0.5-2 ml for intramuscular injection. The concentration (mg/ml) of each drug in the pharmaceutical composition can be calculated by dividing the amount (mg) by the volume (ml).

The liquid pharmaceutical formulation contains ketorolac or ketorolac tromethamine and tramadol or its pharmaceutically acceptable salt in water, at pH 5.0-8.0, preferably pH 6-8. The liquid pharmaceutical formulation may contain saline. The liquid pharmaceutical formulation may also contain a buffer to stabilize the pH. The liquid pharmaceutical formulation may contain a pharmaceutically acceptable carrier, known to those skilled in the art. For example, known pharmaceutically acceptable carriers for injection form or for oral form can be added to the liquid pharmaceutical formulation. The liquid pharmaceutical formulation preferably does not contain any other drug or any other active ingredient in addition to ketorolac and tramadol. For example, the liquid pharmaceutical formulation does not contain metoclopramide or MgSO₄.

**Pharmaceutical Use of the Ketorolac-Tramadol Formulation**

Based on the known analgesic-related mechanism of actions and reported clinical potentials, the ketorolac-tramadol formulation of the present invention is useful in the management of pain of moderate to moderately severe intensity (scale 4-9 or 6-9), preferably in the management of pain of moderately severe intensity (scale 8-9). The ketorolac-
tramadol formulation is particularly useful in the management of postoperative pain, cancer pain, visceral pain and trauma pain.

The present invention is directed to a method for treating a patient with moderate to moderately severe pain (pain scale 4-9, preferably 6-9, more preferably 8-9). The method comprises: identifying a patient suffering from pain, and administering to said patient a liquid ketorolac-tramadol formulation, in an effective amount. "An effective amount," as used herein, refers to an amount that is effective to reduce or relief pain from a patient. The present invention reduces pain score to ≤ 5.3.

In one embodiment, the effective amount of ketorolac or ketorolac tromethamine is 42-52.5 mg, and the effective amount of tramadol or its pharmaceutically acceptable salt is 28-35 mg. Preferably, the effective amount of ketorolac or ketorolac tromethamine is 45-52.5 mg, and the effective amount of tramadol or its pharmaceutically acceptable salt is 30-35 mg.

In another embodiment, the effective amount of ketorolac or ketorolac tromethamine is 18.75-26.25 mg, and the effective amount of tramadol or its pharmaceutically acceptable salt is 62.5-87.5 mg. Preferably, the effective amount of ketorolac or ketorolac tromethamine is 21-26.25 mg, and the effective amount of tramadol or its pharmaceutically acceptable salt is 70-87.5 mg.

The liquid ketorolac/tramadol formulation can be administered by intravenous injection, intramuscular injection, or oral administration.

The intravenous injection can be administered by bolus injection or continuous infusion; bolus of 1, 2, 3, or 4 times is preferred. In general, the total volume for intravenous injection is 1-20 ml, or 2-10 ml, and for intramuscular injection is < 2 ml, e.g., 0.5-1.5 ml.

The present method is useful in treating moderately severe pain with pain intensity of 8-9. The method is also useful in treating postoperative pain, such as pain after Cesarean, postoperative pain after other surgeries, severe cancer pain, visceral pain, or trauma pain.

**Postoperative pains**

Postoperative pain is resulted from the somatic pain and visceral pain. The somatic pain arises from the direct noxious impulse at injury sites (cut). The sensitization of afferent fibers at injury sites driving central sensitization. Visceral pain arises from the compression, extension, or inflammation of internal organs. The liquid ketorolac-tramadol formulation offers benefit to patients whose pain is caused from inflammation (COX1/COX2) and visceral pain. It also enhances anti-nociceptive response from central by modulation of µ receptor and the level of serotonin and noradrenalin.
The liquid ketorolac-tramadol formulation is particularly effective in the management of postoperative pain after cesarean for the following reasons:

(a) Visceral pain caused by uterus contraction is the main component of pain after cesarean delivery. Ketorolac is highly effective in relief visceral pain.

(b) Prostaglandin involves in both tissue injury and uterus contraction. Inhibition of PGE2 by ketorolac offer better anti-inflammatory and analgesic effects than acetaminophen alone.

(c) The mechanisms of action of the liquid ketorolac-tramadol formulation responsible for Cesarean pain relief include inhibition on COX1 and COX2, sodium current, serotonin and noradrenaline reuptake and activation of g receptor.

Over half of the postoperative pain patients still experience inadequate pain relief with currently available treatment. The liquid ketorolac-tramadol formulation is useful in the pain control after other types of surgery, such as coronary artery bypass grafting (CABG), lumbar disc surgery, orthopaedia, and tonsillectomy.

Postoperative pain is mostly acute and severe. The management of postoperative pain usually starts at one hour after surgery and continue for another 48-72 hours. Since most patients are hospitalized after major surgeries, parenteral administration of analgesics is considered to be easy and convenient. Parenteral administration of the liquid ketorolac-tramadol formulation offers benefit in the increase of drug exposure and shorter onset. In addition, drug absorption can be variable in the first 24 hours following surgery. The preferred route of administration for post-operative pain is intravenous injection or intramuscular injection.

Cancer Pain

Cancer pain is the result of tissue damage caused by the tumor, the effects of chemotherapy, radiation, or surgery. Cancer pain can occur at any stage of cancer. The pain intensity ranges from moderate to severe pain. Cancer patients at terminal phase often experience an intolerable severe pain, in which the highly potent opioids like morphine are commonly used.

Prostaglandins-induced inflammation and nociceptor sensitization contributes to a varying extent in the process of cancer and exacerbation of nociception. Cancer pain can be nociceptive, neuropathic, or both depending on the course of cancer. The liquid ketorolac-tramadol formulation offers benefit to the cancer patients whose pain results from severe inflammation (prostaglandin) and abnormal excitability of sodium channels. It also enhances
anti-nociceptive response from central by modulation of µ receptor and the level of serotonin and noradrenalin.

The liquid ketorolac-tramadol formulation is useful in the management of cancer pain for the following reasons:

(a) Cancer pain is mainly both inflammatory and neuropathic. The liquid ketorolac-tramadol formulation, which offers both anti-inflammation and nerve block activity, is effective in the management of cancer pain with moderately severe intensity.

(b) The liquid ketorolac-tramadol formulation can be used in cancer patients at terminal stage for reducing the use of morphine in pain relief.

Terminal stage cancer patients with severe pain can be acute and chronic with occasional breakthrough pain with moderate to severe intensity. For the management of acute and breakthrough pain, parenteral administration by IM or IV provides rapid and effective pain relief.

The invention is illustrated further by the following examples that are not to be construed as limiting the invention in scope to the specific procedures described in them.

**EXAMPLES**

**Example 1. Compatibility Experiment**

a. Stability of Ketonolac tromethamine

Ketorolac tromethamine (30 mg/ml, pH 6-8) was obtained from Yung Shin Pharmaceuticals. The Ketorolac tromethamine solutions were adjusted to different pH (pH 5, 6, 7, 8, and 9) with HCl or NaOH and stored at room temperature. The solutions having different pH's were tested at day 0, 1, 3, and 7 to measure the contents of ketorolac tromethamine by HPLC.

The results showed that ketorolac tromethamine (30 mg/ml) was stable for 7 days at room temperature at pH 5-9; the contents of ketorolac tromethamine were 98.4-101.7% after 7 days.

b. Stability of Tramadol

Tramadol (50 mg/ml, pH 6-8) was obtained from Grunenthal GMBH Products. The tramadol solutions were adjusted to different pH (pH 5, 6, 7, 8, and 9) with HCl or NaOH and stored at room temperature. The solutions having different pH's were tested at day 0, 1, 3, and 7 to measure the contents of tramadol by HPLC.
The results showed that tramadol was stable for 7 days at room temperature at pH 5-8; the contents of tramadol were 97.4-102.4% after 7 days. At pH 9, tramadol precipitated out and had 70.4% of the initial amount remained in the solution at day 0, and had 56.4% of the initial amount remained in the solution after day 1, 3, 7, days.

c. Stability of Ketorolac and Tramadol

Ketorolac tromethamine (30 mg/ml) and tramadol (50 mg/ml) were mixed together with saline to provide a mixture solution containing ketorolac tromethamine (2 mg/ml) and Tramadol (20 mg/ml). The mixture solutions were adjusted to different pH (pH 5, 6, 7, 8, and 9) with HC1 or NaOH and stored at room temperature. The mixture solutions were observed for its appearance at day 0, 1, 3, and 7.

At pH 5.0 and 6.0, the mixture solutions were clear but having little suspended solids at day 0, with no significant changes at day 1, 3, and 7. At pH 7.0 and 8.0, the mixture solutions were clear at day 0-7. At pH 9, turbulent precipitation was observed immediately at day 0, and needle-like crystals were seen from day 1-7.

The results showed that the mixture solution was stable for 7 days at room temperature at pH 5-8, but was not stable at pH 9.

Example 2. Use of Ketorolac and Tramadol for Post-Operative Pain

Objectives

The objective of this study is to test the safety profiles and efficacy for pre-mixed ketorolac and tramadol liquid formulation for treatment of post-operative pain.

Subjects

A total of 63 subjects were randomized in this study. Most subjects (>90%) underwent an elective major abdominal surgery or gynecologic surgery (including laparoscopic surgery). Other subjects (<10%) underwent mastectomy.

Drug Dosage

Ketorolac tromethamine (Keto, 30 mg/ml) was obtained from Yung Shin Pharmaceuticals Ind. Co., Ltd. Tramadol hydrochloride (50 mg/ml) was obtained from Grunenthal GMBH Products. The two drugs were pre-mixed together with saline to a total volume of 12.0 or 12.5 ml to provide 5 different concentrations as follows.

Group 1. Keto 6 mg/ml only (maximum dose 60 mg in 10 ml), n=12
Group 2. Keto 6 mg/ml, tramadol 4 mg/ml (maximum doses 60 mg keto and 40 mg tramadol in 10 ml), n=13

Group 3. Keto 4.5 mg/ml, tramadol 7.5 mg/ml (maximum doses 45 mg keto and 75 mg tramadol in 10 ml), n=13

Group 4. Keto 3 mg/ml, tramadol 10 mg/ml (maximum doses 30 mg keto and 100 mg tramadol in 10 ml), n=12

Group 5. Tramadol 10 mg/ml only (maximum doses 100 mg tramadol in 10 ml), n=13

The initial dose (quarter of the maximum dose) of 2.5 ml was given by intravenous injection to each patient at time zero, and then doses of 2.5 ml were given by intravenous injection to the patient every 10 minutes, until the patient's pain score was < 5 or the dose is used up.

Study Protocols

After awaking from surgery, subjects rated their most severe pain score > 5 were randomized to one of the five groups of ketorolac and/or tramadol. An initial dose of a quarter of volume (2.5 ml) treatment was given to patients, and subsequently 2.5 ml was given at about 10 minutes, 20 minutes, and 30 minutes, if subject's most severe pain level was still moderate to severe (pain score ≥ 5). The pain scores and vital signs were assessed every 5 minutes after each dose. If the subject rated the most severe pain score < 5 or the subject had received the maximum dose, then the subject stopped taking the liquid ketorolac and tramadol formulation and the subject was given direct access to a morphine PCA pump.

Visual Analog Scale (VAS) scoring system was used to assess the pain intensity (0-10) by patient. 10 means the most severe pain and 0 means no pain. A horizontal line, 10 cm (100 mm) in length, was anchored by word descriptors, "No pain" and "Very severe pain", at each end. The VAS score was determined by measuring in millimeters from the left hand end of the line to the point that the subject marks. The study nurse measured the length from point 0 (no pain) to the mark and transcript to a number between 0.0 to 10.0 cm. The pain score at 0, 5, 10, 15, 20, 35, 30, 35, and 40 minutes of each patient were recorded.

Analysis of Results

All tests are based on two-sided alternative hypotheses and were made at 5% significance level.
For the efficacy endpoints, the Van Der Waerden test was conducted for accumulative total unit dose of combination ketorolac and tramadol.  
(en.wikipedia.org/wiki/Van_der_Waerden_test)  In addition, the correlation between combinative rate (ketorolac dose: tramadol dose) and accumulative total unit dose for combination of ketorolac and tramadol for pain relief are modeled by regression method, if appropriate.

Fisher exact test was used to compare treatment groups for the proportion of subjects with a score of less than 5. (en.wikipedia.org/wiki/Fisher's_exact_test)

For the safety variables, summary frequency tables for adverse events were provided by the treatment group. Descriptive statistics were used for vital signs data.

Results and Conclusions

The mean VAS score of each group at 0, 5, 10, 15, 20, 35, 30, 35, and 40 minutes was plotted vs. time from the initial injection and shown as FIG. 1.

As shown in FIG. 1, patients treated with Group I (Keto only), III (maximum doses 45 mg keto and 75 mg tramadol in 10 ml), and V (Tramadol only) did not reduce their pain scores reduced to less than 6.

In contrast, patients treated with Group II (maximum doses 60 mg keto and 40 mg tramadol in 10 ml) reduced pain score to ≤ 5 at about 28-35 minutes, or 30-35 minutes. The accumulated dosages at 28-35 minutes are calculated to be ketorolac, 42-52.5 mg, and tramadol, 28-35 mg. The accumulated dosages at 30-35 minutes are calculated to be ketorolac, 45-52.5 mg, and tramadol, 30-35 mg.

In addition, patients treated with Group IV (maximum doses 30 mg keto and 100 mg tramadol in 10 ml) reduced pain score to ≤ 5.3 at about 25-35 minutes, or 28-35 minutes, and the pain score was even lower at 40 minutes. In considering the adverse effect of high dosage of tramadol, a lower dosage of tramadol for reaching pain score ≤ 5.3 is preferred. The accumulated dosages at 25-35 minutes are calculated to be ketorolac, 18.75-26.25 mg, and tramadol, 62.5-87.5 mg. The accumulated dosages at 28-35 minutes are calculated to be ketorolac, 21-26.25 mg, and tramadol, 70-87.5 mg.
WHAT IS CLAIMED IS:
1. A liquid pharmaceutical composition for treating a patient having moderate to severe pain, comprising an effective amount of ketorolac or ketorolac tromethamine, and an effective amount of tramadol or its pharmaceutically acceptable salt, in an aqueous formulation,
   wherein the effective amount of ketorolac or ketorolac tromethamine is 42-52.5 mg, and the effective amount of tramadol or its pharmaceutically acceptable salt is 28-35 mg.

2. The liquid pharmaceutical composition according to Claim 1, wherein the effective amount of ketorolac or ketorolac tromethamine is 45-52.5 mg, and the effective amount of tramadol or its pharmaceutically acceptable salt is 30-35 mg.

3. A liquid pharmaceutical composition for treating a patient having moderate to severe pain, comprising an effective amount of ketorolac or ketorolac tromethamine, and an effective amount of tramadol or its pharmaceutically acceptable salt, in an aqueous formulation,
   wherein the effective amount of ketorolac or ketorolac tromethamine is 18.75-26.25 mg, and the effective amount of tramadol or its pharmaceutically acceptable salt is 62.5-87.5 mg.

4. The liquid pharmaceutical composition according to Claim 3, wherein the effective amount of ketorolac or ketorolac tromethamine is 21-26.25 mg, and the effective amount of tramadol or its pharmaceutically acceptable salt is 70-87.5 mg.

5. The liquid pharmaceutical composition according to Claim 1 or 3, wherein the patient has pain intensity of 6-9.

6. The liquid pharmaceutical composition according to Claim 1 or 3, wherein the patient has pain intensity of 8-9.

7. The liquid pharmaceutical composition according to Claim 6, for reducing the pain score of the patient from 8-9 to 5.3 or less.
8. The liquid pharmaceutical composition according to Claim 1 or 3, wherein the composition is in a solution form, a suspension form, or an emulsion form.

9. The liquid pharmaceutical composition according to Claim 1 or 3, which has a pH of 5-8.

10. The liquid pharmaceutical composition according to Claim 1 or 3, wherein the pain is post-operative pain, cancer pain, visceral pain, or trauma pain.

11. The liquid pharmaceutical composition according to Claim 1 or 3, which is administered by intravenous injection.

12. The liquid pharmaceutical composition according to Claim 1 or 3, which is administered by intramuscular injection.
### INTERNATIONAL SEARCH REPORT

**International application No.:** PCT/US2013/037737

#### A. CLASSIFICATION OF SUBJECT MATTER

A61K 31/407(2006.01)i, A61K 31/135(2006.01)i, A61K 31/40(2006.01)i, A61K 31/405(2006.01)i, A61K 9/08(2006.01)i, A61P 25/00(2006.01)i

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 31/407; A61K 31/137; A61K 31/135; A61K 31/405; A61K 9/08; A61P 25/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Korean utility models and applications for utility models
Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
eKOMPASS(KIPO internal) & Keywords: Ketorolac, Tramadol

#### C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<td>US 2004-0087644 AI (GARCIA ARMENIA, M. E. et al.) 06 May 2004 See claims 1-7</td>
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* Further documents are listed in the continuation of Box C.

See patent family annex.

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