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WO 2001/035942 A2 **US 5149538 A**
US 20030232744 A1

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(54) Abstract Title: **Analgesic composition containing buprenorphine and nalmeferne**

(57) An analgesic composition, in parenteral unit dosage form or in a unit dosage form suitable for delivery via the dermis or mucosa, comprises buprenorphine and an amount nalmeferne such that the ratio by weight of buprenorphine to nalmeferne delivered to or reaching the plasma of a patient is in the range 22.6:1 to 40:1.

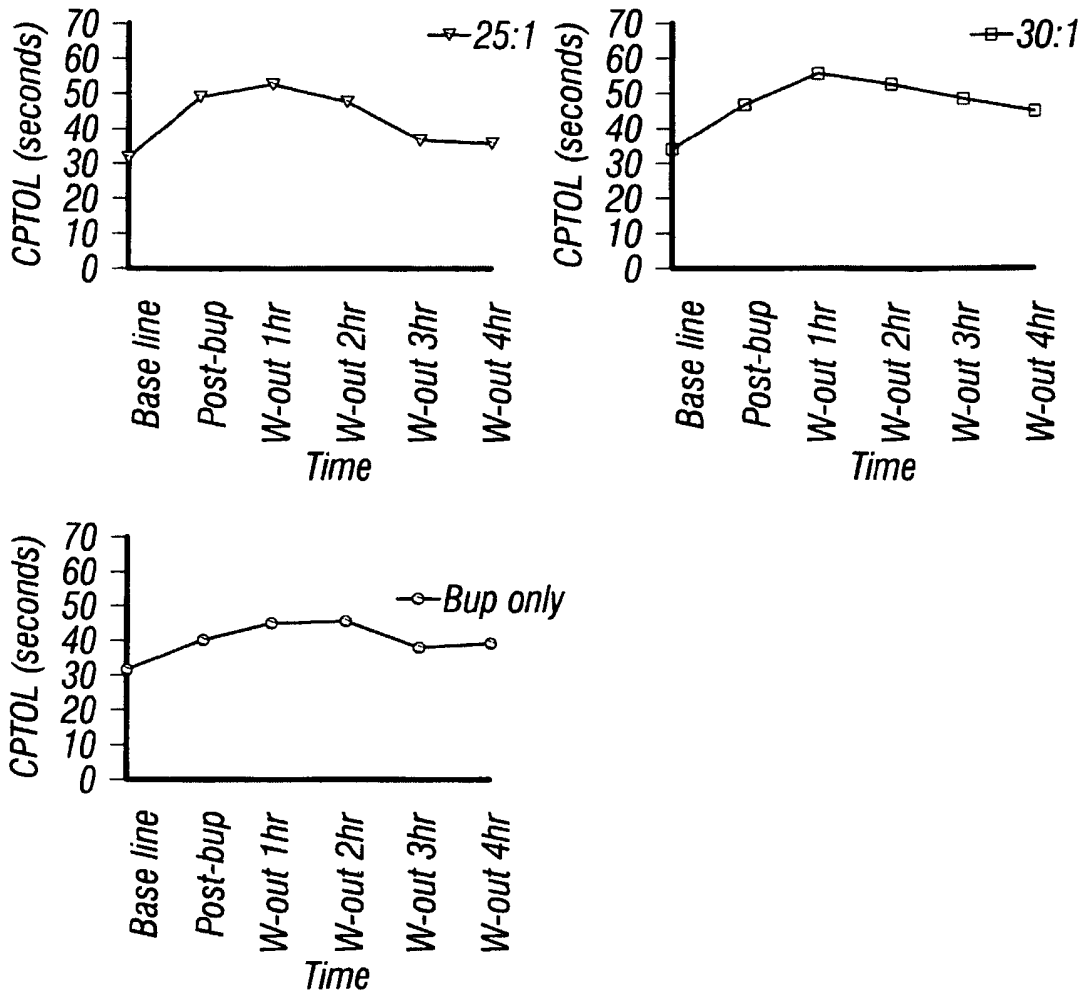


FIG. 1

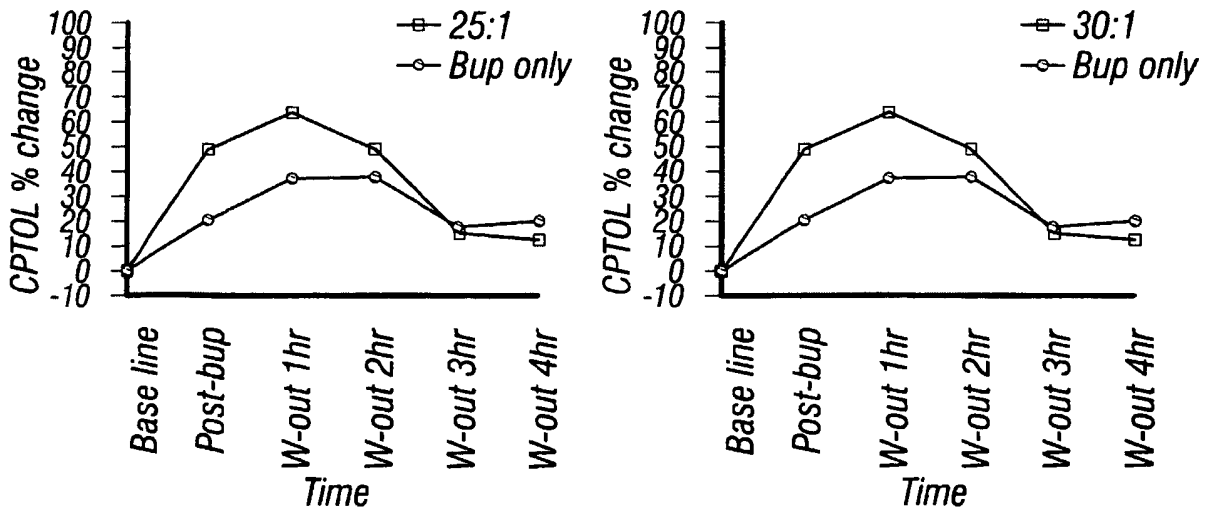


FIG. 2

IMPROVEMENTS IN OR RELATING TO MEDICINAL COMPOSITIONS

The present invention relates to medicinal compositions
5 containing buprenorphine in combination with nalmeferne; as
well as to their use in the manufacture of such
compositions and in clinical practice, as analgesics.

Whilst opioids are particularly effective in the
10 management of moderate to severe pain their use is limited
by unpleasant and potentially dangerous adverse effects.
Such adverse effects can include sedation, respiratory
depression, nausea and gastrointestinal problems. Thus
efforts have been made to minimise adverse effects.

15

There are many opioids and some produce more significant
adverse effects than others. Accordingly, careful
selection of the opioid employed in an analgesic
composition may itself reduce the incidence and severity
20 of adverse effects. One particularly suitable opioid is
buprenorphine which has been shown to have both agonist
(morphine-like) and antagonist properties without
producing significant physical dependence.

25 Buprenorphine (International Non-proprietary Name for N-
cyclopropylmethyl-7[alpha]-[1-(S)-hydroxy-1,2,2-trimethyl-
propyl]6,14-endoethano-6,7,8,14-tetrahydronoropipavine) is
a potent opiate partial agonist analgesic lacking the
psychotomimetic effects found with other opiate
30 analgesics. However, buprenorphine suffers from side
effects typical of opiate agonists such as nausea and
vomiting, constipation and respiratory depression in some
patients, although there is a ceiling to its effects on

respiratory depression as a direct consequence of its partial agonist properties.

Attempts have also been made to enhance the analgesic effect of opioids while minimising the incidence and severity of adverse effects by combining opioid treatment with other drugs.

One approach is the addition of a non-opioid analgesic to the opioid treatment. The rationale here is that lower levels of opioid should be required to achieve antinociception and thus there should be a reduction of adverse effects.

Another approach is the co-administration of an opioid agonist and low doses of an opioid antagonist. One such opioid antagonist is nalmefene (International Non-Proprietary Name for (5)-17-(cyclopropylmethyl)-4,5-epoxy-6-methylene-morphinan-3,14-diol).

20

In EP 1242087A it is disclosed that parenteral and sublingual dosage forms of buprenorphine are potentiated and enhanced by low doses of nalmefene. Based testing on rats, there is stated a suitable ratio by weight of buprenorphine to nalmefene of 12.5:1 to 22.5:1, preferably 15:1 to 20:1.

Human studies have now been carried out and have generated new findings for the combined use of buprenorphine, as opioid agonist, and nalmefene, as opioid antagonist. These new findings extend our understanding of the therapeutic doses which will give effective analgesia in humans.

According to a first aspect of the present invention there is provided an analgesic composition, in parenteral unit dosage form or in a unit dosage form suitable for delivery
5 via the mucosa or dermis, the composition comprising buprenorphine and an amount of nalmeferine such that the ratio by weight of buprenorphine to nalmeferine delivered to or reaching the plasma of a patient is in the range 22.6:1 to 40:1.

10

It is believed that the analgesic action of buprenorphine is potentiated by the relatively small level of nalmeferine.

It is to be understood that the terms buprenorphine and
15 nalmeferine as used herein are intended to cover simple related, pharmaceutical compounds such as esters, bases and salts, for example acid addition salts. Particularly preferred salts are the hydrochlorides. However the ratios and weights referred to herein refer to
20 buprenorphine and nalmeferine per se, not salts, bases or esters.

The term parenteral is intended to encompass administration of the compositions by any way other than
25 through the alimentary tract.

The term mucosa or mucosal is intended to encompass any mucous membrane and includes oral mucosa, rectal mucosa, vaginal mucosa and nasal mucosa. The term dermal denotes
30 non-mucosal skin.

Administration may take a few minutes. Preferably it takes place over a period of at least one minute,

preferably at least two minutes, preferably at least three minutes. Preferably it takes place over a period of up to ten minutes, preferably up to seven minutes, preferably up to five minutes.

5

The unit dosage form for transdermal or transmucosal administration may, for example, be a tablet, film, spray, patch, rub-in composition or lozenge. Administration, which will be further described in the second aspect, may
10 comprise the delivery of a medicament comprising buprenorphine and nalmeffene, preferably in such a form.

Transdermal administration may encompass any mode of administration through the dermis. Transmucosal
15 administration may encompass any mode of administration through the mucosa, and sites of administration may include, for example, vaginal and rectal mucosa and, preferably, mucosa of the oral-nasal cavity, for example nasal, throat, buccal and, sublingual sites. Nasal and
20 sublingual administration is especially preferred.

Preferably the defined ratio of buprenorphine to nalmeffene is achieved within sixty minutes after administration means herein within sixty minutes after administration
25 being completed, that is, preferably at some time within sixty minutes of administration being completed, the defined drug ratio in the plasma is achieved.

Preferred compositions comprise buprenorphine and
30 nalmeffene such that the ratio by weight of buprenorphine to nalmeffene delivered to or reaching the plasma of the patient is at least X:1 (X to 1) where X is 23, preferably 24, preferably 25.

Preferred compositions comprise buprenorphine and nalmefene such that the ratio by weight of buprenorphine to nalmefene provided delivered to or reaching the plasma of the patient is no greater than Y:1 (Y to 1) where Y is 36, preferably 32, preferably 30.

Surprisingly, it has been found that even at the low levels of nalmefene to buprenorphine employed in the present invention the nalmefene is able to potentiate the agonist action of buprenorphine. Additionally, through the use of nalmefene adverse effects and/or misuse of buprenorphine may be minimised. A surprising finding is that ratios of buprenorphine to nalmefene of 25:1 or greater, for example 30:1 are particularly effective.

The composition may comprise a parenteral unit dosage form and the ratio of buprenorphine to nalmefene within the parenteral composition may be substantially the same as that produced in the plasma of a patient upon application. Thus the parenteral dosage form may comprise buprenorphine and nalmefene in any of the weight ratios stated above for the weight ratios in the plasma.

In a human being, as stated in EP 1242087B dosages of about 40 μg of buprenorphine per kilogram of body weight are suitably required to obtain satisfactory pain relief in the absence of potentiation. Thus for typical body weights of 50 to 80 kg, the buprenorphine dosage would be from 2 mg to 3.2 mg of buprenorphine per day. This would conveniently be administered as four unit doses.

The amounts of buprenorphine which are required to be effective in the compositions of the invention are less than the amounts which are required to be effective in the absence of the potentiating effects of nalmeferene.

5

Importantly when equal doses of buprenorphine with and without the potentiating effect of nalmeferene are compared, the magnitude and duration of analgesia achieved by the former compositions (i.e. also containing nalmeferene), are
10 markedly increased. Therefore the same analgesic performance can be achieved with a lower buprenorphine dose when combined with nalmeferene. It is proposed that an increased analgesic effect can be achieved and/or reduced concentration of buprenorphine can be used, within or
15 across the therapeutic range.

Suitably, unit doses of the compositions of the present invention (containing nalmeferene) contain buprenorphine in an amount which is below that required to obtain
20 corresponding pain relief in a unit dose of buprenorphine without nalmeferene.

Suitably, the compositions of the present invention comprise at least 10 μg of buprenorphine per unit dose,
25 preferably at least 15 μg , preferably at least 20 μg , preferably at least 30 μg , and most preferably at least 40 μg . These values reflect the benefit of the invention in achieving analgesia at low dosages.

30 Suitably, the compositions of the present invention may contain any amount of buprenorphine, up to the upper end of conventional clinical practice. Suitably, they may contain up to 8 mg buprenorphine per unit dose, preferably

up to 4 mg, preferably up to 2 mg, preferably up to 1 mg, preferably up to 600 µg, preferably up to 400 µg, preferably up to 200 µg, preferably up to 160 µg, and most preferably up to 100 µg.

5

Suitably, in accordance with the present invention, a patient is administered at least 0.25 µg of buprenorphine per kg (of body weight) per 24 hours. Preferably the amount is at least 0.5 µg, preferably at least 1 µg, preferably at least 1.5 µg and most preferably at least 2 µg.

Suitably, in accordance with the present invention, a patient is administered up to 640 µg of buprenorphine per kg per 24 hours. Preferably the amount is up to 320 µg, preferably up to 160 µg, preferably up to 80 µg, preferably up to 40 µg, preferably up to 20 µg, preferably up to 16 µg, and preferably up to 12 µg. Most preferably the amount is not greater than 8 µg.

20

Suitably by use of compositions of the present invention the amount of buprenorphine administered to a patient for the purpose of achieving relief from pain is at least 40 µg per 24 hours, preferably at least 60 µg, preferably at least 80 µg, preferably at least 120 µg, and most preferably at least 160 µg.

Suitably by use of compositions of the present invention the amount of buprenorphine administered to a patient for the purpose of achieving relief from pain is up to 32 mg, preferably up to 16 mg, preferably up to 8 mg, preferably up to 4 mg, preferably up to 2 mg, preferably up to 1 mg,

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preferably up to 800 μg , preferably up to 600 μg , and most preferably up to 400 μg .

Suitably, a composition containing nalmefene comprises
5 from 0.4 μg to 24 μg of nalmefene per unit dose, preferably 0.6 to 12 μg , most preferably 0.8 to 6 μg .

Suitably the amount of nalmefene administered is between
0.01 and 0.8 μg per kg per 24 hours. Preferably the
10 amount is at least 0.02 μg , preferably at least 0.03 μg . Preferably the amount is not greater than 0.4 μg , preferably not greater than 0.4 μg , preferably not greater than 0.05 μg . Preferably it is not greater than 0.04 μg .

15 Suitably the amount of nalmefene administered is in the range from 1 μg to 80 μg per 24 hours, preferably 2 to 36 μg , preferably 3 to 20 μg , preferably 4 to 10 μg .

References above to the amounts of compounds which may be
20 administered to a patient are with reference to an adult patient.

Whatever the absolute amounts of buprenorphine and
nalmefene administered, the definition(s) stated herein of
25 the ratio of buprenorphine to nalmefene must be satisfied.

It is preferable to formulate the compositions in unit
dosage forms i.e. physically discrete units containing the
appropriate amounts of buprenorphine and nalmefene,
30 together with pharmaceutically acceptable diluents and/or carriers. Such unit dosage forms for parenteral administration are suitably in the form of ampoules. For

delivery via the mucosa may for example be in the form of sublingual tablets, films or lozenges.

5 Compositions of the invention may contain a buffer system, for example an organic acid and a salt thereof, such as citric acid and sodium citrate.

10 Compositions in the form of sublingual dosage forms suitably contain soluble excipients selected from materials such as lactose, mannitol, dextrose, sucrose or mixtures thereof. They suitably also contain granulating and disintegrating agents selected from materials such as starch, binding agents such as povidone or hydroxypropyl-methyl cellulose and lubricating agents such as magnesium
15 stearate.

20 Compositions intended for parenteral administration may comprise an isotonic solution of buprenorphine and nalmeffene in sterile water. Conveniently the solution may be made isotonic by use of dextrose and sterilised by autoclaving or by filtration through a membrane filter. The compositions may be administered intramuscularly, intradermally, intraperitoneally, intravenously, intraarterially, subcutaneously or by the epidural route.

25

The compositions for parenteral administration, or for delivery via the mucosa, such as by sublingual administration, as detailed above, may be prepared by manufacturing techniques which are well known to those
30 skilled in the art.

According to a second aspect the present invention there is provided a method for the treatment of pain in a human

patient, which method comprises the administration to a human patient, by a parenteral or dermal or mucosal route, of buprenorphine and nalmeferene such that the ratio by weight of buprenorphine to nalmeferene delivered to or reaching the plasma of a patient is in the range 22.6:1 to 40:1.

Preferred ratios of buprenorphine to nalmeferene delivered to or reaching plasma of the patient are as defined above with respect to the first aspect.

Suitably, the method comprises delivery via the mucosa. The method may comprise delivery in a sublingual unit dosage form.

Suitably, the method comprises the administration of buprenorphine and an amount of nalmeferene for the purpose of potentiating the analgesic action of the buprenorphine and in particular to optimising the balance between the analgesic action of the buprenorphine and the anti-abuse presence of the nalmeferene. It will be appreciated that this balance is extremely important. The medicament must be a potent analgesic for it to fulfil its intended function. At the same time in the present day it is vitally important that opioid medicaments discourage abuse by addicts. It is believed that the present invention is extremely effective in these respects.

Separate administration of buprenorphine and or nalmeferene is not excluded in the method. Suitably, however, the method comprises administering a composition comprising buprenorphine and nalmeferene, to a human. Suitably, the method employs a composition according to the first

aspect. The definitions given above in relation to the first aspect apply to the second aspect, noting however that the buprenorphine and nalmeferene may in principle be administered separately in the second aspect.

5

Suitably, the method comprises administering to the human or animal from 0.25 µg to 20 µg per kilogram of body weight of buprenorphine per day.

10 The method may comprise administering a dose of buprenorphine which would, if administered alone, produce minimal or no antinociception. The method may comprise administering to the human amounts of buprenorphine and nalmeferene as stated above in relation to the first aspect
15 of the invention.

The method may comprise any feature as described in relation to the first aspect.

20 According to a third aspect of the present invention there is provided the use of buprenorphine and nalmeferene in the manufacture of a medicament for the treatment of pain, wherein the buprenorphine and nalmeferene are used in an amount such that the medicament is delivered to a patient
25 at, or reaches in the plasma of a patient, a ratio by weight in the range 22.6:1 to 40:1.

Suitably this aspect comprises the use of buprenorphine and of nalmeferene in the manufacture of a medicament for
30 the treatment of pain, wherein buprenorphine is used for its analgesic effect, but at lower level than would be needed, for a given analgesic effect against a given pain in a given patient, in the absence of nalmeferene. Thus the

nalmefene potentiates the analgesic effect of buprenorphine. Further, it renders the medicament less attractive to drug addicts.

5 The use of buprenorphine and of nalmefene in the manufacture of a medicament according to the third aspect may comprise any feature as described in relation to the first or second aspect.

10 Suitably, the use of buprenorphine and of nalmefene in the manufacture of a medicament comprises the manufacture of a medicament comprising a composition according to the first aspect. However the use of buprenorphine and of nalmefene in the manufacture of a medicament having two dosage
15 units, containing buprenorphine and nalmefene respectively, is not excluded.

The present invention will now be illustrated by way of example with reference to the accompanying drawings in
20 which:

Figure 1 comprises graphs showing pain tolerance for buprenorphine and combinations with nalmefene; and

25

Figure 2 comprises comparative graphs.

Methods

30 Nociceptive testing

The cold pressor (CP) test was used to assess antinociception of buprenorphine and buprenorphine and

nalmefene or nalmefene combinations. The compound forms were buprenorphine HCl and nalmefene HCl dihydrate. The CP test utilised two plastic cylindrical containers, one of which was filled with warm water and the other with a combination of water and crushed ice to achieve a "slushy" consistency. The subject immersed the non-dominant forearm and hand into the warm water for exactly 2 minutes. At 1 minute 45 seconds, a blood pressure cuff on the immersed arm was inflated to a pressure 20 mm Hg below the diastolic blood pressure. The blood pressure cuff minimised the role of blood flow in determining the reaction to cold. At exactly 2 minutes, the forearm was transferred from the warm water to the cold water bath. The subject's eyes were covered for the entire procedure to minimise distraction and cues for time. Upon immersion of the limb in the cold water bath, subjects were asked to indicate when they first experienced pain (pain threshold, CPTHR), then asked to leave their arm submerged until they can no longer tolerate the pain (pain tolerance, CPTOL). Pain threshold and tolerance times were recorded in seconds from immersion in cold. An undisclosed cut-off of 180 seconds was imposed, after which time pain tolerance can no longer be accurately assessed due to numbness. Pain tolerance (CPTOL) is the reported pain response parameter in the current investigations.

For the present tests nociceptive testing was conducted in the same environment, with minimal background noise, audible voices and no clock with audible ticking. Ambient room temperature and lighting was consistent. At no time did the experimenter discuss with the subject his/her performance on the test, or answer any questions related

to the average pain tolerance time or any previous results.

Screening

5

Before testing subjects were screened according to the inclusion and exclusion criteria based upon such factors as previous medical conditions and drug abuse.

10 Test Procedure

Suitable screened subjects were tested according to the following procedure. Subjects provided a urine sample upon arrival on the day of testing, which was tested for
15 drugs of abuse (opioids, cannabinoids, benzodiazepines and sympathomimetic amines) and, for female subjects, pregnancy. A 22 gauge indwelling venous catheter was inserted into the best available forearm vein on each arm (above the CP immersion line for the non-dominant arm). A
20 male luer lock adaptor injection site was attached to each catheter. One catheter was used for blood sampling throughout the testing day, and the other for infusions. The participant was then connected to a monitor, which was set to continuously monitor physiological parameters for
25 the duration of the testing session.

On each testing day, subjects received a 30 minute unblinded intravenous infusion of saline, followed by one or more 30 minute drug (or placebo) infusions. The
30 purpose of the initial saline infusion was two-fold: to establish whether any changes in pain or physiological parameters would occur as a response to the infusion process itself, and to ensure that there was no

obstruction to venous access via the catheter and the infusion pump was operating correctly.

Infusions were administered using a Syringe Pump. Drugs
5 and saline were prepared in 30ml BD Plastipak syringes.
Infusions were run at a rate of 20ml per hour for 30
minutes. Each syringe was attached to a minimum volume
extension set (150cm tubing, female luer lock, male luer
lock, 0.5mL/30cm). The male luer lock was attached to a
10 lever lock cannula. The extension set was primed with the
drug/saline, and inserted into the injection site. In
buprenorphine:antagonist ratio studies, BUP and antagonist
were administered simultaneously. For the simultaneous
infusion of two drugs (via one cannula), a Y-type catheter
15 extension set with two injection sites was attached to
the catheter, and the lever lock cannulas (connected via
the minimum volume extension set to each syringe) were
inserted in each of the injection sites.

20 Testing sessions were conducted on numerous occasions
during each testing day. Each testing session consisted
of the following measures in the order listed: nausea and
sedation recorded, blood sample taken, physiological
parameters recorded (pulse, oxygen saturation and blood
25 pressure), nociceptive testing (as detailed above)
completed, and respiration recorded (breaths per minute
counted for one full minute during warm water component of
CP).

30 Testing sessions were conducted at set intervals
throughout each testing day. These were as follows: 1.
Prior to the commencement of infusions; 2. Twenty minutes
after the commencement of the 30 minute saline infusion;

3. Twenty minutes after the commencement of the 30 minute drug infusion, and hourly following the cessation of the (last) drug infusion. This is referred to as the washout period. The purpose of conducting the testing session 20 minutes after commencing each 30 minute infusion was to allow time for the testing to be completed before starting the subsequent infusion.

Comparison of results

10

As baseline values were different between conditions, CPTOL data were expressed as percent change from baseline in order to compare the effect associated with different drug combinations. Each participant's response at each time point for each condition was expressed as a percent change from baseline response according to the equation below. Data are expressed as the mean (\pm SEM) of these values at each post-drug testing session for each condition.

20

$$\frac{\text{Post-drug latency} - \text{baseline latency}}{\text{baseline latency}} * 100$$

This provided a value for percentage change CPTOL.

Examples

25

Example 1

Four healthy Caucasian participants (2 males, 2 females) ranging in age from 19 to 27 years (Mean \pm SEM, 21.7 \pm 1.8 years) were enrolled in the study. Mean body weight was 77.5 kg (\pm 9.1, range 63 - 104 kg) and mean CPTOL at

30

screening was 38.7 seconds (± 5.6 , range 25 - 52 seconds). There were no significant differences between males and females in terms of age ($p=0.277$) or CPTOL at screening ($p=0.974$).

5

Subjects were administered buprenorphine and nalmefene in a ratio of 25:1 by IV infusion with buprenorphine administered at a dose of 0.5 $\mu\text{g}/\text{kg}$ body weight. The CPTOL results are presented in Figure 5. No adverse effects causing concern were noted.

10

Example 2 - comparative

As a comparative example the same subjects from Example 1 were administered, on a separate day, buprenorphine and saline (referred to subsequently as "BUP only") by IV infusion. Buprenorphine was again administered at a dose of 0.5 $\mu\text{g}/\text{kg}$ body weight. The CPTOL results are presented in Figure 5.

15
20

Example 3

The same subjects from Example 1 were administered, on a separate day, buprenorphine and nalmefene in a ratio of 30:1 by IV infusion with buprenorphine administered at a dose of 0.5 $\mu\text{g}/\text{kg}$ body weight. The CPTOL results are presented in Figure 1. No adverse effects causing concern were noted.

30 Comparison of Examples 4-6

The percentage change for CPTOL from the baseline was calculated for Examples 1, 2 and 3 and the results are

presented in Figure 2. It may be seen that there was a marked benefit of the buprenorphine and nalmeferine combinations compared to buprenorphine alone.

5 Example 7 - Buprenorphine/Nalmeferine parenteral composition

A parenteral formulation having the following composition:

	mg/ml.
Buprenorphine as HCl salt	0.01
Nalmeferine as HCl salt	0.004
Anhydrous dextrose	52.0
Hydrochloric acid	to pH 4.0
Water for injection	to 1.0 ml

10

was prepared by dissolving dextrose, buprenorphine hydrochloride and nalmeferine or nalmeferine hydrochloride in that order with stirring, in about 95% batch volume of water for injection. The acidity of the solution was
 15 adjusted to pH 4.0 by the addition of 0.1M hydrochloric acid, and the solution was made up to volume with water for injection. The solution was filtered through a membrane filter and transferred to sterilised 2 ml glass ampoules containing 2 ml of the solution. The ampoules
 20 were sealed and the product sterilised by autoclaving.

CLAIMS

1. An analgesic composition, in parenteral unit dosage form or in a unit dosage form suitable for delivery via
5 the mucosa or dermis, the composition comprising buprenorphine and an amount of nalmeferne such that the ratio by weight of buprenorphine to nalmeferne delivered to or reaching the plasma of a patient is in the range 22.6:1 to 40:1.
10
2. A composition as claimed in claim 1, wherein the amount of buprenorphine in the unit dosage form is from 10 μ g, to 8 mg.
- 15 3. A composition as claimed in claim 1 or 2, wherein the composition contains buprenorphine and nalmeferne in a ratio of 23 to 36, preferably 24 to 32, preferably 25 to 30.
- 20 4. A method for the treatment of pain in a human patient, which method comprises the administration to a human patient, by a parenteral or dermal or mucosal route, of buprenorphine and nalmeferne such that the ratio by weight of buprenorphine to nalmeferne delivered to or reaching the
25 plasma of a patient is in the range 22.6:1 to 40:1 for buprenorphine:nalmeferne.
- 30 5. Use of buprenorphine and nalmeferne in the manufacture of a medicament for the treatment of pain, wherein the buprenorphine and nalmeferne are used in an amount such that the medicament is delivered to a patient at, or reaches in the plasma of a patient, a ratio by weight in the range 22.6:1 to 40:1.

6. A method of use as claimed in claim 5 or 6 wherein the administration of buprenorphine is in the range 0.25 to 640 µg per kg per 24 hours.

5

7. A composition or method or use, substantially as hereinbefore described in accordance with the present invention

10

21

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Examiner: Fiona Warner

Claims searched: 1, 4 & 5

Date of search: 25 June 2007

Patents Act 1977: Search Report under Section 17

Documents considered to be relevant:

Category	Relevant to claims	Identity of document and passage or figure of particular relevance
X	1, 4 & 5 at least	WO 01/35942 A2 (RECKITT BENCKISER) Whole document relevant
A	-	US 2003/0232744 A1 (CRAIN)
A	-	US 5149538 A (WARNER-LAMBERT)

Categories:

X	Document indicating lack of novelty or inventive step	A	Document indicating technological background and/or state of the art
Y	Document indicating lack of inventive step if combined with one or more other documents of same category.	P	Document published on or after the declared priority date but before the filing date of this invention
&	Member of the same patent family	E	Patent document published on or after, but with priority date earlier than, the filing date of this application.

Field of Search:

Search of GB, EP, WO & US patent documents classified in the following areas of the UKC^X:

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Worldwide search of patent documents classified in the following areas of the IPC

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The following online and other databases have been used in the preparation of this search report

EPODOC, WPI, PAJ, BIOSIS, MEDLINE

International Classification:

Subclass	Subgroup	Valid From
A61K	0031/485	01/01/2006
A61P	0025/04	01/01/2006