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(63) Related by Continuation
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US 812,523 (CON) Filed on 20 December 1991 (20.12.91)


(72) Inventors; and

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(81) Designated States: AT (European patent), AU, BB, BE (European patent), BF (OAPI patent), BG, BJ (OAPI patent), BR, CA, CF (OAPI patent), CG (OAPI patent), CH (European patent), CI (OAPI patent), CM (OAPI patent), CS, DE (European patent), DK (European patent), ES (European patent), FI, FR (European patent), GA (OAPI patent), GB (European patent), GN (OAPI patent), GR (European patent), HU, IT (European patent), JP, KR, LK, LU (European patent), MC (European patent), MO, ML (OAPI patent), MN, MR (OAPI patent), MW, NL (European patent), NO, PL, RO, RU, SD, SE (European patent), SN (OAPI patent), TD (OAPI patent), TG (OAPI patent), US.

Published
With international search report.

(54) Title: IBUPROFEN-DECONGESTANT COMBINATIONS

(57) Abstract

This invention relates to pharmaceutical compositions for use in the treatment of pain and inflammation and the relief of nasal congestion and sinus pressure in a mammalian organism, said composition comprising: (i) an analgesically and anti-inflammatory effective amount of (S)-ibuprofen, or a salt thereof, substantially free of (R)-ibuprofen; and (ii) a sympathomimetically effective amount of at least one of the sympathomimetic amines selected from phenylephrine, phenylpropanolamine, pseudoephedrine, oxymetazoline, ephinephrine, naphazoline, xylometazoline, propylhexedrine, levo-desoxyllephedrine or a therapeutically active stereoisomer thereof substantially free of its other stereoisomers or a pharmaceutically acceptable salt thereof.
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Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

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TITLE OF THE INVENTION
IBUPROFEN-DECONGESTANT COMBINATIONS

BACKGROUND OF THE INVENTION

The non-steroidal anti-inflammatory drugs (NSAID) have been utilized in the treatment of pain/inflammation and have been disclosed as useful in the treatment, management and mitigation of cold symptoms and the pain associated therewith.

Ibuprofen (2-(4-isobutylphenyl)propionic acid) is a well known and commonly employed NSAID. Recently, it has been found that a faster onset of pain relief and an enhanced analgesic response can be obtained by the utilization of the single enantiomer (S)-ibuprofen in comparison to racemic ibuprofen, (see for example U.S. Patent 4,877,620).
The sympathomimetic amines, phenylephrine, phenylpropanolamine, pseudoephedrine, oxymetazoline, ephinephrine, naphazoline, xylometazoline, propylhexedrine, levo-desoxyephedrine are sympathomimetic agents (Decongestants) which are useful for the treatment of nasal congestion arising from cold, allergy, flu or sinus conditions. These agents function by constricting the smaller arterioles of the nasal passages producing a decongestant effect.

Combinations of ibuprofen with decongestants have been disclosed, however despite the fact that the cold/pain sufferer is in need of quick and enhanced relief there has been no consideration given to the employment of (S)-ibuprofen, or a salt thereof, in combination with a decongestant for the treatment of pain and the relief of allergy, cold symptoms.

DETAILED DESCRIPTION OF THE INVENTION

This invention relates to pharmaceutical compositions for use in the treatment of pain and inflammation and the relief of nasal congestion and sinus pressure symptoms in a mammalian organism, said composition comprising:

(i) an analgesically and anti-inflammatory effective amount of (S)-ibuprofen, or a salt thereof, substantially free of (R)-ibuprofen; and

(ii) a sympathomimetically effective amount of at least one of the sympathomimetic amines phenylephrine, phenylpropanolamine, pseudoephedrine, oxymetazoline, ephinephrine, naphazoline,
xylometazoline, propylhexedrine, levo-desoxyephedrine
or a therapeutically active stereoisomer thereof
substantially free of its other stereoisomers or a
pharmacologically acceptable salt thereof.

This invention is also directed to a method
of treating pain and inflammation and the relief of
nasal congestion and sinus pressure in a mammalian
organism in need of such treatment comprising
administering to such organism:

(i) an analgesically and anti-inflammatory
effective amount of (S)-ibuprofen, or a salt thereof,
substantially free of (R)-ibuprofen; and
(ii) a sympathomimetically effective amount of at
least one of the sympathomimetic amines
phenylephrine, phenylpropanolamine, pseudoephedrine,
oxymetazoline, ephinephrine, naphazoline,
xylometazoline, propylhexedrine, levo-desoxyephedrine
or a therapeutically active stereoisomer thereof
substantially free of its other stereoisomers or a
pharmacologically acceptable salt thereof.

This invention is also directed to a method
of treating pain and inflammation and the relief of
nasal congestion and sinus pressure in a mammalian
organism in need of such treatment comprising
administering to such organism:

(i) an analgesically and anti-inflammatory
effective amount of (S)-ibuprofen, or a salt thereof,
substantially free of (R)-ibuprofen; and
(ii) a sympathomimetically effective amount of at
least one of the sympathomimetic amines
phenylephrine, phenylpropanolamine, pseudoephedrine,
oxymetazoline, ephinephrine, naphazoline,
xylometazoline, propylhexedrine, levo-desoxyephedrine or a therapeutically active stereoisomer thereof substantially free of its other stereoisomers or a pharmaceutically acceptable salt thereof.

The compositions and methods of the present invention may be used to treat pain and inflammation, or pain alone or inflammation alone where only one is present, along with the treatment of nasal congestion and sinus pressure symptoms.

Substantially free of (R)-ibuprofen should be taken to mean that the ratio of (S)-ibuprofen to (R)-ibuprofen is at least 90:10. Substantially free with respect to a sympathomimetic amine stereoisomer should be taken to mean that the ratio of that stereoisomer to all other stereoisomers of the sympathomimetic amine is at least 90:10.

Salts of (S)-ibuprofen include salts with alkali metals, such as sodium or potassium, salts with alkaline earth metals, such as calcium, or salts with other metals such as magnesium, aluminum, iron, zinc, copper, nickel or cobalt.

Salts of (S)-ibuprofen further include the amino acid salts, particularly the basic amino acids such as lysine or arginine. Specifically included within the above composition is (S)-ibuprofen-(S)-lysine and (S)-ibuprofen-(R)-lysine.

Salts of the sympathomimetic amine include, but are not limited to, the hydrochloride, sulfate or bitartrate.

(S)-ibuprofen may be prepared following the procedures disclosed in U.S. Patent 4,877,620. Metal salts of ibuprofen may be obtained by contacting a
hydroxide, or carbonate with ibuprofen. Amino acid salts of ibuprofen may be obtained by contacting an amino acid in solution with ibuprofen.

The utilization of (S)-ibuprofen in an analgesic/decongestant combination offers significant advantages over the combination of racemic ibuprofen with a decongestant. (S)-ibuprofen provides a faster onset of pain relief and an enhanced degree of relief compared to racemic ibuprofen. These benefits are increased in an (S)-ibuprofen/decongestant combination as the decongestant may potentiate the action of (S)-ibuprofen. This has not heretofore been observed because the art has not proposed the combination of the (S)-ibuprofen enantiomer, absent (R)-ibuprofen, with a decongestant. Furthermore the decongestant also may potentiate the duration of the analgesic and anti-inflammatory response. The presence of the (R)-ibuprofen may blur the potentiated effect.

Furthermore, the absence of (R)-ibuprofen provides significant benefits particularly to the subject in the weakened state of a cold, flu, or allergy condition. The allergic contraindications sometimes associated with ibuprofen administration, and which may be particularly detrimental to the cold/allergy/flu sufferer, may be absent or reduced in a composition wherein the (R)-ibuprofen is absent.

The subject using the (S)-ibuprofen/decongestant combination will no longer need to divert metabolic energy to the inversion of the (R)-enantiomer or the removal of this enantiomer. The absence of inversion reduces or eliminates the
formation and incorporation into fatty tissue of hybrid-ibuprofen containing triglycerides. The renal burden and renal toxicities sometimes associated with ibuprofen therapy are reduced or absent in a substantially (R)-ibuprofen free composition.

The absence of inactive enantiomers, particularly (R)-ibuprofen, provides for significant size and weight advantages in a combination dosage form, particularly a sustained release dosage form. Where a sustained release dosage of ibuprofen may have required 800 to 1000 mg, the employment of (S)-ibuprofen reduces the weight to 650 to 800 mg and provides for a more practical size tablet for an ibuprofen/decongestant combination.

Where only a single stereoisomer of the decongestant is active (therapeutically active stereoisomer), the absence of the inactive substances in the present composition may avoid undesirable toxic interactions and clearly avoids the metabolism necessary to remove the nonactive entity.

An effective amount of (S)-ibuprofen, or a salt thereof, for use in an unit dose composition of this invention may range from 50 to 800 mg (S)-ibuprofen. The preferred amount of (S)-ibuprofen is about 100 to 400 mg. The amount of a salt such as (S)-ibuprofen-(S)-lysine is determined based on the amount of (S)-ibuprofen contained therein.

The sympathomimetic amine (Decongestant) employed herein is selected from phenylephrine, phenylpropanolamine, pseudoephedrine, oxymetazoline, ephinephrine, naphazoline, xylometazoline, propylhexedrine, levo-desoxyephedrine or a pharmaceutically acceptable salt. Included within
this invention are any diastereomers and/or enantiomers of each decongestant. Where a particular therapeutically active stereoisomer is not commercially available it may be prepared following standard resolution chemistry from the available racemic mixture.

The amount of the decongestant useful in the practice of the present invention may vary from about 1 mg to 100 mg depending on the specific decongestant. The amount of a salt, such as pseudoephedrine hydrochloride, is determined based on the amount of active decongestant, such as pseudoephedrine, contained therein.

The present compositions may be administered in the form of tablets, capsules, elixirs, syrups drops, granules, liquids, nasal spray inhaler, or a suspension. For oral administration the active components may be admixed with a pharmaceutically acceptable diluent such as lactose, starch, sucrose, cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol and in a liquid composition, ethyl alcohol. Acceptable binders such as PVP, starch, gelatin, natural sugars, corn sweeteners, natural and synthetic gums such as acacia, sodium alginate, carboxymethylcellulose, polyethylene glycol and waxes, may also be admixed with the active components. Where necessary lubricants such as magnesium stearic acid talc, and disintegrators such as starch, methylcellulose, agar, bentonite and guar gum and super disintegrators such as docusate sodium, sodium starch glycollate or cross linked PVP may also be included.

The active components may also be formulated in sustained release formulations. These
formulations may be employed in oral, dermal, rectal or vaginal administrations. Such sustained release forms also include layered formulations which provide for distinct release ratio and thus may be more beneficial in allowing for short and long term relief.

The following examples illustrate the compositions of the present invention and as such are not to be considered as limiting the invention set forth in the claims appended hereto.

**EXAMPLE 1**

**(S)-ibuprofen-(S)-lysine. Decongestant Tablet**

15  
(S)-ibuprofen-(S)-lysine  342 mg  
Pseudoephedrine HCl  30 mg  
PVP  15 mg  
Avicel PH101  40 mg  
Magnesium Stearate  4 mg

**EXAMPLE 2**

**(S)-ibuprofen-(S)-lysine. Decongestant Sustained Release**

25  
(S)-ibuprofen-(S)-lysine  685 mg  
Pseudoephedrine HCl  60 mg  
PVP  30 mg  
Avicel PH101  80 mg  
Magnesium Stearate  8 mg  
Methocel E10MCR  66 mg  
Methocel K100MLV  200 mg
### EXAMPLE 3

(S)-ibuprofen, Decongestant Sustained Release

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<tr>
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<td>Pseudoephedrine HCl</td>
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<td>Methocel K100MLV</td>
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### EXAMPLE 4

(S)-ibuprofen-(S)-lysine/decongestant Solution

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<th>Ingredient</th>
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<td>(S)-ibuprofen-(S)-lysine</td>
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<tr>
<td>Pseudoephedrine HCl</td>
<td>15 mg</td>
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<tr>
<td>q.s. syrup</td>
<td>5 ml</td>
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WHAT IS CLAIMED IS:

1. A pharmaceutical composition for use in the treatment of pain and inflammation and the relief of nasal congestion and sinus pressure in a mammalian organism and adapted for unit dosage oral administration said composition comprising:
   (i) an analgesically and anti-inflammatory effective amount of (S)-ibuprofen, or a salt thereof, substantially free of (R)-ibuprofen; and
   (ii) a sympathomimetically effective amount of at least one of the sympathomimetic amines phenylephrine, phenylpropanolamine, pseudoephedrine, oxymetazoline, ephinephrine, naphazoline, xylometazoline, propylhexedrine, levo-desoxyephedrine or a therapeutically active stereoisomer thereof substantially free of its other stereoisomers or a pharmaceutically acceptable salt thereof.

2. A composition of Claim 1 where the ibuprofen is present as the salt (S)-ibuprofen-(S)-lysine, or (S)-ibuprofen-(R)-lysine.

3. A composition of Claim 1 comprising at least 50 mg of (S)-ibuprofen.

4. A composition of Claim 3 wherein the sympathomimetic amine is selected from: phenylephrine, phenylpropanolamine, pseudoephedrine, or a therapeutically active stereoisomer thereof substantially free of its other stereoisomers, or a pharmaceutically acceptable salt.
5. A method of treating pain and inflammation and the relief of allergy and cold symptoms in a mammalian organism in need of such treatment comprising administering to such organism:

(i) an analgesically and anti-inflammatory effective amount of (S)-ibuprofen, or a salt thereof, substantially free of (R)-ibuprofen;

(ii) a sympathomimetically effective amount of at least one of the sympathomimetic amines phenylephrine, phenylpropanolamine, pseudoephedrine, oxymetazoline, ephinephrine, naphazoline, xylometazoline, propylhexedrine, levo-desoxyephedrine or a therapeutically active stereoisomer thereof substantially free of its other stereoisomers or a pharmaceutically acceptable salt thereof.

6. A method of eliciting an onset hastened and enhanced response for the treatment of pain and inflammation and the relief of allergy and cold symptoms in a mammalian organism in need of such treatment comprising administering to such organism.

(i) an analgesically and anti-inflammatory effective amount of (S)-ibuprofen, or a salt thereof, substantially free (R)-ibuprofen; and

(ii) a sympathomimetically effective amount of at least one of the sympathomimetic amines phenylephrine, phenylpropanolamine, pseudoephedrine, oxymetazoline, ephinephrine, naphazoline, xylometazoline, propylhexedrine, levo-desoxyephedrine or a therapeutically active stereoisomer thereof substantially free of its other stereoisomers or a pharmaceutically acceptable salt thereof.
7. A method of reducing the side effects associated with the administration of an ibuprofen/decongestant combination which comprises the administration of (S)-ibuprofen, or a salt thereof, substantially free of (R)-ibuprofen, and at least one of the sympathomimetic amines, phenylephrine, phenylpropanolamine, pseudoephedrine, oxymetazoline, ephinephrine, naphazoline, xylometazoline, propylhexedrine, levo-desoxyephedrine or a therapeutically active stereoisomer thereof substantially free of its other stereoisomers, or a pharmaceutically acceptable salt thereof.

8. A method of reducing the size and weight of an ibuprofen/decongestant combination dosage form which comprises combining (S)-ibuprofen, or a salt thereof, substantially free of (R)-ibuprofen and at least one of the sympathomimetic amines, phenylephrine, phenylpropanolamine, pseudoephedrine, oxymetazoline, ephinephrine, naphazoline, xylometazoline, propylhexedrine, levo-desoxyephedrine or a therapeutically active stereoisomer thereof substantially free of its other stereoisomers, or a pharmaceutically acceptable salt thereof.
# INTERNATIONAL SEARCH REPORT

**Classification of Subject Matter**
- IPC (S): A61K 31/19
- U.S. Cl. : 514-570

**Fields Searched**
- Minimum Documentation Searched
  - Classification System: U.S.
  - Classification Symbols: 514-570

**CAS on Line - Parent**

**Documents Considered to be Relevant**

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<td>US, A, 4,840,962 (SUNSHINE ET AL.) 20 June 1989 See the entire document.</td>
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<td>X</td>
<td>Chemical Abstracts, Volume 127 042f, &quot;Analgesics containing S(+) ibuprofen substantially free of its R(-) antipode, Sunshine (1989).</td>
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* Special categories of cited documents:
  - "A" document defining the general state of the art which is not considered to be of particular relevance
  - "E" earlier document but published on or after the international filing date
  - "L" document which may throw doubts on priority claim(s) or which is cited to establish the 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

"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

"Z" document member of the same patent family

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**Certification**

- Date of the Actual Completion of the International Search: 11 June 1992
- Date of Mailing of this International Search Report: 30 Jun 1992

International Searching Authority: ISA/US

Signature of Authorized Officer: S. J. Friedman
FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claim numbers , because they relate to subject matter not required to be searched by this Authority, namely:

2. Claim numbers , because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. Claim numbers , because they are dependent claims not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This International Searching Authority found multiple inventions in this international application as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

☐ The additional search fees were accompanied by applicant's protest.

☐ No protest accompanied the payment of additional search fees.