Title: THIOCOLOCOSIDE AND NON-STEROIDAL ANTI-INFLAMMATORY DRUG COMBINATIONS

Abstract: This invention relates to pharmaceutical compositions and unit dosage forms containing in combination: the muscle relaxant thiocholicic acid or a salt of thereof or any therapeutically active stereoisomer thereof, substantially free of its other stereoisomers; a non-steroidal anti-inflammatory drug (NSAID).
Thiocolchicoside and non-steroidal anti-inflammatory drug combinations

This invention relates to pharmaceutical compositions and unit dosage forms containing in combination:

i. the muscle relaxant thiocolchicoside or a salt of thereof or any therapeutically active stereoisomer thereof, substantially free of its other stereoisomers;

ii. a non-steroidal anti-inflammatory drug (NSAID).

The pharmaceutical compositions are useful for the treatment of musculo-skeletal disorders and the treatment of pain and inflammation in mammalian organism, especially for the treatment of low back pain.

Thiocolchicoside is a glycosulfurated analogue of colchicine and is a well known centrally acting muscle relaxant used in the treatment of musculo-skeletal disorders. Its chemical structure is shown in the Formula 1.

![Formula 1]

The chemical name of thiocolchicoside is N-[3-(β-D-glucopyranosyloxy)-1,2-dimethoxy-10-(methylthio)-9-oxo-5,6,7,9-tetrahydrobenzo[a]heptalen-7-yl]acetamide.

The usual initial dose is 16 mg daily by oral administration in the form of capsules or tablets. It is also used for intramuscular administration in doses up to 8 mg per day or for topical application as cream, ointment, gel or aerosol.

The non-steroidal anti-inflammatory drugs have been utilized in the treatment of pain and inflammation, as well as for a variety of disorders including rheumatoid and osteoarthritis. They vary widely in their chemical structure and biological profiles as analgesics, anti-inflammatory agents and antipyretic agents. They present a superior analgesic and anti-inflammatory activity compared to aspirin and paracetamol but also
less side effects like gastrointestinal ulcerations and bleeding experienced with aspirin or hepatic toxicity with large doses of paracetamol.

Centrally acting skeletal muscle relaxants are generally prescribed either as single agents or as components of combination products. Several commercial combinations of a muscle relaxant and aspirin have been approved by the US FDA and are marketed in the USA like carisoprodol + aspirin (Soma Compound, Meda Pharms), carisoprodol + aspirin + codeine (Soma Compound W/ Codeine), methocarbamol + aspirin (Methocarbarbamol and Aspirin, Ivax Pharms) and orphenadrine + aspirin + caffeine (Norgesic Forte, Graceway).

However, few combinations of the muscle relaxant thiocolchicoside with NSAID have been described in the past and none of the descriptions includes the combinations disclosed in the present invention.

French patent FR 2725134 B1 (Laboratoire Lederle), filed on 04.10.1994, describes a new combination comprising ibuprofen or a pharmaceutically acceptable salt thereof and thiocolchicoside or a pharmaceutically salt salt thereof in a weight ratio generally comprising between approximately 1:50 and approximately 1:200 for oral administration in a form of a capsule, a tablet or granules.

European patent EP 0837684 B1 (Sanofi-Synthelabo), filed on 12.06.1996, describes a new combination comprising a diclofenac salt and thiocolchicoside with at least one pharmaceutically acceptable excipient and provided in a solid form which is stable over time.

European patent EP 1992333 A1 (Sanovel) describes a composition comprising flurbiprofen and an alpha-2 adrenergic receptor agonist or a gamma-aminobutiric acid receptor agonist, in particular tizanidine and thiocolchicoside.

The physicochemical compatibility of the injectable mixture of thiocolchicoside and other drugs frequently used in association, like anti-inflammatory drugs or vitamins, have been shown for a period of three hours at room temperature in solution (Farmaco. 2002 Nov; 57(11):925-30).

The addition of thiocolchicoside to NSAID standard treatment has shown more effective results for the treatment of low back pain than the NSAID alone. In addition, the
combination was well tolerated and produced no more adverse reactions than the NSAID alone (J Orthopaed Traumatol (2002) 3-103-108).

The present invention describes new combinations of thiocolchicoside and NSAID in unit dosage form which is stable over time.

The present invention relates to a combination of the muscle relaxant thiocolchicoside and its pharmaceutically acceptable salts with at least one non-steroidal anti-inflammatory drug and at least one pharmaceutically acceptable non-toxic carrier adapted for unit dose administration.

The muscle relaxant for use in the pharmaceutical compositions and methods of use of the present invention is thiocolchicoside. The invention includes any pharmaceutically acceptable salt of thiocolchicoside and any therapeutically active stereoisomer of thiocolchicoside, substantially free of its other stereoisomers. The amount of thiocolchicoside useful in the practice of the present invention may vary from 4 mg to 16 mg depending on the mode of administration. The preferred amount of thiocolchicoside is selected from a range 4 to 8 mg per unit for parenteral administration. The preferred amount of thiocolchicoside is selected from a range 8 to 16 mg per unit for oral administration.

The NSAID for use in the pharmaceutical compositions and methods of use of the present invention may be chosen from the group consisting of, but not limited to, the oxicams, the fenamic acid derivatives, the acetic acid derivatives, the propionic acid derivatives, the coxibs and other NSAIDs. They include all their pharmaceutically acceptable salts of thereof or therapeutically active stereoisomers thereof, substantially free of their other stereoisomers. These compounds are well known to those skilled in art and described in various literature reference sources like the Merck Index for their chemical structures, pharmacological activities, side effects, normal dosage ranges, etc.

The preferred oxicams for use in the present invention include, but are not limited to, lornoxicam, tenoxicam, meloxicam and piroxicam.

The preferred fenamic acid derivatives for use in the present invention include, but are not limited to, mefenamic acid and etofenamate.

The preferred acetic acid derivatives for use in the present invention include, but are not limited to, etodolac, acemetacin and indometacin.
The preferred propionic acid derivatives for use in the present invention include, but are not limited to, tiaprofenic acid, naproxen and oxaprozin.

The preferred coxibs for use in the present invention include, but are not limited to, celecoxib, rofecoxib, lumiracoxib and valdecoxib.

The preferred other NSAID’s for use in the present invention include, but are not limited to, nimesulide.

The preferred unit dose for the preferred compounds mentionned hereinabove are listed in Table 1.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Preferred unit dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acemetacin</td>
<td>30 - 180 mg</td>
</tr>
<tr>
<td>Etodolac</td>
<td>300 - 1200 mg</td>
</tr>
<tr>
<td>Etofenamate</td>
<td>500 - 1000 mg</td>
</tr>
<tr>
<td>Indometacin</td>
<td>25 - 200 mg</td>
</tr>
<tr>
<td>Lornoxicam</td>
<td>4 - 16 mg</td>
</tr>
<tr>
<td>Mefenamic acid</td>
<td>250 - 1500 mg</td>
</tr>
<tr>
<td>Meloxicam</td>
<td>3,75 - 15 mg</td>
</tr>
<tr>
<td>Naproxen</td>
<td>250 - 1000 mg</td>
</tr>
<tr>
<td>Nimesulide</td>
<td>50 - 200 mg</td>
</tr>
<tr>
<td>Oxaprozin</td>
<td>300 - 1200 mg</td>
</tr>
<tr>
<td>Piroxicam</td>
<td>5 - 40 mg</td>
</tr>
<tr>
<td>Tenoxicam</td>
<td>10 - 40 mg</td>
</tr>
<tr>
<td>Thiocolchicoside</td>
<td>4 - 16 mg</td>
</tr>
<tr>
<td>Tiaprofenic acid</td>
<td>200 - 600 mg</td>
</tr>
</tbody>
</table>

Table 1

The present pharmaceutical compositions may be used for oral, buccal, ocular, otic, dermal, rectal, epidermal, topical, transdermal, implantal, mucosal, parenteral, sublingual, nasal, or pulmonary administration in the form of gel, cream, ointment, tablet, capsule, bead, granule, liquid, suspension, syrup, powder, injectable suspension, injectable powder and injectable liquid.
The present pharmaceutical compositions may be administrated in a mixture with suitable non-toxic pharmaceutical carriers or excipients suitably selected with respect to the intened route of administration and conventional pharmaceutical practices known by the people skilled in the art.

For oral administration in a form of a tablet or a capsule, the active substances may be combined with any oral non-toxic pharmaceutically acceptable inert carrier such as lactose, starch, pregelatinized starch, sucrose, cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol and the like. When desired or necessary, suitable binders, lubricants, disintegrating agents and flavoring, sweetening or coloring agents can also be added. Examples of suitable binders include starch, pregelatinized starch, gelatin, natural sugars, corn sweeteners, natural and synthetic gums, sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes, etc. Examples of suitable lubricants / glidants include magnesium stearate, talc, boric acid, sodium benzoate, sodium acetate, sodium chloride, etc. Examples of suitable disintegrators include starch, methylcellulose, agar, etc. Examples of suitable coating agents include hydroxypropylmethyl cellulose as film former, PEG 400 as plasticizer, titanium dioxide and iron oxide as colouring agent. Optionnally the invention may be formulated in the form of a extended, modified or extended release tablet or capsule to provide the control of the release of thiocolchicoside and / or the NSAID in order to optimize the therapeutic effects and minimize the undesirable side effects.

Similarly, the present invention may be an injectable dosage unit for intravenous, intramuscular or subcutaneous administration formulated as aqueous or non-aqueous solution, suspension or powder for injection with the appropriate non-toxic pharmaceutically acceptable excipients.

The present pharmaceutical compositions are useful for the treatment of musculo-skeletal disorders and the treatment of pain and inflammation in mammalian organism, especially for the treatment of low back pain. They can be administrated in unit dose 1 or 2 times per day.

The following examples illustrate the compositions of the present invention and as such are to be considered as limiting the invention set forth in the claims appended hereto.
Example 1: Powder for injection

<table>
<thead>
<tr>
<th></th>
<th>Weight per unit dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tenoxicam</td>
<td>10,0 mg</td>
</tr>
<tr>
<td>Thiocolchicoside</td>
<td>4,0 mg</td>
</tr>
<tr>
<td>Mannitol</td>
<td>50,0 mg</td>
</tr>
<tr>
<td>Trometamol</td>
<td>1,5 mg</td>
</tr>
<tr>
<td>NaOH</td>
<td>1,6 mg</td>
</tr>
<tr>
<td>Na metabisulfite</td>
<td>2,0 mg</td>
</tr>
<tr>
<td>Na EDTA</td>
<td>0,2 mg</td>
</tr>
</tbody>
</table>

The compounds are dissolved and mixed in water for injection. The obtained solution is filtered at 0,2 μm, filled in vials and lyophilized.

Example 2: Coated tablet

<table>
<thead>
<tr>
<th></th>
<th>Weight per unit dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Core:</strong></td>
<td></td>
</tr>
<tr>
<td>Tenoxicam</td>
<td>10,0 mg</td>
</tr>
<tr>
<td>Thiocolchicoside</td>
<td>8,0 mg</td>
</tr>
<tr>
<td>Lactose Monohydrate</td>
<td>90,0 mg</td>
</tr>
<tr>
<td>Starch</td>
<td>86,0 mg</td>
</tr>
<tr>
<td>Talc</td>
<td>3,0 mg</td>
</tr>
<tr>
<td>Magnesium Stearate</td>
<td>1,0 mg</td>
</tr>
<tr>
<td><strong>Coating:</strong></td>
<td></td>
</tr>
<tr>
<td>Hydroxypropylmethyl cellulose</td>
<td>2,9 mg</td>
</tr>
<tr>
<td>Titanium Dioxide</td>
<td>1,8 mg</td>
</tr>
<tr>
<td>PEG 400</td>
<td>0,3 mg</td>
</tr>
<tr>
<td>Iron Oxide</td>
<td>0,6 mg</td>
</tr>
</tbody>
</table>

The compounds are mixed by conventional techniques then pressed into tablet forms and coated.
CLAIMS

1. A pharmaceutical composition for use in the treatment of musculoskeletal disorders and the treatment of pain and inflammation in mammalian organism and adapted for unit administration comprising a pharmaceutically effective amount of:
   a) one muscle relaxant;
   b) at least one non-steroidal anti-inflammatory drug;
   c) at least one pharmaceutically acceptable non-toxic carrier.

2. The pharmaceutical composition of claim 1 where the said muscle relaxant is thiocolchicoside, or a salt of thereof or any therapeutically active stereoisomer thereof, substantially free of its other stereoisomers.

3. The pharmaceutical composition of claim 1 where the said non-steroidal anti-inflammatory agent is selected from the group consisting of oxicams, fenamic acid derivatives, acetic acid derivatives, propionic acid derivatives, coxibs and other non-steroidal anti-inflammatories.

4. The pharmaceutical composition of claim 3 where the said oxicam is lornoxicam or a salt of thereof or any therapeutically active stereoisomer thereof, substantially free of its other stereoisomers.

5. The pharmaceutical composition of claim 3 where the said oxicam is tenoxicam or a salt of thereof or any therapeutically active stereoisomer thereof, substantially free of its other stereoisomers.

6. The pharmaceutical composition of claim 3 where the said oxicam is meloxicam or a salt of thereof or any therapeutically active stereoisomer thereof, substantially free of its other stereoisomers.

7. The pharmaceutical composition of claim 3 where the said oxicam is piroxicam or a salt of thereof or any therapeutically active stereoisomer thereof, substantially free of its other stereoisomers.

8. The pharmaceutical composition of claim 3 where the said fenamic acid derivative is mefenamic acid or a salt of thereof or any therapeutically active stereoisomer thereof, substantially free of its other stereoisomers.
9. The pharmaceutical composition of claim 3 where the said fenamic acid derivative is etofenamate or a salt of thereof or any therapeutically active stereoisomer thereof, substantially free of its other stereoisomers.

10. The pharmaceutical composition of claim 3 where the said acetic acid derivative is etodolac or a salt of thereof or any therapeutically active stereoisomer thereof, substantially free of its other stereoisomers.

11. The pharmaceutical composition of claim 3 where the said acetic acid derivative is acemetacin or a salt of thereof or any therapeutically active stereoisomer thereof, substantially free of its other stereoisomers.

12. The pharmaceutical composition of claim 3 where the said acetic acid derivative is indomethacin or a salt of thereof or any therapeutically active stereoisomer thereof, substantially free of its other stereoisomers.

13. The pharmaceutical composition of claim 3 where the said propionic acid derivative is tiaprofenic acid or a salt of thereof or any therapeutically active stereoisomer thereof, substantially free of its other stereoisomers.

14. The pharmaceutical composition of claim 3 where the said propionic acid derivative is naproxen or a salt of thereof or any therapeutically active stereoisomer thereof, substantially free of its other stereoisomers.

15. The pharmaceutical composition of claim 3 where the said propionic acid derivative is oxaprozin or a salt of thereof or any therapeutically active stereoisomer thereof, substantially free of its other stereoisomers.

16. The pharmaceutical composition of claim 3 where the said coxib is celecoxib or a salt of thereof or any therapeutically active stereoisomer thereof, substantially free of its other stereoisomers.

17. The pharmaceutical composition of claim 3 where the said coxib is rofecoxib or a salt of thereof or any therapeutically active stereoisomer thereof, substantially free of its other stereoisomers.

18. The pharmaceutical composition of claim 3 where the said coxib is lumiracoxib or a salt of thereof or any therapeutically active stereoisomer thereof, substantially free of its other stereoisomers.
19. The pharmaceutical composition of claim 1 where the said coxib is valdecoxib or a salt of thereof or any therapeutically active stereoisomer thereof, substantially free of its other stereoisomers.

20. The pharmaceutical composition of claim 3 where the said other non-steroidal anti-inflammatory is nimesulide or a salt of thereof or any therapeutically active stereoisomer thereof, substantially free of its other stereoisomers.

21. The pharmaceutical composition of claim 1, wherein the weight ratio of muscle relaxant to non-steroidal anti-inflammatory agent varies from 1:300 to 16:3,75.

22. The pharmaceutical composition as defined by claim 1, comprising from about 4 mg to 16 mg of thiocolchicoside and from about 4 mg to 16 mg of lornoxicam.

23. The pharmaceutical composition as defined by claim 1, comprising from about 4 mg to 16 mg of thiocolchicoside and from about 10 mg to 40 mg of tenoxicam.

24. The pharmaceutical composition as defined by claim 1, comprising from about 4 mg to 16 mg of thiocolchicoside and from about 3,75 mg to 15 mg of meloxicam.

25. The pharmaceutical composition as defined by claim 1, comprising from about 4 mg to 16 mg of thiocolchicoside and from about 5 mg to 40 mg of piroxicam.

26. The pharmaceutical composition as defined by claim 1, comprising from about 4 mg to 16 mg of thiocolchicoside and from about 250 mg to 1500 mg of mfenamic acid.

27. The pharmaceutical composition as defined by claim 1, comprising from about 4 mg to 16 mg of thiocolchicoside and from about 500 mg to 1000 mg of etofenamate.

28. The pharmaceutical composition as defined by claim 1, comprising from about 4 mg to 16 mg of thiocolchicoside and from about 300 mg to 1200 mg of etodolac.

29. The pharmaceutical composition as defined by claim 1, comprising from about 4 mg to 16 mg of thiocolchicoside and from about 30 mg to 180 mg of acemetacin.

30. The pharmaceutical composition as defined by claim 1, comprising from about 4 mg to 16 mg of thiocolchicoside and from about 25 mg to 200 mg of indometacin.

31. The pharmaceutical composition as defined by claim 1, comprising from about 4 mg to 16 mg of thiocolchicoside and from about 200 mg to 600 mg of tiaprofenic acid.

32. The pharmaceutical composition as defined by claim 1, comprising from about 4 mg to 16 mg of thiocolchicoside and from about 250 mg to 1000 mg of napro xen.
33. The pharmaceutical composition as defined by claim 1, comprising from about 4 mg to 16 mg of thiocolchicoside and from about 300 mg to 1200 mg of oxaprozin.

34. The pharmaceutical composition as defined by claim 1, comprising from about 4 mg to 16 mg of thiocolchicoside and from about 50 mg to 200 mg of nimesulide.

35. The pharmaceutical dosage form of claim 1, wherein the pharmaceutical dosage form is adapted for oral, buccal, ocular, otic, dermal, rectal, epidermal, topical, transdermal, implant, mucosal, parenteral, sublingal, nasal, or pulmonary delivery.

36. The pharmaceutical dosage form of claim 1, wherein the pharmaceutical dosage form is used for oral administration.

37. The pharmaceutical dosage form of claim 1, wherein the pharmaceutical dosage form is used for parenteral administration.

38. The pharmaceutical dosage form of claim 1, wherein the dosage form is selected from the group consisting of a gel, cream, ointment, tablet, capsule, bead, pellet, granule, liquid, suspension, syrup, powder, injectable suspension, injectable powder and injectable liquid.

39. The pharmaceutical composition of claim 1 wherein the composition is administrated in the form of a tablet.

40. The pharmaceutical composition of claim 1 wherein the composition is administrated in the form of a capsule.

41. The pharmaceutical composition of claim 1 wherein the composition is administrated in the form of a solution for injection.

42. The pharmaceutical composition of claim 1 wherein the composition is administrated in the form of a powder for injection.

43. The pharmaceutical composition of claim 1 wherein the composition is administrated in the form of a suspension for injection.

44. The pharmaceutical dosage form of claim 1, wherein the dosage form independently provides a controlled, delayed, sustained, immediate, timed, slow or rapid release of each of the muscle relaxant and the non-steroidal anti-inflammatory agent.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/704 A61K45/06 A61P19/00 A61K31/5415 A61K31/542

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
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<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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<tr>
<td>X</td>
<td>ANACARDIO R ET AL: &quot;Physicochemical compatibility between thiocolchicoside injections (Miotens(R)) and pharmaceutical products frequently used for combined therapy&quot; FARMACO, SOCIETA CHIMICA ITALIANA, PAVIA, IT, vol. 57, no. 11, 1 November 2002 (2002-11-01), pages 925-930, XP008111399 ISSN: 0014-827X cited in the application abstract page 925, column 1, paragraph 1; tables 1,4</td>
<td>1-7, 21-25, 35-44</td>
</tr>
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</table>

Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents:
  *A* document defining the general state of the art which is not considered to be of particular relevance
  *E* earlier document but published on or after the international filing date
  *L* document which may throw doubts on priority claim(s) or which is cited to establish the 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
  *I* 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
15 February 2010

Date of mailing of the international search report
02/07/2010

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

Authorized officer
Leherte, Chantal
<table>
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<th>Category</th>
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<td>X</td>
<td>PIFFERI G: &quot;COMPATIBILITA CHIMICO-FI-SICA TRA TIOCOLCHICOSIDE E FARMACI ANTINFIA MMATORI NON STEROIDEI. - Chemico-physical compatibility of thio-colchicoside with nonsteroidal anti-inflammatory drugs&quot; BOLLETTINO CHIMICO FARMACEUTICO, SOCIETA EDITORIALE FARMACEUTICA, MILANO, IT, vol. 132, no. 6, 1 June 1993 (1993-06-01), pages 203-209, XP000566124 ISSN: 0006-6648 page 205, column 1, paragraph 1; tables 5, 6, 7</td>
<td>1-7, 21-25, 35-44</td>
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<td>X</td>
<td>WO 2006/097149 A1 (PHARMAFILE S R L [IT]; CILURZO FRANCESCO [IT]; MINGHETTI PAOLA [IT]) 21 September 2006 (2006-09-21) example 3</td>
<td>1-7, 21-25, 35-44</td>
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</tbody>
</table>
This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [ ] Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

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

3. [ ] Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

see additional sheet

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

2. [ ] As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

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

4. [x] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

see annex

Remark on Protest

[ ] The additional search fees were accompanied by the applicant’s protest and, where applicable, the payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant’s protest but the applicable protest fee was not paid within the time limit specified in the invitation.

[ ] No protest accompanied the payment of additional search fees.
This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 4-7, 22-25(completely); 1-3, 21, 35-44(partially)

   A pharmaceutical composition for use in the treatment of musculoskeletal disorders and the treatment of pain and inflammation in mammalian organism and adapted for unit administration comprising a pharmaceutically effective amount of:
   a) one muscle relaxant;
   b) at least one non-steroidal anti-inflammatory drug selected from oxicams,
   c) at least one pharmaceutically acceptable non-toxic carrier.

2. claims: 8-9, 26-27(completely); 1-3, 21, 35-44(partially)

   A pharmaceutical composition for use in the treatment of musculoskeletal disorders and the treatment of pain and inflammation in mammalian organism and adapted for unit administration comprising a pharmaceutically effective amount of:
   a) one muscle relaxant;
   b) at least one non-steroidal anti-inflammatory drug selected from fenamic acid derivatives,
   c) at least one pharmaceutically acceptable non-toxic carrier.

3. claims: 10-12, 28-30(completely); 1-3, 21, 35-44(partially)

   A pharmaceutical composition for use in the treatment of musculoskeletal disorders and the treatment of pain and inflammation in mammalian organism and adapted for unit administration comprising a pharmaceutically effective amount of:
   a) one muscle relaxant;
   b) at least one non-steroidal anti-inflammatory drug selected from acetic acid derivatives,
   c) at least one pharmaceutically acceptable non-toxic carrier.

4. claims: 13-15, 31-33(completely); 1-3, 21, 35-44(partially)
A pharmaceutical composition for use in the treatment of musculoskeletal disorders and the treatment of pain and inflammation in mammalian organism and adapted for unit administration comprising a pharmaceutically effective amount of:
   a) one muscle relaxant;
   b) at least one non-steroidal anti-inflammatory drug selected from propionic acid derivatives,
   c) at least one pharmaceutically acceptable non-toxic carrier.

5. claims: 16-19(completely); 1-3, 21, 35-44(partially)

A pharmaceutical composition for use in the treatment of musculoskeletal disorders and the treatment of pain and inflammation in mammalian organism and adapted for unit administration comprising a pharmaceutically effective amount of:
   a) one muscle relaxant;
   b) at least one non-steroidal anti-inflammatory drug selected from coxibs,
   c) at least one pharmaceutically acceptable non-toxic carrier.

6. claims: 20, 34(completely); 1-3, 21, 35-44(partially)

A pharmaceutical composition for use in the treatment of musculoskeletal disorders and the treatment of pain and inflammation in mammalian organism and adapted for unit administration comprising a pharmaceutically effective amount of:
   a) one muscle relaxant;
   b) nimesulide,
   c) at least one pharmaceutically acceptable non-toxic carrier.
<table>
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<th>Patent document cited in search report</th>
<th>Publication date</th>
<th>Patent family member(s)</th>
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<td></td>
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