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(71) Applicant *(for all designated States except US)*: **BIOLAB SANUS FARMACÊUTICA LTDA.** [BR/BR]; Av. Dos Bandeirantes 5386, Planalto Paulista, 04071-900 São Paulo (BR).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: **JÚNIOR, Dante Alario** [BR/BR]; Rua Ângelo Paris Fornazza 211, Chácara Santo Ântônio, 04728-170 São Paulo (BR).

(74) Agents: **DI BLASI, Gabriel** et al.; Rua do Ouvidor 121, 11° andar, Centro, 20040-030 Rio De Janeiro (BR).

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(54) Title: PHARMACEUTICAL COMPOSITION COMPRISING CYCLOBENZAPRINE AND ACECLOFENAC IN ASSOCIATION

(57) Abstract: The present invention relates to an association of active ingredients. More specifically: to an association of cyclobenzaprine and aceclofenac. Additionally, the present invention is also related to the use of aceclofenac and cyclobenzaprine, in association for the preparation of a medicine useful in the treatment of painful muscular diseases, as well as to a method of treatment of painful muscular diseases using an association of aceclofenac and cyclobenzaprine.

"PHARMACEUTICAL COMPOSITION COMPRISING CYCLOBENZAPRINE AND ACECLOFENAC IN ASSOCIATION".

Field of the invention

The present invention refers to a pharmaceutical composition comprising an association of active ingredients. More specifically: the pharmaceutical composition comprises an association of cyclobenzaprine and aceclofenac. Additionally, the present invention also refers to the use of aceclofenac and cyclobenzaprine in association for preparing a medicine useful in the treatment of painful muscular conditions, as well as a method for treatment of painful muscular conditions using a pharmaceutical composition comprising an association of aceclofenac and cyclobenzaprine.

Background of the invention:

Aceclofenac, also named 2-[2-[2-[(2,6-dichlorophenyl)amino]phenyl]acetyl]oxyacetic acid (CAS RN: 89796-99-6) is a nonsteroidal anti-inflammatory agent, with remarkable anti-inflammatory, analgesic and antipyretic properties. The usual dosage of aceclofenac, normally presented in its acid form, is of two daily doses of 100 mg.

Cyclobenzaprine, also named 3-(5H-dibenzo[a,d]cyclohepten-5-ylidene)-N,N-dimethyl-1-propanamine is a tricyclic muscle relaxant used in the treatment of muscular spasm related with painful musculoskeletal conditions. Usual dosages of cyclobenzaprine (normally presented in the form of hydrochloride salt) are of 3 daily dosages of 5 mg or 10 mg, and the main side effects of the drug are related to drowsiness and dizziness.

Although there are several references about the

combined use of cyclobenzaprine with nonsteroidal anti-inflammatory drugs, results of clinical controlled studies are non-conclusive about the real benefit of the use of said association, mainly when the potential side effects of cyclobenzaprine are considered.

Aiming for the obtainment of products with a suitable safety and efficacy profile, as well as easiness of administration for the treatment of diseases which have concomitancy between inflammatory, painful spasm and excessive muscular contraction components, the present inventors noted that association of cyclobenzaprine with aceclofenac can be specially interesting, due to the high analgesic and anti-inflammatory strength of aceclofenac associated to its favorable safety profile, its fast action outset and its prolonged effect.

In a complementary aspect, the present inventors noted that, due to chemical interactions, it is particularly interesting the vehiculation of cyclobenzaprine and aceclofenac in pharmaceutical products that avoid contact between the two active ingredients and/or prevent such interactions.

Within the best knowledge of the present inventors, there is not, in the present state of the art, any publication concerning the efficacy and safety of the specific association of aceclofenac with cyclobenzaprine, neither about the chemical interaction between said active ingredients.

Description of the invention

In a first main aspect, the present invention is related to a pharmaceutical composition comprising an association of (i) cyclobenzaprine, its salts or solvates, (ii) aceclofenac, its salts or solvates and, optionally,

(iii) one or more excipients pharmaceutically acceptable.

According to the present invention, the term association comprises products in which cyclobenzaprine and aceclofenac are comprised in a single dosage unit (for example, single tablet or capsule), as well as in the form of kits for combined drug vehiculation (for example, blisters comprising aceclofenac tablets and cyclobenzaprine tablets or set of flasks comprising cyclobenzaprine capsules and flasks comprising aceclofenac capsules).

According to the present invention, the term cyclobenzaprine comprises a cyclobenzaprine in the form of free base, as well as salts of cyclobenzaprine with organic or inorganic acids and hydrates or solvates thereof. According to a preferred aspect, cyclobenzaprine is in hydrochloride salt form.

According to the present invention, the term aceclofenac comprises aceclofenac in acid form, as well as salts of aceclofenac with organic or inorganic bases and hydrates or solvates thereof. According to a preferred aspect, aceclofenac is in acid form.

Examples of pharmaceutically acceptable excipients are, for instance, described in the publication: Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, Pennsylvania, USA.

In a preferred aspect of the present invention, cyclobenzaprine and aceclofenac are vehicled in pharmaceutical forms and/or products that avoid contact between the two active ingredients.

Examples of pharmaceutical forms that avoid contact between two active ingredients are: triple layer tablets wherein each active ingredient is disposed in a separate layer by an intermediate isolating layer; capsules

comprising cyclobenzaprine based granulates and aceclofenac based granulates, separately and preferably coated; capsules comprising cyclobenzaprine based tablets and aceclofenac based tablets, separately and preferably coated.

Examples of pharmaceutical products that avoid contact between the two ingredients are: blisters comprising cyclobenzaprine tablets and aceclofenac tablets, separately; groups of flasks comprising aceclofenac capsules and flasks comprising cyclobenzaprine capsules, separately; cyclobenzaprine and aceclofenac based capsules and/or tablets comprising coated crystals of cyclobenzaprine and/or coated crystals of aceclofenac.

The present invention is not limited by the type or release path of the active ingredients; involving products of immediate, controlled, programmed release, or products of fast disintegration, etc. In the same way, the present invention is not limited by the route of administration of the active ingredients; involving oral, intramuscular, transdermic, intranasal, rectal administration, etc. According to a preferred aspect, the administration route is oral.

The present invention refers to associations of cyclobenzaprine and aceclofenac in pharmaceutically acceptable dosages. According to a preferred aspect, the aceclofenac dosage, in each take, is about 100 mg and preferably cyclobenzaprine dosages in each take are about 2.5 mg to about 10.0 mg.

In a second preferred aspect, the present invention comprises the use of aceclofenac and cyclobenzaprine, together in the preparation of a medicine useful in the treatment of painful muscular diseases.

In a third preferred aspect, the present invention is related to a method for treatment of painful muscular diseases comprising administration of aceclofenac and cyclobenzaprine together.

Examples of painful muscular diseases are: acute and chronic low back pain, cervicalgia, cervicobrachial syndrome, lumbosciatalgia, chronic fatigue syndrome, myofascial pain syndrome, complex regional pain syndrome, polymyalgia rheumatica, polymyositis, dermatomyositis, among others.

According to a preferred aspect, the present invention comprises simultaneously administration of cyclobenzaprine and aceclofenac or administration of cyclobenzaprine and aceclofenac in a time interval less than 60 minutes between the dosages of each drug.

According to a preferred aspect, the present invention still comprises administration of an effective amount of the pharmaceutical composition of the present invention, preferably, in dosages of about 100 mg aceclofenac in each take and dosages of about 2.5 mg to about 10 mg of cyclobenzaprine in each take.

According to another preferred aspect, the present invention comprises a dosage of two daily doses of cyclobenzaprine and two daily doses of aceclofenac.

Examples:

Experimental examples are following described in a detailed manner that illustrates the present invention without limiting its scope:

Example 1: Production of aceclofenac 100 mg tablets

Batch size: 3,960 tablets

Tablet core:	
(a) aceclofenac	396 g

Tablet core:	
(b) microcrystalline cellulose	356 g
(c) sodium croscamelose	12 g
(d) glyceryl stearate palmitate	8 g
(e) Povidone	24 g
(f) Ethyl alcohol	350 mL

- Sieve in mesh 20 the ingredients (a), (b) and half of the (c) volume. Transfer in a mixer-granulator and mix for 5 minutes.

- In a proper recipient, add and dissolve (e) and (f), forming the granulating solution.

- Add the granulating solution over the powder formed in the first step, in the mixer-granulator, and proceed to a new mixture until the formation of a wet mass.

- Pass the wet mass through mesh 6 and dry in a fluidized bed at 37 – 40 °C.

- Calibrate the granulated in 1.0 mm rough mesh.

- Sieve the other (c) half in mesh 40, add to the calibrated granulate and mix for 5 minutes.

- Sieve (d) in mesh 60, add to the granulate and mix for 3 minutes.

- The resulting final mixture was compressed in oblong tablets, with the use of punctures of 11 x 6.5 mm, with the following characteristics: average weight: 202 mg; dimensions: 11 x 6.5 mm; hardness: 4.5 to 12.5 kPa; moisture content to 105°C/10min: maximum of 3%; friability: maximum of 1%.

Coated tablet production:

Coating suspension	
(g) Hypromelose / macrogol	19 g
(h) Titanium dioxide	4 g

Coating suspension	
(i) Polyethylene glycol	0.8 g
(j) Distilled water	250 mL

- In an suitable vessel containing 200 mL of (j), add (g), under agitation and keep agitation until the solution gets clear (I).

- Prepare the suspension of the add pigment, in an suitable vessel, (h) over 50 mL of (j) and homogenize in a shaker for 3 minutes (II).

- Mix the solution (I), (II) and (i), with smooth agitation, until the formation of a homogeneous suspension (coating suspension).

- Make the application of the coating suspension over the tablet cores, by aspersion, in a coating equipment with air forced circulation.

Average weight of the tablet core: 202 mg; average weight of the coated tablet: 208 mg.

Example 2A: Production of cyclobenzaprine 2.5 mg tablets

Batch size: 3,440 tablets

Tablet core:	
(a) cyclobenzaprine hydrochloride	8.6 g
(b) microcrystalline cellulose	68.8 g
(c) tricalcium phosphate	6.9 g
(d) sodium croscamelose	3.1 g
(e) lactose	100.4 g
(f) magnesium stearate	1.4 g

- Sieve in mesh 20 the ingredients (a), (b), (c), (d) and (e). Transfer for a mixer-granulator and mix for 10 minutes.

- Sieve (f) in mesh 60, add to the granulate and mix for 3 minutes.

- The resulting final mixture was compressed in oblong tablets, with the use of punctures of 6.5 x 3.2 mm, with the following characteristics: average weight: 55 mg; dimensions: 6.5 x 3.2 mm; hardness: 4 to 9.0 kPa; tablet's moisture content in 105°C/10 min: maximum of 6%; friability: maximum of 1%.

Coated tablet production:

Coating suspension	
(g) Hypromelose / macrogol	5.5 g
(h) Titanium dioxide	1.4 g
(i) Yellow iron oxide	0.1 g
(j) Distilled water	250 mL

- In an suitable vessel containing 200 mL of (j), add (g), under agitation and keep agitation until the solution becomes clear (I).

- Prepare the suspension of the add pigment, in a suitable vessel, (h) and (i) over 50 mL of (j) and homogenize in a shaker for 3 minutes (II).

- Mix (I) and (II) with smooth agitation, until the formation of a homogeneous suspension (coating suspension).

- Make the application of the coating suspension over the tablet cores, by aspersion, in a coating equipment with air forced circulation.

Average weight of the tablet core: 55 mg; average weight of the coated tablet: 57 mg.

Example 2B: Production of cyclobenzaprine 5,0 mg tablets

Batch size: 3,404 tablets

Tablet core:

Tablet core:	
(a) cyclobenzaprine hydrochloride	17.0 g
(b) microcrystalline cellulose	138.2 g
(c) tricalcium phosphate	14.3 g
(d) sodium croscamelose	6.5 g
(e) lactose	195.4 g
(f) magnesium stearate	3.06 g

The tablet's core was prepared as the example 2A. The final mixture was compressed in oblong tablets, with the use of punctures of 8.5 x 5 mm, with the following characteristics: average weight: 110 mg; dimensions: 8.5 x 5 mm; hardness: 5 to 9.0 kPa; tablet's moisture content at 105°C/10 min: maximum of 6%; friability: maximum of 1%.

Coated tablet production:

Coating suspension	
(g) Hypromelose / macrogol	9.0 g
(h) Titanium dioxide	2.0 g
(i) Yellow iron oxide	0.2 g
(j) Distilled water	250 mL

The coating suspension was produced as in Example 2A.

Average weight of the tablet core: 100 mg; average weight of the coated tablet: 113 mg.

Example 2C: Production of cyclobenzaprine 10.0 mg tablets.

Batch size: 3,333 tablets

Tablet core:	
(a) cyclobenzaprine hydrochloride	33.4 g
(b) microcrystalline cellulose	340 g
(c) tricalcium phosphate	33.3 g
(d) sodium croscamelose	13.3 g

Tablet core:	
(e) lactose	339.6 g
(f) magnesium stearate	7.0 g

The tablet's core was prepared as the example 2A. The final mixture was compressed in oblong tablets, with the use of punctures of 12 x 5.5 mm, with the following characteristics: average weight: 230 mg; dimensions: 12 x 5.5 mm; hardness: 7 to 10.0 kPa; tablet's moisture content at 105°C/10 min: maximum of 6%; friability: maximum of 1%.

Coated tablet production:

Coating suspension	
(g) Hypromelose / macrogol	19.0 g
(h) Titanium dioxide	4.0 g
(i) Yellow iron oxide	0.33 g
(j) Distilled water	250 mL

The coating suspension was produced as in Example 2A.

Average weight of the tablet core: 230 mg; average weight of the coated tablet: 237 mg.

Example 3: Kit containing aceclofenac tablets and cyclobenzaprine tablets in single blisters.

In a PVDC blister with two vesicles are conditioned: one aceclofenac 100 mg tablet (Example 1) and one cyclobenzaprine 5.0 mg tablet (Example 2B). After the closure with an aluminum foil, fourteen of the said blisters are packed in a hard paper cartridge with the instructions to take the blister content in intervals of 12 hours.

Example 4: Kit containing aceclofenac tablets and cyclobenzaprine tablets in cardboards.

Two aceclofenac tablets with 100 mg of dosage (Example

1) are conditioned in a blister with two vesicles. Two cyclobenzaprine tablets with 10.0 mg of dosage (Example 2C) are conditioned in a blister with two vesicles. After the closure with aluminum foil, each of the two blisters are then stick to cardboard made of hard paper, with two lines of 4 orifices, aligned in a way to permit blister's mortise, with the formation of two lines of blistered tablets, with the vesicles exposed through the holes; being each of the lines composed by an aceclofenac tablet and a cyclobenzaprine tablet. Five of said cardboards are packed in a hard paper cartridge, along with intake instructions, at intervals of 12 hours, of the content of one line of 2 tablets, composed by one aceclofenac tablet and one cyclobenzaprine tablet.

Example 5. Production of aceclofenac granulate.

Batch size: 800 g

Aceclofenac granulate:	
(a) aceclofenac	396 g
(b) microcrystalline cellulose	356 g
(c) sodium croscamelose	12 g
(d) glyceryl stearate palmitate	8 g
(e) povidone	24 g
(f) ethylic alcohol	350 mL

- Sieve in mesh 20 the ingredients (a), (b), and half of the (c) volume. Transfer for a mixer-granulator and mix for 5 minutes.

- In a proper recipient, add and dissolve (e) and (f), forming the granulating solution.

- Add and solubilize (e) in the granulating solution.

- Add the granulating solution over the powder formed in the first step, in the mixer-granulator, and proceed to

a new mixture until the formation of a wet mass.

- Pass the wet mass through mesh 6 and dry in a fluidized bed to 37 - 40 °C.

- Calibrate the granulate in 1,0 mm rough mesh.

- Sieve the other (c) half in mesh 40, add to the calibrated granulate and mix for 5 minutes.

- Sieve (d) in mesh 60, add to the granulate and mix for 3 minutes.

Example 6. Production of aceclofenac granulate.

Batch size: 767 g

Tablet core:	
(a) cyclobenzaprine hydrochloride	33.4 g
(b) microcrystalline cellulose	340 g
(c) tricalcium phosphate	33.3 g
(d) sodium croscamelose	13.3 g
(e) lactose	339.6 g
(f) magnesium stearate	7.0 g

- Sieve in mesh 20 the ingredients (a), (b), (c), (d) and (e). Transfer for a mixer-granulator and mix for 10 minutes.

- Sieve (f) in mesh 60, add to the granulate and mix for 3 minutes.

Example 7: Production of capsules containing one aceclofenac based tablet and one cyclobenzaprine based tablet.

In a zero size gelatin capsule are conditioned: one aceclofenac tablet with 100 mg dosage (Example 1) and one cyclobenzaprine tablet with 5.0 mg dosage (Example 2B).

Example 8. Comparative stability study of cyclobenzaprine hydrochloride and aceclofenac together and in an isolate manner.

One sample of pure cyclobenzaprine hydrochloride, one sample of pure aceclofenac and one sample of a mixture of cyclobenzaprine hydrochloride and aceclofenac in a ratio of 1 to 1 were disposed in opened glass flasks and were put in an oven with temperature of 50°C and relative moisture of 90%.

The chromatographic analysis of the samples after a 30 day period showed a significant drop in the content of cyclobenzaprine and aceclofenac in the flask in which the active ingredients were mixed, while the active contents remained unaltered in the flasks that were isolated.

Example 9. Study of stability of aceclofenac coated tablets (100 mg) and cyclobenzaprine hydrochloride coated tablets (10 mg).

Aceclofenac coated tablets (Example 1) and 10 mg cyclobenzaprine hydrochloride coated tablets (Example 2C) were encapsulated in gelatin capsules, which where then packaged in glass flasks hermetically closed. The samples were put in an oven at 40°C and 75% of relative moisture. After a 60 day period the tablet analysis was made, and it was verified that the content of the actives was practically unaltered.

Example 10: Evaluation of the safety and efficacy of the association of cyclobenzaprine hydrochloride and aceclofenac in comparison with the isolated drugs.

To evaluate the safety and synergism of the drugs in association in the treatment of acute low back pain in the 7 day period, a multicentric clinical study will be made, phase IIb/III, randomized, double-blind, with 228 assessable patients, conducted under the orientation of qualified physicians.

In the clinical study will be evaluated: (a) the

efficacy of the association of cyclobenzaprine hydrochloride and aceclofenac in the treatment of acute lombalgia in comparison with the single drugs; (b) the safety and tolerability of the association of cyclobenzaprine hydrochloride and aceclofenac in the treatment of acute low back pain in comparison with the single drugs; (c) the efficacy and safety of two different doses of cyclobenzaprine hydrochloride (2.5 mg and 5.0 mg) in association with aceclofenac.

For the fulfillment of the clinical study the patients will be selected in accordance with the following criteria: (a) men and women between 18 and 65 years old; (b) back pain narration in the last 5 days, the continuous pain being increased by movement attempts associated with the painful palpation in the back area, with irradiation at maximum to the knees. Will be included both patients that had its first pain episode, as the ones with recurrent pain; and (c) evaluation of the Analogical Visual Scale (AVS) must be ≥ 60 mm in the basal evaluation; and (d) signature of the term of compliance free and explained by the ethical committee.

The selected patients will be divided in 4 groups that will receive the following treatment: (group 1) aceclofenac 100 mg + cyclobenzaprine hydrochloride 2.5 mg BID; (group 2) aceclofenac 100 mg + cyclobenzaprine hydrochloride 5.0 mg BID; (group 3) aceclofenac 100 mg BID; (group 4) cyclobenzaprine hydrochloride 10 mg BID; Paracetamol 750 will be used in the rescue medicine.

To verify the efficacy the evaluation will be divided in two visits in the 4^{th} and 8^{th} days.

In the visit made in the 4^{th} day will be evaluated: (a) the reduction of pain intensity in relation with the

basal (day 1) through AVS; (b) changes in the punctuation of the questionnaire of Roland Morris' life quality in comparison with the basal (day 1).

In the visit made in the 8th day, end of treatment, will be evaluated: (a) the intensity's reduction of the pain in comparison to the basal (day 1) through AVS; (b) the number of days for the significant pain remission, defined as punctuation in AVS $\leq$ 10 mm; (c) change in the punctuation of the questionnaire of Roland Morris' life quality in comparison with the basal (day 1); (d)_ rescue medicine's consumption; (e) patient's global evaluation by the physician; and (f) treatment's global evaluation by the patient itself.

To verify the treatment's safety will be evaluated: (a) the spontaneous narration of adverse events; (b) changes in the punctuation of the questionnaire of Epworth's daytime somnolence in the days 4 and 8 compared with the basal (day 1); and (c) the compliance to the treatment.

It is important to highlight that the present invention is not limited to the description here presented, also contemplating all changes and adaptations that does not apart from the spirit and scope of the invention.

CLAIMS

1. Pharmaceutical composition wherein it comprises an association of: (i) cyclobenzaprine, its salts or solvates, (ii) aceclofenac, its salts or solvates and, optionally, (iii) one or more pharmaceutically acceptable excipients.

2. Pharmaceutical composition according to claim 1 wherein cyclobenzaprine is not in contact with aceclofenac.

3. Pharmaceutical composition according to claim 1 or 2 wherein it comprises aceclofenac and cyclobenzaprine in separated dosage units.

4. Pharmaceutical composition according to any of the preceding claims wherein it is in the form of blisters comprising cyclobenzaprine dosage units and aceclofenac dosage units, separately.

5. Pharmaceutical composition according to claim 1, 2 or 3 wherein it is in the form of a group of flasks comprising aceclofenac dosage units and other flasks comprising cyclobenzaprine dosage units, separately.

6. Pharmaceutical composition according to any of the preceding claims wherein it is in the oral usage's pharmaceutical form.

7. Pharmaceutical composition according to any of the preceding claims wherein it comprises aceclofenac and cyclobenzaprine in a single dosage unit.

8. Pharmaceutical composition according to claim 7 wherein it is a tablet.

9. Pharmaceutical composition according to claim 7 wherein it is a hard capsule.

10. Pharmaceutical composition according to claim 8 wherein it is a multilayer tablet in which the layer comprising cyclobenzaprine is physically separated

from the layer comprising aceclofenac by an isolating intermediate layer.

11. Pharmaceutical composition according to claim 9 wherein it is a capsule comprising cyclobenzaprine granules or tablets and aceclofenac granules or tablets.

12. Pharmaceutical composition according to claim 11 wherein the referred cyclobenzaprine or aceclofenac granules or tablets are coated.

13. Use of aceclofenac and cyclobenzaprine together wherein it is in the preparation of a medicine useful in the treatment of painful muscular diseases.

14. Use according to claim 13 wherein it comprises simultaneously administration of cyclobenzaprine and aceclofenac or administration of cyclobenzaprine and aceclofenac in a time interval, between the doses of each drug, of less than 60 minutes.

15. Use according to claim 13 or 14 wherein it is in doses of about 100 mg of aceclofenac in each take, and doses of about 2.5 mg to about 10.0 mg of cyclobenzaprine in each take.

16. Use according to claim 13, 14 or 15 wherein it comprises two daily doses of cyclobenzaprine and two daily doses of aceclofenac.

17. Use according to any claims from 13 to 16 wherein said painful muscular disease is selected from the group consisting of: acute and chronic low back pain, cervicalgia, cervicobrachial syndrome, lumbosciatalgia, chronic fatigue syndrome, myofascial pain syndrome, complex regional pain syndrome, polymyalgia rheumatica, polymyositis, dermatomyositis.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/BR07/00139

A. CLASSIFICATION OF SUBJECT MATTER
IPC: **A01N 37/12**(2006.01),**37/44**(2006.01);**A61K 31/195**(2006.01)

USPC: 514/563
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)
U.S. : 514/563

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 6,599,529 B1 (SKINHOJ et al) 29 July 2003 (29.07.2003), abstract, columns 17-18.	1-3, 13 and 14
Y	US 2003/0068365 A1 (SUVANPRAKORN et al) 10 April 2003 (10.04.2003), abstract, pages 5, 12 and 17.	1-3, 13 and 14

☐ 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 application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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Authorized officer
Leonard M. Williams Telecia D. Roberts for

Telephone No. 571-272-1600

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/BR07/00139

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

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.: 4-12 and 15-17
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of any 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. ☐ 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.:

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.