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(54) Title: ORAL ANTIDEPRESSANT FORMULATION COMPRISING A SELECTIVE SEROTONIN REUPTAKE INHIBITOR

(57) Abstract: Oral antidepressant formulation comprising an effective antidepressant amount of one or more selective serotonin reuptake inhibitors, and an effective amount of at least a compound selected from the group consisting of acetylsalicylic acid, derivatives of acetylsalicylic acid, heparin, heparin like compounds, and mixtures thereof, for reducing the onset of action of the selective serotonin reuptake inhibitor(s).



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**ORAL ANTIDEPRESSANT FORMULATION COMPRISING A
SELECTIVE SEROTONIN RUPTAKE INHIBITOR**

5 The present invention relates to a formulation and a method for reducing the onset of action of the selective serotonin reuptake inhibitor(s).

Selective serotonin reuptake inhibitors (SSRI) are compounds having a higher selectivity for serotonin over noradrenaline uptake or dopamine uptake, preferably over noradrenaline and dopamine uptake.

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The major problem of SSR is the onset time required for obtaining an action, said onset being often greater than 4 weeks. This means a great risk that the patient decides him self to stop the treatment in view of the lack of action after two weeks treatment.

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The present invention has for object an oral antidepressant formulation with a reduced onset of action. It has been discovered that by using specific compound(s), it was possible to reduce the onset of action of drugs, such as SSRIs.

20 The invention relates to an oral antidepressant formulation comprising an effective antidepressant amount of one or more selective serotonin reuptake inhibitors, and an effective amount of at least a compound or additive selected from the group consisting of acetylsalicylic acid (ASA), derivatives of acetylsalicylic acid (such as salts thereof, ester thereof, etc., the acid form being however preferred), heparin,
25 heparin like compounds, and mixtures thereof, for reducing the onset of action of the selective serotonin reuptake inhibitor(s). ASA and derivatives thereof (such as salts, esters thereof) and mixtures thereof are however the preferred compound(s) to be combined with the SSRI compound.

30 While the mechanism of action is not clear, it seems that the reduced onset is due to one or more of the following reasons :

- better passage of the SSRI in the blood

- higher fluidity of the blood
 - SSRI is mainly deposited in the brain
 - activation of the brain, so that the brain has a higher receptivity for the SSRI
- 5 - production of serotonin in the brain due to the additive.

One or more other advantages of the formulation of the invention are :

- quicker action
 - less headaches
- 10 - possibility to reduce the doses
- less risk factor for suicide (for example due to the immediate action of ASA)
 - etc.

15 The formulation comprises advantageously an effective amount of at least a compound selected from the group consisting of acetylsalicylic acid, derivatives of acetylsalicylic acid, heparin, heparin like compounds, and mixtures thereof, for reducing at least 15%, advantageously at least 20%, preferably at least 50% the average onset of action of the selective serotonin reuptake inhibitors.

20 Preferably, the effective amount of one or more compounds for reducing the onset of action of the selective serotonin reuptake inhibitor(s) is lower than 50 times the amount of selective serotonin reuptake inhibitor(s).

Most preferably, the effective amount of one or more compounds for reducing the onset of action of the selective serotonin reuptake inhibitor(s) is lower than 10

25 times, advantageously lower than 5 times, preferably lower than 1 times the amount of selective serotonin reuptake inhibitor(s).

According to a preferred embodiment, the formulation comprises a quick release effective amount of at least a compound selected from the group consisting of acetylsalicylic acid, derivatives of acetylsalicylic acid, diaspirin, heparin, heparin

30 like compounds, and mixtures thereof, for reducing the onset of action of the selective serotonin reuptake inhibitor(s).

According to a detail of a specific embodiment, the formulation comprises particles, core, microparticles, spherical particles comprising at least one selective serotonin reuptake inhibitor and possibly at least a compound selected from the group consisting of acetylsalicylic acid, derivatives of acetylsalicylic acid, heparin, heparin like compounds, and mixtures thereof, said particles, core, microparticles, spherical particles being advantageously provided with a coating comprising at least a compound selected from the group consisting of acetylsalicylic acid, derivatives of acetylsalicylic acid, diaspirin, heparin, heparin like compounds, and mixtures thereof, for reducing the onset of action of the selective serotonin reuptake inhibitor(s), said coating being substantially free of selective serotonin reuptake inhibitor. The coating is for example made by using a water soluble polymer. It has however to be noted that in case the SSRI and the additive selected from the group consisting of acetylsalicylic acid, derivatives of acetylsalicylic acid, heparin, heparin like compounds, and mixtures thereof, are mixed together so as to prepare matrix comprising both compounds, the additive acts as means for ensuring a better dissolution of the SSRI and/or a better passage in the organism. It can be advantageous to provide a barrier coating between the SSRI containing core, particles, etc. and the coating containing the additive, so as to avoid any interaction between the SSRI and the additive. Such a barrier coating is for example a water insoluble coating (polymer, etc.). This is advantageous for avoiding any stability problem.

Advantageously, the selective serotonin reuptake inhibitor is selected from the group consisting of citalopram, especially escitalopram or the s-isomer of citalopram, paroxetine, sertraline, fluvoxamine, fluoxetine, venlafaxine, clomipramine, imipramine, amitriptyne. Fluoxetine, citalopram, escitalopram and sertraline are the most preferred SSRI.

While the formulation can be liquid, the formulation is advantageously solid. Solid formulation means a formulation which has a solid aspect, even if the SSRI is in a liquid or semi liquid form in a carrier or on a carrier. For example, the solid form comprises from 4mg up to 100mg, preferably from 4 to 20mg selective serotonin reuptake inhibitor.

The invention relates further to an antidepressant system comprising at least a formulation, advantageously an oral formulation, with an effective antidepressant amount of one or more selective serotonin reuptake inhibitors, and at least a formulation, advantageously an oral formulation, with an effective amount of at least a compound selected from the group consisting of acetylsalicylic acid, derivatives of acetylsalicylic acid, diaspirin, heparin, heparin like compounds, and mixtures thereof, for reducing the onset of action of the selective serotonin reuptake inhibitor(s). The two formulations can be administered simultaneously or successively, and/or with different administration pathways (oral, rectal, parenteral, etc.) or with the same administration pathways.

The system of the invention has advantageously one or more characteristics of the oral formulation of the invention as described here above.

The invention relates also to a method of treatment of a patient suffering a depression, in which the patient is administered an effective antidepressant amount of one or more selective serotonin reuptake inhibitors, and an effective amount of at least an additive compound selected from the group consisting of acetylsalicylic acid, derivatives of acetylsalicylic acid, diaspirin, heparin, heparin like compounds, and mixtures thereof, for reducing the onset of action of the selective serotonin reuptake inhibitor(s).

In said method, a formulation of the invention is preferably used. However, the method of the invention can be carried out by other means. For example, the SSRI and the additive compound are administered successively, preferably first the additive is administered and then the SSRI. The SSRI and the additive can be administered by different way, for example the SSRI orally, while the additive through the skin or subcutaneous injection (for example in a vein).

In the method of the invention, the doses of SSRI to be administered to the patient are for example the doses proposed in the commercial formulation of SSRI or by the doctors with such commercial formulation. However, these doses can possibly be lowered, for example by a factor 2 or 3.

As it seems also that the time of action (or time efficiency) of the drug SSRI is increased by the additive, less doses have to be taken with respect to the commercial formulations. For example one daily dose with the formulation of the invention, while two or more doses were required for a commercial SSRI formulation.

EXAMPLES

Example 1

10

A PROZAC solid form containing 20mg fluoxetine was coated with a thin water insoluble barrier coating. The so coated solid form was then coated with a water soluble polymer mixed with ASA (acetyl salicylic acid). The water soluble outer coating comprised about 5mg ASA.

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Examples 2 to 5

Example 1 was repeated except that the amount of ASA in the outer coating was respectively 10mg, 20mg, 50 mg and 100mg.

20

Examples 6 to 10

Examples 1 to 5 were repeated but with a 10mg fluoxetine solid form.

Example 11

A solid form containing 50 mg ASA was prepared.
The form was coated with a (water insoluble) barrier coating. The so coated form was then overcoated with a layer (made of a water soluble polymer) in which 10 mg fluoxetine is dispersed. An outer protective layer is advantageously added.

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Example 12

Example 11 is repeated except that the fluoxetine containing layer contains 20mg fluoxetine.

5

Examples 11 and 12 have been repeated, except that the central ASA solid form contained respectively 10mg, 20mg, 40mg, 100mg, 200mg ASA.

It is obvious that the above formulation can be prepared by any technic, such as spheronisation, so as to prepare microgranules or microspheres of fluoxetine coated with ASA containing layer or microgranules or microspheres of ASA coated with fluoxetine containing layer, with or without intermediate barrier layer.

Examples 1 to 12 have been repeated, except that fluoxetine was replaced by sertraline, paroxetine, citalopram, escitalopram or the s isomer of citalopram, and fluvoxamine.

Example 13

A citalopram solid form containing 20mg citalopram was coated with a thin water insoluble barrier coating. The so coated solid form was then coated with a water soluble polymer mixed with ASA. The water soluble outer coating comprised about 5mg ASA.

25 Examples 14 to 17

Example 13 was repeated except that the amount of ASA in the outer coating was respectively 10mg, 20mg, 50 mg and 100mg.

30 Example 18

A solid form containing 50 mg ASA was prepared.

The form was coated with a (water insoluble) barrier coating. The so coated form was then overcoated with a layer (made of a water soluble polymer) in which 20 mg citalopram is dispersed. An outer protective layer is advantageously added.

5 Example 19

Example 18 was repeated except that the solid form contains 25mg ASA.

Example 20

10

A solid form containing 10mg escitalopram was coated with a thin water insoluble barrier coating. The so coated solid form was then coated with a water soluble polymer mixed with ASA. The water soluble outer coating comprised about 5mg ASA.

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Examples 21 to 24

Example 20 was repeated except that the amount of ASA in the outer coating was respectively 10mg, 20mg, 50 mg and 100mg.

20

Example 25

A solid form containing 50 mg ASA was prepared.

25 The form was coated with a (water insoluble) barrier coating. The so coated form was then overcoated with a layer (made of a water soluble polymer) in which 10 mg escitalopram is dispersed. An outer protective layer is advantageously added.

Example 26

30 Example 25 was repeated except that the solid form contains 25mg ASA.

Tests made on rats

Four groups of rats have been stressed. One group of rats remain unstressed so as to serve as control.

5

After being stressed, the rats of the first group received a dose of 50mg ASA per kg. The second group of rats received no treatment. The third group of rats received 5mg fluoxetine per kg, and the fourth group of rats received simultaneously 5mg fluoxetine + 50mg ASA per kg.

10 The treatment was continued during 3 weeks.

The control group of rats had an activity level of 30, while the stressed rats had an activity of 2.

15 The result of this animal test is :

- after 1 week of treatment with the combination fluoxetine+ASA, the fourth group of rats had an activity of 30, i.e. corresponding to the activity of the unstressed rats or control rats. After 1 week of treatment with ASA or fluoxetine alone, there was no increase at all of the activity.
- 20 - after three weeks of treatment, the fourth group of rats had still an activity of 30. The third group of rats (treated with fluoxetine) had after 3 weeks an activity of about 25, while no improvement of activity was observed with ASA.

25 In said test, the doses of ASA and fluoxetine have been adapted for rats.

Said test shows clearly the unexpected action or synergistic activity of ASA + fluoxetine. While not being bound to any theory, it is believed that ASA promotes or activates the sites on which the fluoxetine has to bind.

CLAIMS

- 5 1. Antidepressant system comprising at least a formulation, advantageously an oral formulation, with an effective antidepressant amount of one or more selective serotonin reuptake inhibitors, and at least a formulation, advantageously an oral formulation, with an effective amount of at least a compound selected from the group consisting of acetylsalicylic acid, derivatives of acetylsalicylic acid, diaspirin, heparin, heparin like compounds, and mixtures thereof, for reducing the onset of action of the selective serotonin reuptake inhibitor(s).
- 10 2. Oral antidepressant formulation comprising an effective antidepressant amount of one or more selective serotonin reuptake inhibitors, and an effective amount of at least a compound selected from the group consisting of acetylsalicylic acid, derivatives of acetylsalicylic acid, diaspirin, heparin, heparin like compounds, and mixtures thereof, for reducing the onset of action of the selective serotonin reuptake inhibitor(s).
- 15 3. The formulation or system of claim 1 or 2, which comprises an effective amount of at least a compound selected from the group consisting of acetylsalicylic acid, derivatives of acetylsalicylic acid, diaspirin, heparin, heparin like compounds, and mixtures thereof, for reducing at least 15%, advantageously at least 20%, preferably at least 50% the average onset of action of the selective serotonin reuptake inhibitors.
- 20 4. The formulation or system of claim 1 or 2, in which the effective amount of one or more compounds for reducing the onset of action of the selective serotonin reuptake inhibitor(s) is lower than 50 times the amount of selective serotonin reuptake inhibitor(s).
- 25 5. The formulation or system of claim 1 or 2, in which the effective amount of one or more compounds for reducing the onset of action of the selective serotonin reuptake inhibitor(s) is lower than 10 times, advantageously lower
- 30

than 5 times, preferably lower than 2 times the amount of selective serotonin reuptake inhibitor(s).

6. The formulation or system of claim 1 or 2, which comprises a quick release effective amount of at least a compound selected from the group consisting of acetylsalicylic acid, derivatives of acetylsalicylic acid, diaspirin, heparin, heparin like compounds, and mixtures thereof, for reducing the onset of action of the selective serotonin reuptake inhibitor(s).
7. The formulation or system of claim 1 or 2, which comprises particles, core, microparticles, spherical particles comprising at least one selective serotonin reuptake inhibitor and possibly at least a compound selected from the group consisting of acetylsalicylic acid, derivatives of acetylsalicylic acid, diaspirin, heparin, heparin like compounds, and mixtures thereof, said particles, core, microparticles, spherical particles being advantageously provided with a coating comprising at least a compound selected from the group consisting of acetylsalicylic acid, derivatives of acetylsalicylic acid, heparin, heparin like compounds, and mixtures thereof, for reducing the onset of action of the selective serotonin reuptake inhibitor(s), said coating being substantially free of selective serotonin reuptake inhibitor.
8. The formulation or system of claim 1 or 2, in which the selective serotonin reuptake inhibitor is selected from the group consisting of citalopram, escitalopram or the S isomer of citalopram, paroxetine, sertraline, fluvoxamine, fluoxetine, venlafaxine, clomipramine, imipramine, amitriptyne.
9. The formulation or system of claim 1 or 2, which is a solid form comprising from 4mg up to 100mg, preferably from 4 to 20mg selective serotonin reuptake inhibitor.
10. A method of treatment of a patient suffering a depression, in which the patient is administered an effective antidepressant amount of one or more selective serotonin reuptake inhibitors, and an effective amount of at least a compound selected from the group consisting of acetylsalicylic acid, derivatives of acetylsalicylic acid, diaspirin, heparin, heparin like

compounds, and mixtures thereof, for reducing the onset of action of the selective serotonin reuptake inhibitor(s).

INTERNATIONAL SEARCH REPORT

PCT/BE 03/00078

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/00 A61K31/616 A61K31/727 A61P25/24

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)

IPC 7 A61K A61P

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, WPI Data, PAJ, EMBASE, BIOSIS, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 50044 A (CARUSO FRANK S ; ALGOS PHARM CORP (US)) 12 November 1998 (1998-11-12) examples 30,33,38 -----	1-9
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Further documents are listed in the continuation of box C.



Patent family members are listed in 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

- *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
- *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

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INTERNATIONAL SEARCH REPORT

PCT/BE 03/00078

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	----- US 6 245 782 B1 (SEREBRUANY VICTOR L ET AL) 12 June 2001 (2001-06-12)	1
Y	column 6, line 45 - column 8, line 20; claims 19,20; example 1 -----	1-9

INTERNATIONAL SEARCH REPORT

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Box I Observations where certain claims were found unsearchable (Continuation of item 1 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:

Although claim 10 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
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).

Box II Observations where unity of invention is lacking (Continuation of item 2 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 an additional fee, this Authority did not invite payment of any additional fee.
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.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

PCT/BE 03/00078

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