(12) STANDARD PATENT (11) Application No. **AU 2006209368 B2**
(19) AUSTRALIAN PATENT OFFICE

(54) Title
New association between agomelatine and a noradrenaline reuptake inhibitor and pharmaceutical compositions containing it

(51) International Patent Classification(s)
A61K 31/5375 (2006.01) ***A61P 25/00*** (2006.01)
A61K 31/165 (2006.01) ***A61P 25/24*** (2006.01)

(21) Application No: **2006209368** (22) Date of Filing: **2006.09.08**

(30) Priority Data

(31) Number	(32) Date	(33) Country
05.09206	**2005.09.09**	**FR**

(43) Publication Date: **2007.03.29**
(43) Publication Journal Date: **2007.03.29**
(44) Accepted Journal Date: **2012.07.19**

(71) Applicant(s)
Les Laboratoires Servier

(72) Inventor(s)
Mocaer, Elisabeth

(74) Agent / Attorney
Allens Patent & Trade Mark Attorneys, Level 28 Deutsche Bank Place Corner Hunter and Phillip Streets, Sydney, NSW, 2000

(56) Related Art
WO 2005/002562 A1

2006209368 08 Sep 2006

ABSTRACT

NEW ASSOCIATION BETWEEN AGOMELATINE AND A NORADRENALINE REUPTAKE INHIBITOR, AND PHARMACEUTICAL COMPOSITIONS CONTAINING IT

Association comprising agomelatine, or *N*-[2-(7-methoxy-1-naphthyl)ethyl]acetamide, in association with a noradrenaline reuptake inhibitor agent.

Medicaments

2006209368 08 Sep 2006

P001
Section 29
Regulation 3.2(2)

AUSTRALIA

Patents Act 1990

COMPLETE SPECIFICATION

STANDARD PATENT

Application Number:

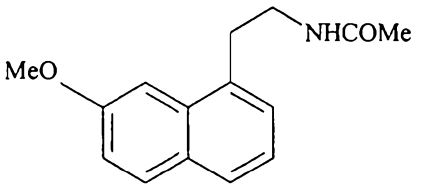
Lodged:

Invention Title: **New association between agomelatine and a noradrenaline reuptake inhibitor and pharmaceutical compositions containing it**

The following statement is a full description of this invention, including the best method of performing it known to us:

2006209368 08 Sep 2006

The present invention relates to a new association between agomelatine, or *N*-[2-(7-methoxy-1-naphthyl)ethyl]acetamide of formula (I) :



(I),

or its hydrates, crystalline forms and addition salts with a pharmaceutically acceptable acid or base, and a noradrenaline reuptake inhibitor agent or any agent capable of increasing the concentration of noradrenaline at the extracellular level, for obtaining pharmaceutical compositions useful in the treatment of depression and, more especially, in the treatment of resistant depressions.

Agomelatine, or *N*-[2-(7-methoxy-1-naphthyl)ethyl]acetamide, has the double characteristic of being, on the one hand, an agonist of receptors of the melatoninergic system and, on the other hand, an antagonist of the 5-HT_{2C} receptor. These properties provide it with activity in the central nervous system and, more especially, in the treatment of major depression, seasonal affective disorder, sleep disorders, cardiovascular pathologies, pathologies of the digestive system, insomnia and fatigue due to jet-lag, and appetite disorders and obesity.

Agomelatine, its preparation and its use in therapeutics have been described in European Patent Specification EP 0 447 285.

The Applicant has now found that agomelatine, or *N*-[2-(7-methoxy-1-naphthyl)ethyl]-acetamide or its hydrates, crystalline forms and addition salts with a pharmaceutically acceptable acid or base, used in association with a noradrenaline reuptake inhibitor agent, has valuable properties allowing its use in the treatment of major depressive disorder, seasonal affective disorder and, more especially, in the treatment of resistant depressions, and also in the treatment of psychiatric co-morbidity associated with mood disorder : anxiety, panic, stress, sleep disorders...

2006209368 28 Jun 2012

Disorders of the central nervous system, such as depression and anxiety, affect a large number of people of all ages. Although many effective molecules exist in that field, none of them allows those various pathological states to be fully cured and some of them have significant side effects. Accordingly, the development of new alternative treatments is ongoing and continues to be a necessity. This is especially true in the case of patients who are totally resistant to all treatments. A conventional so-called "strategy of association" consists of combining a plurality of treatments having different mechanisms of action in order to obtain a positive effect. As a general rule, the beneficial effect observed is patient-dependent and arises from the response to one or another of the compounds of the association.

The most conventional associations described in the literature are concerned with associations with mood stabilisers, such as lithium, with other antidepressants either of different clinical profile or of different neurochemical profile.

The Applicant has now discovered, surprisingly, that the effects of agomelatine are potentiated by noradrenaline reuptake inhibitor agents, or by agents capable of increasing the concentrations of noradrenaline at the extracellular level. Those agents have the characteristic of potentiating the effects of agomelatine.

That unpredictable effect allows the use of the association to be considered in the treatment of major depressive disorder, seasonal affective disorders and, more especially, in the treatment of resistant depressions, as well as of psychiatric co-morbidity associated with mood disorder: anxiety, panic, stress, and sleep disorders. Even more especially, that potentiation of the effects will allow the use of the association according to the invention in the treatment of patients resistant to all treatments.

Accordingly, in a first aspect the invention relates to agomelatine, or *N*-[2-(7-methoxy-1-naphthyl)ethyl]acetamide, or its hydrates, crystalline forms and addition salts with a pharmaceutically acceptable acid or base, and a noradrenaline reuptake inhibitor agent or an agent allowing the concentration of noradrenaline at the extracellular level to be increased, when used in combination to achieve a synergistic effect in a patient.

In a second aspect the invention relates to a pharmaceutical composition comprising as active ingredient agomelatine or its hydrates, crystalline forms and addition salts with a pharmaceutically acceptable acid or base, in association with a noradrenaline reuptake inhibitor agent or an agent allowing the concentration of noradrenaline at the extracellular level to be increased, alone or in combination with one or more pharmaceutically acceptable excipients.

2006209368 28 Jun 2012

A further aspect of the invention relates to the use of a pharmaceutical composition according to the second aspect of the invention in the manufacture of a medicament for the treatment of major depressive disorder, seasonal affective disorder, resistant depressions, or psychiatric co-morbidity associated with mood disorder selected from anxiety, panic, stress, sleep disorders.

Another aspect of the invention relates to the use of agomelatine, or *N*-[2-(7-methoxy-1-naphthyl)ethyl]acetamide, or its hydrates, crystalline forms and addition salts with a pharmaceutically acceptable acid or base, and a noradrenaline reuptake inhibitor agent or an agent allowing the concentration of noradrenaline at the extracellular level to be increased, in the manufacture of a pharmaceutical composition for the treatment of major depressive disorder, seasonal affective disorder, resistant depressions, or psychiatric co-morbidity associated with mood disorder selected from anxiety, panic, stress, sleep disorders.

A further aspect of the invention relates to a method of treating major depressive disorder, seasonal affective disorder, resistant depressions, or psychiatric co-morbidity associated with mood disorder selected from anxiety, panic, stress and sleep disorders, the method comprising administering to a patient requiring sucah treatment an effective amount of agomelatine, or *N*-[2-(7-methoxy-1-naphthyl)ethyl]acetamide, or its hydrates, crystalline forms and addition salts with a pharmaceutically acceptable acid or base, in combination with a noradrenaline reuptake inhibitor agent or an agent allowing the concentration of noradrenaline at the extracellular level to be increased, or a pharmaceutical composition according to the second aspect of the invention.

Among the noradrenaline reuptake inhibitor agents according to the invention there may be mentioned, more especially and without implying any limitation, reboxetine and desipramine.

2006209368 08 Sep 2006

The noradrenaline reuptake inhibitor agent preferred according to the invention is reboxetine.

The invention accordingly relates to the use of the association between agomelatine or its hydrates, crystalline forms and addition salts with a pharmaceutically acceptable acid or base, and a noradrenaline reuptake inhibitor compound or a compound capable of increasing the concentration of noradrenaline at the extracellular level in obtaining pharmaceutical compositions intended for the treatment of major depressive disorder, seasonal affective disorder and, more especially, resistant depressions, as well as in the treatment of psychiatric co-morbidity associated with mood disorder : anxiety, panic, stress, and sleep disorders.

The invention relates also to pharmaceutical compositions comprising the association between agomelatine or its hydrates, crystalline forms and addition salts with a pharmaceutically acceptable acid or base, and a noradrenaline reuptake inhibitor compound or a compound capable of increasing the concentration of noradrenaline at the extracellular level in combination with one or more pharmaceutically acceptable excipients.

Among the pharmaceutical compositions according to the invention there may be mentioned, more especially, those which are suitable for oral, parenteral or nasal administration, tablets or dragées, sublingual tablets, gelatin capsules, lozenges, suppositories, creams, ointments, dermal gels etc.

Besides agomelatine and the noradrenaline reuptake inhibitor compound, the pharmaceutical compositions according to the invention comprise one or more excipients or carriers selected from diluents, lubricants, binders, disintegration agents, absorbents, colourants, sweeteners etc..

By way of example, and without implying any limitation, there may be mentioned :

- *as diluents* : lactose, dextrose, sucrose, mannitol, sorbitol, cellulose, glycerol,

2006209368 08 Sep 2006

- *as lubricants* : silica, talc, stearic acid and its magnesium and calcium salts, polyethylene glycol,
- *as binders* : aluminium and magnesium silicate, starch, gelatin, tragacanth, methyl-cellulose, sodium carboxymethylcellulose and polyvinylpyrrolidone,
- *as disintegrants* : agar, alginic acid and its sodium salt, effervescent mixtures.

The useful dosage varies according to the sex, age and weight of the patient, the administration route, the nature of the disorder and any associated treatments and ranges from 1 mg to 50 mg of agomelatine per 24 hours and is more preferably 25 mg per day. The dose of the noradrenaline reuptake inhibitor agent will be less than that used when it is administered on its own.

Pharmaceutical composition :

Formula for the preparation of 1000 tablets each containing 25 mg of active ingredient :

N-[2-(7-methoxy-1-naphthyl)ethyl]acetamide	25 g
Lactose monohydrate	62 g
Magnesium stearate	1.3 g
Povidone	9 g
Anhydrous colloidal silica	0.3 g
Cellulose sodium glycolate	30 g
Stearic acid	2.6 g

Clinical study :

The clinical study is carried out in patients having major depressive disorder treated either with agomelatine and placebo or with agomelatine and reboxetine for a duration of 6 weeks. The diagnostic system used is that of DSM-IV; the principal criterion of efficacy is the total score of the Hamilton Rating Scale for Depression. A compilation of undesirable events is carried out. The study demonstrates a superior activity of the agomelatine-reboxetine association compared with agomelatine alone.

2006209368 10 Oct 2011

Throughout this specification the terms 'association' and 'combination' are synonymous.

Comprises/comprising and grammatical variations thereof when used in this specification are to be taken to specify the presence of stated features, integers, steps or components or groups thereof, but do not preclude the presence or addition of one or more other features, integers, steps, components or groups thereof.

Any discussion of documents, acts, materials, devices, articles or the like which has been included in the present specification is solely for the purpose of providing a context for the present invention. It is not to be taken as an admission that any or all of these matters form part of the prior art base or were common general knowledge in the field relevant to the present invention as it existed before the priority date of each claim of this specification.

2006209368 28 Jun 2012

The claims defining the invention are as follows:

1. Agomelatine, or *N*-[2-(7-methoxy-1-naphthyl)ethyl]acetamide, or its hydrates, crystalline forms and addition salts with a pharmaceutically acceptable acid or base, and a noradrenaline reuptake inhibitor agent or an agent allowing the concentration of noradrenaline at the extracellular level to be increased, when used in combination to achieve a synergistic effect in a patient.

2. Agomelatine, or *N*-[2-(7-methoxy-1-naphthyl)ethyl]acetamide, or its hydrates, crystalline forms and addition salts with a pharmaceutically acceptable acid or base, and a noradrenaline reuptake inhibitor agent or an agent allowing the concentration of noradrenaline at the extracellular level to be increased, when used in combination according to claim 1, wherein the noradrenaline reuptake inhibitor agent is reboxetine.

3. A pharmaceutical composition comprising as active ingredient agomelatine or its hydrates, crystalline forms and addition salts with a pharmaceutically acceptable acid or base, in association with a noradrenaline reuptake inhibitor agent or an agent allowing the concentration of noradrenaline at the extracellular level to be increased, alone or in combination with one or more pharmaceutically acceptable excipients.

4. A pharmaceutical composition according to claim 3, wherein the noradrenaline reuptake inhibitor agent is reboxetine.

5. Use of a pharmaceutical composition according to claim 3 or 4 in the manufacture of a medicament for the treatment of major depressive disorder, seasonal affective disorder, resistant depressions, or psychiatric co-morbidity associated with mood disorder selected from anxiety, panic, stress, sleep disorders.

6. Use of agomelatine, or *N*-[2-(7-methoxy-1-naphthyl)ethyl]acetamide, or its hydrates, crystalline forms and addition salts with a pharmaceutically acceptable acid or base, and a noradrenaline reuptake inhibitor agent or an agent allowing the concentration of noradrenaline at the extracellular level to be increased, in the manufacture of a pharmaceutical composition for the treatment of major depressive disorder, seasonal affective disorder, resistant depressions, or psychiatric co-morbidity associated with mood disorder selected from anxiety, panic, stress, sleep disorders.

7. The use according to claim 5 or 6, for the treatment of resistant depressions.

8. A method of treating major depressive disorder, seasonal affective disorder, resistant depressions, or psychiatric co-morbidity associated with mood disorder selected from anxiety, panic, stress and sleep disorders, the method comprising administering to a patient requiring such treatment an effective amount of agomelatine, or *N*-[2-(7-methoxy-1-

2006209368 28 Jun 2012

naphthyl)ethyl]acetamide, or its hydrates, crystalline forms and addition salts with a pharmaceutically acceptable acid or base, in combination with a noradrenaline reuptake inhibitor agent or an agent allowing the concentration of noradrenaline at the extracellular level to be increased, or a pharmaceutical composition according to claim 3 or 4.