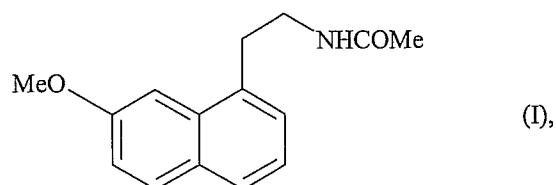


Use of agomelatine in obtaining medicaments intended for the treatment of bipolar disorders

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



and also its hydrates, crystalline forms and addition salts with a pharmaceutically acceptable acid or base, on their own or in association, in obtaining medicaments intended for the treatment of bipolar disorders, especially bipolar disorders of types I and II, and more especially bipolar disorders of type I.

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, appetite disorders and obesity.

Agomelatine, its preparation and its use in therapeutics have been described in European Patent Specifications EP 0 447 285 and EP 1 564 202.

The Applicant has now found that agomelatine, or *N*-[2-(7-methoxy-1-naphthyl)ethyl]-acetamide, and also its hydrates, crystalline forms and addition salts with a pharmaceutically acceptable acid or base, used on their own or in association, has valuable properties allowing their use in the treatment of bipolar disorders, especially bipolar disorders of types I and II, and more especially in bipolar disorders of type I.

Bipolar disorders are a psychopathological condition having a very severe impact on the life of patients, both on the social and family level and on the professional level. They are characterised by the generally repeated occurrence of depressive, manic, hypomanic or mixed episodes separated by periods during which the patients are *a priori* unaffected by major psychological dysfunction. In other words, patients suffering from bipolar disorders are marked by a vulnerability to marked fluctuations in mood in recurrent manner. The characteristics of the attacks and their development over time allow several clinical forms to be distinguished: type I bipolar disorder is the most typical and is characterised by one or more manic or mixed episodes usually accompanied by major depressive episodes; for its part, type II bipolar disorder involves the association of at least one major depressive episode and an episode of hypomania, a moderated form of mania. The risk of suicide in bipolar patients is very high, 25 to 50 % of them having made at least one suicide attempt.

There is currently no satisfactory, recognised treatment for bipolar disorders. First-line treatments are usually mood stabilisers or thymoregulators but these treatments are often unable to relieve the depressive symptoms (J. Clin. Psychiatry, 2004, 65(4), 569-579). The concomitant prescription of an antidepressant, although frequently used, is a highly controversial practice because antidepressants may trigger or aggravate manic states and mixed states and must be stopped when a manic episode occurs.

Antidepressants are especially reputed to promote the causation or acceleration of hyperthymic cycles and to promote, by two to three times, the occurrence of a manic or hypomanic course, and finally their prolonged use seems to lead to an increase in the number of depressive and manic episodes.

The Applicant has now found, surprisingly, that agomelatine can be used, on its own or in association, in the treatment of bipolar disorders, especially bipolar disorders of types I and II, and more especially in bipolar disorders of type I.

Because of the very fact of its activity in depression, the effects that were to be expected in using agomelatine in bipolar disorders, and more especially in bipolar disorders of type I, were the same as the effects of the antidepressants described in the literature such as, for example, paroxetine.

Surprisingly, agomelatine does not behave like a conventional antidepressant, as has been observed in the course of a clinical study carried out in patients suffering from type I bipolar disorders. These results make it possible to consider its use, even its prolonged use, in bipolar disorders, especially bipolar disorders of types I and II, and more especially in
5 bipolar disorders of type I.

The invention accordingly relates to the use of agomelatine, and also its hydrates, crystalline forms and addition salts with a pharmaceutically acceptable acid or base, on their own or in association, in obtaining pharmaceutical compositions intended for the treatment of bipolar disorders, especially bipolar disorders of types I and II, and more
10 especially bipolar disorders of type I.

The invention relates also to the association between agomelatine and a mood stabiliser or thymoregulator for obtaining pharmaceutical compositions intended for the treatment of bipolar disorders, especially bipolar disorders of types I and II, and more especially bipolar disorders of type I.

15 The mood stabilisers or thymoregulators according to the invention relate to lithium and antiepileptics such as, for example, carbamazepine, valproate and lamotrigine etc..

More especially, the mood stabiliser or thymoregulator of the association according to the invention will be lithium or valproate.

When the agomelatine is associated with a mood stabiliser, it may be administered before,
20 at the same time as or after the mood stabiliser provided that the time interval between the two administrations allows the expected synergistic effect to be obtained in the central nervous system. In the case of simultaneous administration of the two components of the association according to the invention, preference will be given to a pharmaceutical composition comprising the agomelatine and the mood-stabilising agent in combination
25 with one or more pharmaceutically acceptable excipients.

The pharmaceutical compositions will be presented in forms suitable for administration by the oral, parenteral, transcutaneous, nasal, rectal or perlingual route, and especially in the form of injectable preparations, tablets, sublingual tablets, glossettes, gelatin capsules, capsules, lozenges, suppositories, creams, ointments, dermal gels etc..

Besides agomelatine and the mood stabiliser optionally associated therewith, 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..

5 By way of non-limiting example there may be mentioned :

- ♦ *as diluents* : lactose, dextrose, sucrose, mannitol, sorbitol, cellulose, glycerol,
- ♦ *as lubricants* : silica, talc, stearic acid and its magnesium and calcium salts, polyethylene glycol,
- ♦ *as binders* : aluminium and magnesium silicate, starch, gelatin, tragacanth,
- 10 methylcellulose, 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.

15 The daily dose of agomelatine will preferably be 25 mg per day.

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
20	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 :

This study was carried out in 21 patients suffering from bipolar disorders of type I, treated for at least 6 months with lithium (n = 14) or valproate (n = 7). Treatment for 6 weeks with agomelatine (25 mg/day) was carried out. Of these patients, 19 continued treatment beyond the 6 weeks of acute treatment, and 11 of those continued treatment up to 1 year. The results obtained showed that 81 % of patients responded positively to the treatment - about 50 % by the end of just one week of treatment. Only three manic or hypomanic episodes were observed after the 6 weeks of treatment, a level entirely compatible with those encountered with a mood stabiliser, clearly demonstrating that the positive action of agomelatine in type I bipolar patients is not associated with an increase in the incidence of manic and/or hypomanic episodes even over a long period of treatment.

CLAIMS

- 1-** Use of agomelatine, or *N*-[2-(7-methoxy-1-naphthyl)ethyl]acetamide, and also its hydrates, crystalline forms and addition salts with a pharmaceutically acceptable acid or base, in obtaining a medicament intended for the treatment of bipolar disorders.
- 2-** Use of agomelatine, or *N*-[2-(7-methoxy-1-naphthyl)ethyl]acetamide, and also its hydrates, crystalline forms and addition salts with a pharmaceutically acceptable acid or base, in obtaining a medicament intended for the treatment of bipolar disorders of type I.
- 3-** Compositions comprising agomelatine or one of its hydrates, crystalline forms and addition salts with a pharmaceutically acceptable acid or base, and a thymoregulatory agent.
- 4-** Compositions according to claim 3, wherein the thymoregulatory agent is lithium.
- 5-** Compositions according to claim 3, wherein the thymoregulatory agent is valproate.
- 6-** Pharmaceutical compositions comprising a composition according to any one of claims 3 to 5, on its own or in combination with one or more pharmaceutically acceptable excipients.

- 7- Pharmaceutical compositions according to claim 6 for use in the manufacture of a medicament for the treatment of bipolar disorders.
- 8- Pharmaceutical compositions according to claim 6 for use in the manufacture of a medicament for the treatment of bipolar disorders of type I.
- 9- Use of a composition according to any one of claims 3 to 5 in the manufacture of a medicament for the treatment of bipolar disorders.
- 10- Use of a composition according to any one of claims 3 to 5 in the manufacture of a medicament for the treatment of bipolar disorders of type I.
- 11- A use according to any one of claims 1, 2, 9, and 10 substantially as herein described with reference to any example thereof.
- 12- A composition according to claim 3 substantially as herein described with reference to any example thereof.
- 13- A pharmaceutical composition according to claim 6 substantially as herein described with reference to any example thereof.