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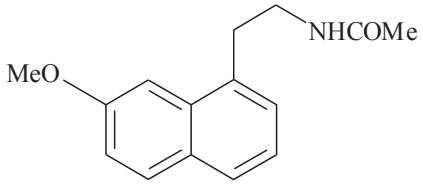
(54) Benevnelse **New crystalline form VI of agomelatine, method of preparation and pharmaceutical compositions thereof**

(56) Anførte publikasjoner

EP-A- 0 447 285
EP-A- 1 564 202
EP-A- 1 752 444
DEPREUX P ET AL: "SYNTHESIS AND STRUCTURE-ACTIVITY RELATIONSHIPS OF NOVEL NAPHTHALENIC AND BIOISOSTERIC AMIDIC DERIVATIVES AS MELATONIN RECEPTOR LIGANDS" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, vol. 37, no. 20, 30 septembre 1994 (1994-09-30), pages 3231-3239, XP002016146 ISSN: 0022-2623
TINANT B ET AL: "N-Ä2-(7-METHOXY-1-NAPHTHYL)ETHYLÜACETAMID E, A POTENT MELATONIN ANALOG" ACTA CRYSTALLOGRAPHICA SECTION C. CRYSTAL STRUCTURECOMMUNICATIONS, MUNKSGAARD, COPENHAGEN, DK, vol. C50, no. 6, 1 janvier 1994 (1994-01-01), pages 907-910, XP009047983 ISSN: 0108-2701
THRELFALL ET AL: "Analysis of Organic Polymorphs" ANALYST, LONDON, GB, vol. 120, 1 octobre 1995 (1995-10-01), pages 2435-2460, XP002101807

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



(I),

to a process for its preparation and to pharmaceutical compositions containing it.

Agomelatine, or *N*-[2-(7-methoxy-1-naphthyl)ethyl]acetamide, has valuable pharmacological properties.

It has the double feature of being on the one hand an agonist of the receptors of the melatoninergic system and on the other hand an antagonist of the 5-HT_{2C} receptor. These properties impart thereto an 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 EP 0 447 285.

Crystalline forms of agomelatine have already been disclosed in the prior art, such as, for example, EP1752444.

In view of the pharmaceutical value of this compound, it was essential to obtain it with excellent purity, and especially in a perfectly reproducible form, having valuable characteristics of dissolution and ease of formulation, allowing it to be stored for prolonged periods without particular conditions of temperature, light, humidity or oxygen level.

The applicant has now developed a process for obtaining agomelatine in a crystalline form which is well defined, reproducible and accordingly has valuable characteristics of dissolution and ease of formulation. This new form additionally has stability over

time which is wholly remarkable, permitting optimum storage without special precautions, which represents an essential advantage in the pharmaceutical industry.

The present invention relates more specifically to the crystalline form VI of the compound of formula (I), characterised by the following X-ray powder diffraction diagram, measured using a Bruker D5000matic diffractometer (copper anticathode) and expressed in terms of interplanar distance d, Bragg's angle 2 theta and relative intensity (expressed as a percentage relative to the most intense line):

2-Theta (°) exp.	**d (Å) exp.**	**Intensity (%)**
5.73	15.411	11.4
10.22	8.645	11.6
20.10	4.413	10.2
23.69	3.751	59.0
29.48	3.027	14.8

The crystalline form VI of the compound of formula (I) has also been characterised by the following infra-red spectroscopy diagram: peaks observed at 907.5 cm^{-1}; 866.7 cm^{-1}; 852.8 cm^{-1}; 827.4 cm^{-1}; 754.6 cm^{-1}; 734.6 cm^{-1}; 698.4 cm^{-1}; 672.1 cm^{-1}; 650.9 cm^{-1}; 611.9 cm^{-1}; 588.1 cm^{-1}.

The invention relates also to a process for the preparation of the crystalline form VI of the compound of formula (I), characterised in that a solution of agomelatine in isopropyl ether is heated at boiling and then rapidly cooled to 0°C. After filtration *in vacuo*, the form VI is obtained in pure form.
In the crystallisation process according to the invention there may be used the compound of formula (I) obtained by any process.

The invention relates also to another process for the preparation of the crystalline form VI of the compound of formula (I), characterised in that agomelatine is crystallised from a water/ethanol mixture (50/50 volume/volume) at ambient temperature under a high pressure for 24 hours.
Preferably, in this second crystallisation process according to the invention, agomelatine will be recrystallised under a high pressure of 10 kbar.
In this second crystallisation process according to the invention there may be used the compound of formula (I) obtained by any process.

Obtaining this crystalline form has the advantage of permitting the preparation of pharmaceutical formulations having a constant and reproducible composition, having excellent stability over time.

The pharmacological study of the form VI so obtained has shown an important activity on the central nervous system and on microcirculation, allowing its usefulness to be established in the treatment of stress, sleep disorders, anxiety, major depression, seasonal affective disorder, cardiovascular pathologies, pathologies of the digestive system, insomnia and fatigue due to jet-lag, schizophrenia, panic attacks, melancholia, appetite disorders, obesity, insomnia, pain, psychotic disorders, epilepsy, diabetes, Parkinson's disease, senile dementia, various disorders associated with normal or pathological ageing, migraine, memory loss, Alzheimer's disease, and also in cerebral circulation disorders. In another field of activity, it appears that in the treatment, the form VI of agomelatine may be used in sexual dysfunctions, that it has properties as an ovulation inhibitor and immunomodulator and that it is capable of being used in the treatment of cancers.

The crystalline form VI of agomelatine will be used preferably 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.

The invention relates also to pharmaceutical compositions comprising as active ingredient the crystalline form VI of the compound of formula (I) with one or more

suitable inert, non-toxic excipients. Among the pharmaceutical compositions according to the invention, there may be mentioned, more especially, those that are suitable for oral, parenteral (intravenous or subcutaneous) or nasal administration, tablets or dragées, granules, sublingual tablets, capsules, lozenges, suppositories, creams, ointments, dermal gels, injectable preparations, drinkable suspensions and chewing gums.

The useful dosage can be adapted according to the nature and severity of the disorder, the administration route and the age and weight of the patient. The dosage varies from 0.1 mg to 1 g per day in one or more administrations.

The examples below illustrate the invention but do not limit it in any way.

Example 1: Crystalline form VI of *N*-[2-(7-methoxy-1-naphthyl)ethyl]acetamide

0.74 g of *N*-[2-(7-methoxy-1-naphthyl)ethyl]acetamide and 36.06 g of isopropyl ether are introduced into a tube. The suspension is heated at boiling (at a temperature of 73°C) for 2 hours. Rapid cooling to 0°C is then carried out. After one hour at 0°C, filtration *in vacuo* over a glass frit of porosity 3 is carried out. The solid obtained is characterised by its melting point and by the following X-ray powder diffraction diagram, measured using a Bruker D5000matic diffractometer (copper anticathode) and expressed in terms of interplanar distance d, Bragg's angle 2 theta and relative intensity (expressed as a percentage relative to the most intense line):

2-Theta (°) exp.	d (Å) exp.	Intensity (%)
5.73	15.411	11.4
10.22	8.645	11.6
20.10	4.413	10.2
23.69	3.751	59.0
29.48	3.027	14.8

Melting point: 94°C

Infra-red spectroscopy diagram: 907.5 cm^{-1}; 866.7 cm^{-1}; 852.8 cm^{-1}; 827.4 cm^{-1}; 754.6 cm^{-1}; 734.6 cm^{-1}; 698.4 cm^{-1}; 672.1 cm^{-1}; 650.9 cm^{-1}; 611.9 cm^{-1}; 588.1 cm^{-1}.

Example 2: Crystalline form VI of *N*-[2-(7-methoxy-1-naphthyl)ethyl]acetamide

2 g of *N*-[2-(7-methoxy-1-naphthyl)ethyl]acetamide are placed in 20 ml of a water/ethanol mixture (50/50 volume/volume) at 25°C. The suspension is filtered over a glass frit of porosity 4. This solution saturated with *N*-[2-(7-methoxy-1-naphthyl)ethyl]acetamide is subjected to a pressure of 10 kbar. After 24 hours, crystallisation is complete and the solid obtained is characterised by its melting point and by the following X-ray powder diffraction diagram, measured using a Bruker D5000matic diffractometer (copper anticathode) and expressed in terms of interplanar distance d, Bragg's angle 2 theta and relative intensity (expressed as a percentage relative to the most intense line):

2-Theta (°) exp.	d (Å) exp.	Intensity (%)
5.73	15.411	11.4
10.22	8.645	11.6
20.10	4.413	10.2
23.69	3.751	59.0
29.48	3.027	14.8

Melting point: 94°C

Infra-red spectroscopy diagram: 907.5 cm^{-1}; 866.7 cm^{-1}; 852.8 cm^{-1}; 827.4 cm^{-1}; 754.6 cm^{-1}; 734.6 cm^{-1}; 698.4 cm^{-1}; 672.1 cm^{-1}; 650.9 cm^{-1}; 611.9 cm^{-1}; 588.1 cm^{-1}.

Example 3: Pharmaceutical composition

Formulation for the preparation of 1000 tablets each containing 25 mg:

Compound of Example 1 or 2..... 25 g

Lactose monohydrate..... 62 g

Magnesium stearate	1.3 g
Maize starch	26 g
Maltodextrins	9 g
Anhydrous colloidal silica	0.3 g
Pregelatinised maize starch type A	4 g
Stearic acid	2.6 g

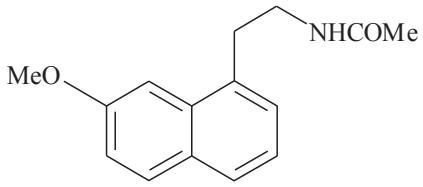
Example 4: Pharmaceutical composition

Formulation for the preparation of 1000 tablets each containing 25 mg:

Compound of Example 1 or 2	25 g
Lactose monohydrate	62 g
Magnesium stearate	1.3 g
Povidone	9 g
Anhydrous colloidal silica	0.3 g
Sodium cellulose glycolate	30 g
Stearic acid	2.6 g

Patentkrav

1. Krystallinsk form VI av agomelatin med formel (I):



(I),

karakterisert ved det følgende røntgenpulverdiffraksjonsdiagram, målt ved bruk av et Bruker D5000matic diffraktometer (kobber-antikatode) og uttrykt med hensyn til den interplanare avstand d, Braggs vinkel 2 theta og relativ intensitet (uttrykt som prosentdel i forhold til den mest intense linjen):

2-Theta (°) eksp.	**d (Å) eksp.**	**Intensitet (%)**
5,73	15,411	11,4
10,22	8,645	11,6
20,10	4,413	10,2
23,69	3,751	59,0
29,48	3,027	14,8

2. Fremgangsmåte ved fremstilling av krystallinsk form VI av forbindelsen med formel (I) ifølge krav 1, karakterisert ved at en oppløsning av agomelatin i isopropyleter varmes opp til kokepunktet, raskt kjøles ned til 0°C og deretter filtreres *in vacuo*.

3. Fremgangsmåte for fremstilling av krystallinsk form VI av en forbindelse med formel (I) ifølge krav 1, karakterisert ved at agomelatin krystalliseres fra en vann/etanol-blanding (50/50 volum/volum) ved omgivelsestemperaturen under et trykk på 10 kbar i 24 timer.

4. Farmasøytisk sammensetning som som aktiv ingrediens omfatter krystallinsk form VI av agomelatin ifølge krav 1, i kombinasjon med én eller flere farmasøytisk akseptable, inerte og ikke-toksiske bærere.

5. Farmasøytisk sammensetning ifølge krav 4 for anvendelse ved fremstilling av et legemiddel for å behandle forstyrrelser i det melatoninergiske system.

6. Farmasøytisk sammensetning ifølge krav 4 for anvendelse ved fremstilling av et legemiddel for behandling av søvnforstyrrelser, stress, angst, sesongavhengig depresjon eller alvorlig depresjon, kardiovaskulære patologier, patologier i fordøyelsessystemet, søvnløshet og tretthet grunnet jet-lag, schizofreni, panikkanfall, melankoli, appetittforstyrrelser, fedme, søvnløshet, smerter, psykotiske forstyrrelser, epilepsi, diabetes, Parkinsons sykdom, senil demens, forskjellige forstyrrelser forbundet med normal eller patologisk aldring, migrene, hukommelsestap, Alzheimers sykdom, cerebrale sirkulasjonsforstyrrelser eller seksuell dysfunksjon, som ovulasjonshemmere eller immunomodulatorer, eller ved behandling av kreft.