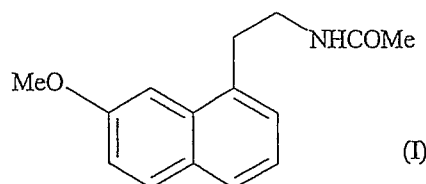


**NEW CRYSTALLINE FORM IV OF AGOMELATINE,
A PROCESS FOR ITS PREPARATION
AND PHARMACEUTICAL COMPOSITIONS CONTAINING IT**

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



a process for its preparation and pharmaceutical compositions containing it.

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

Indeed it has the double feature of being, on the one hand, an agonist of melatoniner-
gic system receptors and, on the other hand, an antagonist of the 5-HT_{2C} receptor. Those
properties confer activity in the central nervous system and, more especially, in the
10 treatment of severe depression, seasonal affective disorders, sleep disorders, cardiovascular
pathologies, pathologies of the digestive system, insomnia and fatigue resulting from
jetlag, appetite disorders and obesity.

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

- 15 In view of the pharmaceutical value of this compound, it has been important to be able to
obtain it with excellent purity, with well defined crystalline form, perfectly reproducible,
which as a result exhibits valuable characteristics in terms of formulation and sufficiently
stable to allow its storage for long periods without particular requirements for temperature,
light, humidity or oxygen level.

- 20 Patent Specification EP 0 447 285 describes the preparation of agomelatine in eight steps,
starting from 7-methoxy-1-tetralone. However, that document does not specify the

conditions for obtaining agomelatine in a form that exhibits those characteristics in a reproducible manner.

The Applicant has now developed a new synthesis process that allows agomelatine to be obtained in a well defined, perfectly reproducible crystalline form that especially exhibits
5 valuable characteristics for formulation.

More specifically, the present invention relates to the crystalline form IV of the compound of formula (I), characterised by the following powder X-ray diffraction diagram, measured using a Siemens D5005 diffractometer (copper anticathode) and expressed in terms of inter-planar distance d, Bragg's angle 2 theta, intensity and relative intensity (expressed as
10 a percentage of the most intense ray) :

2-Theta (°) exp.	d (Å) exp.	Intensité (%)
5.04	17.524	8
10.16	8.703	68
10.51	8.409	9
15.22	5.818	28
16.75	5.288	39
17.41	5.089	60
18.03	4.915	100
18.81	4.714	71
20.48	4.333	37
21.61	4.110	16
23.27	3.819	11
24.04	3.699	26
24.27	3.665	42
24.77	3.591	24
25.57	3.481	13
27.06	3.292	6
27.95	3.190	11

The invention relates also to a process for the preparation of the crystalline form IV of the compound of formula (I), which process is characterised in that agomelatine is heated at

110°C until the melting be completed, and is then rapidly cooled between 50 and 70°C, and maintained for about 5 hours at 70°C until crystallisation.

An advantage of obtaining that crystalline form is that it allows the preparation of pharmaceutical formulations having a consistent and reproducible composition, which is
5 especially advantageous when the formulations are to be used for oral administration.

A pharmacological study of the form IV so obtained has demonstrated that it has substantial activity in respect of the central nervous system and in respect of microcirculation, enabling it to be established that the crystalline form IV of agomelatine is useful in the treatment of stress, sleep disorders, anxiety, severe depression, seasonal
10 affective disorders, cardiovascular pathologies, pathologies of the digestive system, insomnia and fatigue due to jetlag, 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 in cerebral circulation disorders. In
15 another field of activity, it appears that the crystalline IV form of agomelatine can be used in the treatment of sexual dysfunction, that it has ovulation-inhibiting and immunomodulating properties and that it lends itself to use in the treatment of cancers.

The crystalline form IV of agomelatine will preferably be used in the treatment of severe depression, seasonal affective disorders, sleep disorders, cardiovascular pathologies,
20 insomnia and fatigue due to jetlag, appetite disorders and obesity.

The invention relates also to pharmaceutical compositions comprising as active ingredient the crystalline form IV of agomelatine together with one or more appropriate inert, non-toxic excipients. Among the pharmaceutical compositions according to the invention there may be mentioned, more especially, those which are suitable for oral, parenteral
25 (intravenous or subcutaneous) or nasal administration, tablets or dragées, granules, sublingual tablets, gelatin capsules, lozenges, suppositories, creams, ointments, dermal gels, injectable preparations, drinkable suspensions and disintegrable pastes.

The useful dosage can be adapted according to the nature and the 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.

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

100 g of *N*-[2-(7-methoxy-1-naphthyl)ethyl]acetamide are heated at 110°C until the melting be completed, and is then rapidly cooled between 50 and 70°C, and maintained for 5 hours at 70°C until crystallisation. The crystalline form IV obtained is characterised by the following powder X-ray diffraction diagram, measured using a Siemens D5005 diffractometer (copper anticathode) and expressed in terms of inter-planar distance *d*, Bragg's angle 2 theta, intensity and relative intensity (expressed as a percentage of the most intense ray) :

2-Theta (°) exp.	<i>d</i> (Å) exp.	Intensité (%)
5.04	17.524	8
10.16	8.703	68
10.51	8.409	9
15.22	5.818	28
16.75	5.288	39
17.41	5.089	60
18.03	4.915	100
18.81	4.714	71
20.48	4.333	37
21.61	4.110	16
23.27	3.819	11
24.04	3.699	26
24.27	3.665	42
24.77	3.591	24
25.57	3.481	13
27.06	3.292	6
27.95	3.190	11

Example 2 : Pharmaceutical composition

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

	Compound of Example 1	25 g
	Lactose monohydrate.....	62 g
5	Magnesium stearate	1.3 g
	Maize starch.....	26 g
	Maltodextrines	9 g
	Silica, colloidal anhydrous	0.3 g
	Sodium starch glycolate type A.....	4 g
10	Stearic acid	2.6 g

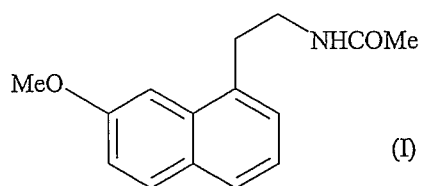
Example 3 : Pharmaceutical composition

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

	Compound of Example 1	25 g
	Lactose monohydrate.....	62 g
15	Magnesium stearate	1.3 g
	Povidone	9 g
	Silica, colloidal anhydrous	0.3 g
	Sodium cellulose glycolate.....	30 g
	Stearic acid	2.6 g

CLAIMS

1. Crystalline form IV of agomelatine of formula (I) :



5 characterised by the following powder X-ray diffraction diagram, measured using a diffractometer (copper anticathode) and expressed in terms of inter-planar distance d, Bragg's angle 2 theta, intensity and relative intensity (expressed as a percentage with respect to the most intense ray) :

2-Theta (°) exp.	d (Å) exp.	Intensité (%)
5.04	17.524	8
10.16	8.703	68
10.51	8.409	9
15.22	5.818	28
16.75	5.288	39
17.41	5.089	60
18.03	4.915	100
18.81	4.714	71
20.48	4.333	37
21.61	4.110	16
23.27	3.819	11
24.04	3.699	26
24.27	3.665	42
24.77	3.591	24
25.57	3.481	13
27.06	3.292	6
27.95	3.190	11

2. Process for the preparation of the crystalline form IV of the compound of formula (I) according to claim 1, characterised in that agomelatine is heated at 110°C until the melting be completed, and is then rapidly cooled between 50 and 70°C, and maintained for about 5 hours at 70°C until crystallisation.
- 5 3. Pharmaceutical compositions comprising as active ingredient crystalline form IV of agomelatine according to claim 1, in combination with one or more pharmaceutically acceptable, inert, non-toxic carriers.
4. Pharmaceutical compositions according to claim 3 for use in the manufacture of a medicament for the treatment of melatoninerbic disorders.
- 10 5. Pharmaceutical compositions according to claim 3 for use in the manufacture of a medicament for the treatment of sleep disorders, stress, anxiety, seasonal affective disorders or severe depression, cardiovascular pathologies, pathologies of the digestive system, insomnia and fatigue due to jetlag, schizophrenia, panic attacks, melancholia, appetite disorders, obesity, insomnia, psychotic disorders, epilepsy, diabetes,
15 Parkinson's disease, senile dementia, various disorders associated with normal or pathological ageing, migraine, memory loss, Alzheimer's disease, cerebral circulation disorders, and also in sexual dysfunction, as ovulation inhibitors, immunomodulators and cancers.
6. A use of a crystalline form IV of agomelatine as defined in claim 1 in the manufacture of a medicament for treating melatoninerbic disorders.
7. A use of a crystalline form IV of agomelatine as defined in claim 1 in the manufacture of a medicament for treating sleep disorders, stress, anxiety, seasonal affective disorders or severe depression, cardiovascular pathologies, pathologies of the digestive system, insomnia and fatigue due to jetlag, schizophrenia, panic attacks, melancholia, appetite disorders, obesity, insomnia, psychotic disorders, epilepsy, diabetes, Parkinson's disease, senile dementia, various disorders associated with normal or pathological ageing, migraine, memory loss, Alzheimer's disease, cerebral circulation disorders, and also in sexual dysfunction, as ovulation inhibitors, immunomodulators and cancers.

8. A crystalline form IV of agomelatine according to claim 1 substantially as herein described with reference to any example thereof.
9. A process according to claim 2 substantially as herein described with reference to any example thereof.
10. A pharmaceutical composition according to claim 3 substantially as herein described with reference to any example thereof.
11. A use according to claim 6 or claim 7 substantially as herein described with reference to any example thereof.