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**Declarations under Rule 4.17**:

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— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

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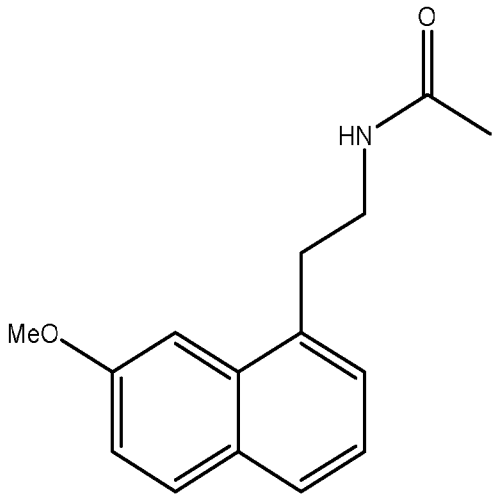
(54) **Title**: FORMULATION COMPRISING AMORPHOUS AGOMELATINE

(57) **Abstract**: The present invention relates to a composition of agomelatine and a copolymer of methacrylic acid and divinylbenzene, a pharmaceutical formulation comprising said composition and the use of either composition or formulation as a medicament, particularly for the treatment of major depressive disorder.

# FORMULATION COMPRISING AMORPHOUS AGOMELATINE

## BACKGROUND OF THE PRESENT INVENTION

Agomelatine (N-[2-(7-methoxynaphthalen-1-yl)ethyl]acetamide) of formula (1)




(1)

is a pharmaceutically active compound used for the treatment of major depressive disorder. It is sold under the trade name Valdoxan® by Servier. The compound was discovered by Servier and is disclosed in EP0447285A. In this publication, agomelatine is obtained by crystallization from diisopropyl ether. The crystalline form I obtained by this process displays polymorphic instability. It transforms into a different, more stable polymorphic form II when subjected to temperatures above 25 °C or when subjected to physical forces, for example, as it occurs during processing into a pharmaceutical formulation.

WO2005077887 describes form II and compositions comprising this polymorphic form. This form II is present in the marketed tablets. When measuring the dissolution of these tablets, a decrease of dissolution upon ageing was observed. Other polymorphic forms of agomelatine are disclosed in WO2007015002, WO2007015003, WO2007015004, WO2009095555, WO2010015747, WO2010102554, and WO2011006387.

The prior art thus teaches that agomelatine is a compound that easily crystallizes in different crystalline forms. These crystalline forms have low aqueous solubility resulting in a lower bioavailability. It is known that generally the solubility of amorphous forms is higher compared to the solubility of crystalline forms. In view of this, it would be desirable to produce amorphous agomelatine.

Compositions comprising agomelatine in an amorphous form are disclosed in WO2012130837. However, these compositions are only obtainable by melt extrusion processes. High temperatures are needed for melt extrusion, which may result in growing of impurities as a result of thermal decomposition of agomelatine. Also, the extrudates require milling in order to be useful for preparing pharmaceutical formulations thereof.

WO2012093402 relates to processes to prepare agomelatine in amorphous form, and compositions of agomelatine in amorphous form. The examples disclosed in WO2012093402 to obtain agomelatine in amorphous form were repeated, but all experiments resulted in crystalline forms of agomelatine. A composition of amorphous agomelatine and polyvinyl pyrrolidone was obtained when repeating Example 6. However, the process requires the use of dichloromethane, which is toxic. During the process extensive foaming is observed and the obtained composition is not a free-flowing powder, thus difficult to handle. This makes the process and composition of WO2012093402 to be unsuitable for use on a commercial scale. Furthermore, after storage at 55°C / 90 %RH, XRPD measurements of the composition showed peaks indicative of crystalline agomelatine. Thus, in view of the prior art, there is still a need for compositions comprising agomelatine that do not have the problems and disadvantages mentioned above.

## BRIEF DESCRIPTION OF THE PRESENT INVENTION

The present invention provides an immediate release pharmaceutical formulation comprising a solid composite consisting essentially of agomelatine and a water insoluble hydrophilic polymer with carboxylic acid groups.

Additionally, the invention provides a process for preparing a pharmaceutical formulation comprising amorphous agomelatine comprising the steps of a) dissolving crystalline agomelatine in a polar solvent or solvent mixture miscible with water, b) adding this solution to an aqueous suspension of a water insoluble hydrophilic polymer with carboxylic acid groups and c) isolating the solid composite by evaporation of the solvent. Further, the invention provides formulations obtainable by said process.

## DETAILED DESCRIPTION OF THE PRESENT INVENTION

The present invention relates to an immediate release pharmaceutical formulation comprising a solid composite consisting essentially of agomelatine and a water insoluble hydrophilic polymer with carboxylic acid groups.

The weight ratio of agomelatine to copolymer in the solid composite typically ranges from 1:1.5 to 1:6, preferably from 1:1.5 to 1:5, more preferably from 1:2 to 1:4. The hydrophilic polymer with carboxylic acid groups to be used in accordance with the present invention has carboxylic acid groups in the H+ form. Typical polymers to be used in accordance with the present invention are polyacrylate a copolymer of methacrylic acid and an acrylic or methacrylic ester or a copolymer of methacrylic acid and divinylbenzene. The copolymer of methacrylic acid and divinylbenzene to be used in accordance with the present invention is also known under the international non-proprietary name (INN) polacrilex resin. Said resin has carboxylic acid groups. Typically, the carboxylic acid groups are in the H+ form. Typical examples of commercially available resins include Amberlite IRP64 and

Indion 214. Preferably the resin has a particle size distribution wherein 90% of the particles are smaller than 100 micron. The smaller particle size improves the dissolution. In the formulations of the present invention, agomelatine is present in a stabilized amorphous form, which means that during stability studies, no conversion of amorphous agomelatine into any crystalline form was observed. The solid composite in accordance with the present invention advantageously is in the form of a free-flowing powder, with excellent handling properties and compressibility. The solid composite is very suitable to be used for the preparation of pharmaceutical formulations.

The pharmaceutical formulations of the present invention comprise said solid composite and one or more pharmaceutically acceptable excipients. The excipients to be used in accordance with the present invention are well-known to and are those excipients which are conventionally used by the person skilled in the art. Depending on the dosage form chosen for the pharmaceutical formulation, the person skilled in the art will be able to select suitable pharmaceutically acceptable excipients. Preferably, the pharmaceutically acceptable excipients are chosen from one or more lubricants, diluents, disintegrants or glidants.

In one embodiment of the present invention, the pharmaceutically acceptable excipients are chosen from one or more lubricants, diluents, or glidants.

In another embodiment of the invention, the pharmaceutically acceptable excipients are chosen from one or more lubricants or diluents. In another embodiment, the pharmaceutically acceptable excipients are lubricants only.

The diluents to be used in accordance with the present invention may be polysaccharides, mono- or disaccharides, or sugar alcohols. Preferably, lactose, microcrystalline cellulose or a mixture thereof is used as a diluent. Most preferred is microcrystalline cellulose.

Suitable disintegrants to be used in accordance with the present invention include crosscarmelose, crospovidone, and sodium starch glycolate, preferably sodium starch glycolate.

Suitable lubricants to be used in accordance with the present invention include stearic acid, magnesium stearate, glyceryl behenate, glyceryl monostearate, and palmitic acid. A preferred lubricant is stearic acid.

Suitable glidants to be used in accordance with the present invention include colloidal silicon dioxide, powdered cellulose, hydrophobic colloidal silica, magnesium silicate, magnesium trisilicate, sodium stearate, and talc. Most preferred is silicon dioxide.

The pharmaceutical formulations of the present invention display dissolution behavior typical for immediate-release formulations. Immediate release typically means that 75% of the API is dissolved within 45 minutes. During preparation and storage of the pharmaceutical formulations of the present invention the agomelatine remains in an amorphous form.

The present invention relates to a composite of agomelatine and a copolymer of methacrylic acid and divinylbenzene, and pharmaceutical formulations comprising this composite and one or more pharmaceutically acceptable excipients.

The weight ratio of agomelatine to copolymer in the composite typically ranges from 1:1.5 to 1:6, preferably from 1:1.5 to 1:5, more preferably from 1:2 to 1:4. The copolymer of methacrylic acid and divinylbenzene to be used in accordance with the present invention is also known under the international non-proprietary name (INN) polacrilex resin. Said resin has carboxylic acid groups. Typically, the carboxylic acid groups are in the H+ form. Typical examples of commercially available resins include Amberlite IRP64 and Indion 214. In the composition of the present invention, agomelatine is present in a stabilized amorphous form, which means that during stability studies no conversion of amorphous agomelatine into any crystalline form was observed. The composite in accordance with the present invention

advantageously is in the form of a free-flowing powder, with excellent handling properties and compressibility. The composite is suitable to be used for the preparation of pharmaceutical formulations.

The present invention further provides a process for preparing a pharmaceutical formulation comprising amorphous agomelatine comprising the steps of a) dissolving crystalline agomelatine in a polar solvent or solvent mixture miscible with water, b) adding this solution to an aqueous suspension of a water insoluble hydrophilic polymer with carboxylic acid groups and c) isolating the solid composite by evaporation of the solvent. Preferably, the solvent or solvent mixture is a polar solvent or a mixture of water and a polar solvent. Preferred polar solvents are alcohols, particularly ethanol or methanol, ethers, particularly tetrahydrofuran, ketones, particularly acetone, and acetonitrile. In an advantageous variant of the process of the present invention, agomelatine is dissolved in a polar solvent and the solution is added to a suspension of the copolymer of methacrylic acid and divinylbenzene in water. An alternative variant of the process of the present invention comprises the step of mixing the copolymer with agomelatine and adding a polar solvent, particularly methanol. In case the water insoluble hydrophilic polymer with carboxylic acid groups is selected from the group consisting of polyacrylate, a co polymer of methacrylic acid and an acrylic or methacrylic ester, a process comprising the steps of a) dissolving crystalline agomelatine and the polymer in a polar solvent, preferably ethanol, methanol, acetone or isopropanol followed by c) removal of the solvent by spray drying is preferred.

Additionally the process comprises the steps of d) blending the solid composite obtained after steps a), b) and c) with one or more excipients, and e) compressing the blend into tablets, using equipment and methods well-known to the skilled artisan. In an alternative embodiment, the solid composite is milled before step e), to further increase dissolution. The

resulting tablets may optionally be coated, using equipment and methods well-known in the art.

The composition and pharmaceutical formulation in accordance with the present invention may be used as medicament. The composition and pharmaceutical formulation typically may be used for the treatment of major depressive disorder.

The present invention further provides an immediate release pharmaceutical composition obtainable by a process comprising the steps of a) dissolving crystalline agomelatine in a polar solvent or solvent mixture miscible with water, b) adding this solution to an aqueous suspension of a water insoluble hydrophilic polymer with carboxylic acid groups, c) isolating the solid composite by evaporation of the solvent d) blending the solid composite obtained after steps a), b) and c) with one or more excipients, and e) compressing the blend into tablets.

Preferably the water insoluble polymer is selected from the group consisting of a copolymer of methacrylic acid and an acrylic or methacrylic ester or a copolymer of methacrylic acid and divinylbenzene. Most preferred is a copolymer of methacrylic acid and divinylbenzene.

The present invention is illustrated by the following Examples.

## EXAMPLES

### Example 1 - weight ratio 1:5

8 g of a copolymer of methacrylic acid and divinylbenzene (Amberlite IRP 64) was transferred to a flask and 1.6 g of agomelatine was added followed by 20 ml of methanol. After stirring the suspension for 15 minutes at room temperature a paste was formed. A further 10 ml of methanol was added and stirring was continued for 45 minutes, then the solvent was evaporated. The resulting powder was dried at room temperature under vacuum

for 2 hours. XRPD measurements showed absence of crystalline agomelatine peaks. XRPD experiments performed four weeks after subjecting the powder in open dish to 55°C/90% RH and 3 months at 40°C/75% RH showed the absence of peaks of crystalline agomelatine.

**Example 2 - weight ratio 1:2**

60 g of a copolymer of methacrylic acid and divinylbenzene (Amberlite IRP 64) was transferred to a flask, 180 ml of water was added and the resulting mixture was stirred for 30 minutes at 50°C. 30 g of agomelatine was dissolved in 240 ml of ethanol. The agomelatine solution was added to the copolymer-water mixture and the suspension was stirred for 1 hour at 50°C. The solvents were evaporated. The resulting powder was dried at 40°C under vacuum overnight. XRPD measurements showed absence of crystalline agomelatine peaks. XRPD experiments performed two weeks after subjecting the powder in open dish to 55°C/-90% RH showed absence of peaks of crystalline agomelatine.

**Example 3 - weight ratio 1:3**

60 g of a copolymer of methacrylic acid and divinylbenzene (Amberlite IRP 64) was transferred to a flask, 180 ml of water was added and the resulting mixture was stirred for 30 minutes at 50°C. 20 g of agomelatine was dissolved in 160 ml of ethanol. The agomelatine solution was added to the copolymer-water mixture and the suspension was stirred for 1 hour at 50°C. The solvents were evaporated. The residue was dried at 40°C under vacuum overnight. XRPD showed that only amorphous material was present (absence of peaks of crystalline agomelatine). XRPD experiments performed two weeks after subjecting the powder in open dish to 55°C/90% RH showed absence of peaks of crystalline agomelatine.

**Example 4**

The composition of agomelatine and copolymer of Example 2 and 3 (weight ratio 1:2 and 1:3, respectively) was blended with 2 wt% of stearic acid. This final blend was compressed into tablets. Final weight of tablets with weight ratio 1:2 was 76.5 mg and with weight ratio 1:3 was 102.0 mg. All tablets showed dissolution typical for immediate release formulations. XRPD experiments showed absence of peaks of crystalline agomelatine.

**Example 5**

The composition of agomelatine and copolymer of Example 2 and 3 (weight ratio 1:2 and 1:3, respectively) was blended with other excipients according to the table below, and the blend subsequently was compressed into tablets. All tablets showed dissolution typical for immediate release formulations.

XRPD experiments showed absence of peaks of crystalline agomelatine.

| **Ingredients** | **mg** | **Ingredients** | **mg** |
|---|---|---|---|
| Agomelatine:copolymer (1:2) | 75.00 | Agomelatine:copolymer (1:3) | 100.00 |
| Lactose monohydrate spray dried | 17.85 | | |
| Microcrystalline cellulose | 30.00 | Microcrystalline cellulose | 22.85 |
| Sodium glycolate starch | 3.90 | Sodium glycolate starch | 3.90 |
| Colloidal silicon dioxide | 0.65 | Colloidal silicon dioxide | 0.65 |
| Stearic acid | 2.60 | Stearic acid | 2.60 |

**Example 6**

A composition of agomelatine and copolymer (weight ratio 1:4) was blended with other excipients according to the table below and the blend subsequently was compressed into tablets. The obtained tablets showed dissolution typical for immediate release formulations. After 4 weeks at 55°C/ 90% RH, XRPD experiments showed absence of peaks of crystalline agomelatine.

| **Ingredients** | **mg** |
|---|---|
| Agomelatine:copolymer (1:4) | 125.00 |
| Lactose monohydrate spray dried | 67.85 |
| Microcrystalline cellulose | 30.00 |
| Sodium glycolate starch | 3.90 |
| Colloidal silicon dioxide | 0.65 |
| Stearic acid | 2.60 |
| Total | 230.0 |

**Example 7**

| **Ingredients** | **Mg/tablet** |
|---|---|
| **Intragranular phase** | |
| Agomelatine | 25.00 |
| Polacrilex resin Amberlite IRP64 | 75.00 |
| Purified water/ethanol 96% (V/V) (Ph.Eur.) | q.s. |
| **Extragranular phase** | |
| Microcrystalline cellulose | 22.85 |

| | |
|---|---|
| Sodium starch glycolate | 3.90 |
| Colloidal silicon dioxide | 0.65 |
| Stearic acid | 2.60 |
| **Tablet weight – uncoated** | **130.00** |
| Opadry II 85F | 6.50 |
| **Tablet weight – coated** | **136.50** |

Agomelatine is dissolved in ethanol 96% v/v (per gram agomelatine 8.3 ml of ethanol is added). To Amberlite IRP64 in a high shear mixer 2.5 mL of water is added for each gram of Amberlite IRP64. The Amberlite IRP64 is suspended for 30 minutes at 70°C±5 °C. Then the Agomelatine solution is added on the Amberlite IRP64 suspension and granulated while heating (e.g. 80°C±2 °C) until organic solvent evaporation (LoD < 50%). The resulting granules are sieved through a conical sieve and dried in a fluid bed dryer at a suitable temperature, e.g. 60±5 °C, in a fluid bed to a LoD of 4.5%). The dried granules are sieved and or milled and added to sieved microcrystalline cellulose, sodium starch glycolate and colloidal silicon dioxide in a diffusion blender and mixed for 15 minutes. Sieved stearic acid is added and blended for 5 minutes. The resulting homogeneous powder is compressed on a rotary tabletting machine using appropriate oblong punches. The resulting tablets are coated with a 15% (w/w) water suspension of Opadry II 85F until 5% weight gain. The obtained tablets showed dissolution typical for immediate release formulations. XRPD measurements show absence of crystalline material.

**Example 8**

| **Ingredients** | **(mg)** | **%** |
|---|---|---|
| Agomelatine:Amberlite IRP 64 complex (1:2) | 75,00 | 57,69 |
| Microcrystalline cellulose | 47,85 | 36,81 |
| Sodium glycolate starch | 3,90 | 3,00 |
| Colloidal Silicon Dioxide | 0,65 | 0,50 |
| Stearic acid | 2,60 | 2,00 |
| Total | 130,00 | 100,00 |

Tablets were prepared according to example 7

## CLAIMS

1. An immediate release pharmaceutical formulation comprising a solid composite consisting essentially of agomelatine and a water insoluble hydrophilic polymer with carboxylic acid groups.
2. The formulation according to claim 1wherein the polymer is a copolymer of methacrylic acid and divinylbenzene.
3. The formulation according to claim 1 or 2, wherein the weight ratio of agomelatine to copolymer ranges from 1:1.5 to 1:6.
4. The formulation according to any of the claims 1 to 3 wherein agomelatine is in amorphous form.
5. The formulation according to claim 1 to 4 comprising one or more pharmaceutically acceptable excipients.
6. The formulation according to claim 5, wherein the one or more pharmaceutically acceptable excipients are one or more diluents, glidants, disintegrants or lubricants.
7. An immediate release pharmaceutical composition obtainable by a process comprising the steps of a) dissolving crystalline agomelatine in a polar solvent or solvent mixture miscible with water, b) adding this solution to an aqueous suspension of a water insoluble hydrophilic polymer with carboxylic acid groups, c) isolating the solid composite by evaporation of the solvent d) blending the solid composite obtained after steps a), b) and c) with one or more excipients, and e) compressing the blend into tablets.
8. The immediate release pharmaceutical composition according to claim 7, wherein the water insoluble polymer is selected from the group consisting of a copolymer of methacrylic acid and an acrylic or methacrylic ester or a copolymer of methacrylic acid and divinylbenzene.

9. A process for preparing a pharmaceutical formulation comprising amorphous agomelatine comprising the steps of a) dissolving crystalline agomelatine in a polar solvent or solvent mixture miscible with water, b) adding this solution to an aqueous suspension of a water insoluble hydrophilic polymer with carboxylic acid groups and c) isolating the solid composite by evaporation of the solvent.

10. The process according to claim 9 wherein the water insoluble hydrophilic polymer with carboxylic acid groups is selected from the group consisting of a copolymer of methacrylic acid and an acrylic or methacrylic ester or a copolymer of methacrylic acid and divinylbenzene.

11. The process according to claims 9 or 10 comprising the additional steps of d) blending the solid composite obtained after steps a), b) and c) with one or more excipients, and e) compressing the blend into tablets.

# INTERNATIONAL SEARCH REPORT

International application No
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A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/18 A61K9/20 A61K31/165
ADD.

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)
A61K

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 practicable, search terms used)
EPO-Internal, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

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| Date of the actual completion of the international search | Date of mailing of the international search report |
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| 10 February 2014 | 18/02/2014 |

| Name and mailing address of the ISA/ | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040,<br>Fax: (+31-70) 340-3016 | Vázquez Lantes, M |

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Information on patent family members

International application No
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