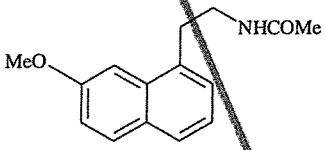
CLAIMS

1. Co-crystal of agomelatine, characterised in that it is composed of:
   - agomelatine, or *N*-[2-(7-methoxy-1-naphthyl)ethyl]acetamide of formula (I)



(I),

   and
   - an organic acid which is in a solid state at ambient temperature.

2. Co-crystal according to claim 1, characterised in that the organic acid used contains from 2 to 10 carbon atoms.

3. Co-crystal according to claim 1 or 2, characterised in that the organic acid used is para-hydroxybenzoic acid, citric acid, oxalic acid, gallic acid, maleic acid, malonic acid, glutaric acid, glycolic acid or ketoglutaric acid.

4. Co-crystal according to one of claims 1 to 3, characterised in that it modifies the active ingredient dissolution rate compared to the form currently marketed in the pharmaceutical product Valdoxan®.

5. Co-crystal according to one of claims 1 to 4, characterised in that it brings about a modification of the active ingredient dissolution rate compared to the dissolution rate of the form currently marketed in the pharmaceutical product Valdoxan® of at least 25% under neutral (pH 6.8) or acid (0.01N HCl) conditions.

6. Co-crystal according to one of claims 1 to 5 which is *N*-[2-(7-methoxy-1-naphthyl)-ethyl]acetamide/para-hydroxybenzoic acid (2/1), characterised in its X-ray powder diffraction diagram by the Bragg's angles 2 theta (expressed in °±0.2) 13.16°, 14.91°, 17.37°, 18.39°, 18.93°, 19.04°, 19.65°, 19.96°, 20.25°, 21.49°, 25.00°.

7. Co-crystal according to one of claims 1 to 5 which is *N*-[2-(7-methoxy-1-naphthyl)-ethyl]acetamide/para-hydroxybenzoic acid (1/2), characterised in its X-ray powder diffraction diagram by the Bragg's angles 2 theta (expressed in °±0.2) 9.50°, 12.28°, 14.00°, 15.76°, 16.18°, 16.62°, 17.56°, 18.15°, 19.96°, 21.00°, 21.30°, 22.00°, 22.97°, 23.55°, 23.76°, 24.44°, 26.09°, 26.82°, 28.42°, 28.71°, 29.85°.

8. Co-crystal according to one of claims 1 to 5 which is *N*-[2-(7-methoxy-1-naphthyl)-ethyl]acetamide/citric acid (1/1), characterised in its X-ray powder diffraction diagram by the Bragg's angles 2 theta (expressed in °±0.2) 5.21°, 12.24°, 17.07°, 19.38°, 20.69°, 21.90°, 22.81°, 27.30°.

9. Co-crystal according to one of claims 1 to 5 which is *N*-[2-(7-methoxy-1-naphthyl)-ethyl]acetamide/oxalic acid (2/1), characterised in its X-ray powder diffraction diagram by the Bragg's angles 2 theta (expressed in °±0.2) 12.48°, 13.80°, 14.02°, 14.22°, 15.30°, 15.43°, 17.61°, 17.82°, 19.64°, 19.77°, 21.53°, 21.72°, 21.79°, 21.97°, 24.95°, 25.39°, 27.36°, 27.47°, 29.29°, 29.77°.

10. Co-crystal according to one of claims 1 to 5 which is *N*-[2-(7-methoxy-1-naphthyl)-ethyl]acetamide/gallic acid (2/1), characterised in its X-ray powder diffraction diagram by the Bragg's angles 2 theta (expressed in °±0.2) 14.47°, 17.68°, 19.82°, 22.33°, 23.93°.

11. Co-crystal according to one of claims 1 to 5 which is *N*-[2-(7-methoxy-1-naphthyl)-ethyl]acetamide/maleic acid (1/1), characterised in its X-ray powder diffraction diagram by the Bragg's angles 2 theta (expressed in °±0.2) 11.30°, 15.40°, 17.28°, 24.29°.

12. Co-crystal according to one of claims 1 to 5 which is *N*-[2-(7-methoxy-1-naphthyl)-ethyl]acetamide/malonic acid (1/1), characterised in its X-ray powder diffraction diagram by the Bragg's angles 2 theta (expressed in °±0.2) 10.47°, 11.95°, 14.78°, 16.05°, 22.32°, 24.50°, 25.05°, 25.24°, 27.38°, 27.91°.

13. Co-crystal according to one of claims 1 to 5 which is *N*-[2-(7-methoxy-1-naphthyl)-ethyl]acetamide/glutaric acid (1/1), characterised in its X-ray powder diffraction diagram by the Bragg's angles 2 theta (expressed in °±0.2) 9.59°, 10.35°, 11.96°, 20.57°, 21.65°, 23.34°.

14. Co-crystal according to one of claims 1 to 5 which is *N*-[2-(7-methoxy-1-naphthyl)-ethyl]acetamide/glycolic acid (1/1), characterised in its X-ray powder diffraction diagram by the Bragg's angles 2 theta (expressed in °±0.2) 10.29°, 14.11°, 14.23°, 17.98°, 18.83°, 19.51°, 20.61°, 23.96°, 24.39°, 26.44°, 28.11°, 29.52°.

15. Co-crystal according to one of claims 1 to 5 which is *N*-[2-(7-methoxy-1-naphthyl)-ethyl]acetamide/ketoglutaric acid (1/1), characterised in its X-ray powder diffraction diagram by the Bragg's angles 2 theta (expressed in °±0.2) 15.36°, 16.34°, 16.54°, 19.24°, 23.57°, 23.90°, 24.41°.

16. Process for obtaining the co-crystal according to one of claims 1 to 15, characterised in that:

- the two constituents are mixed in an organic solvent in the desired proportions (1 equivalent of agomelatine per 0.25 to 4 molar equivalents of organic acid);
- the solution obtained is stirred and optionally heated at a temperature not greater than the boiling point of the selected solvent;
- the mixture is cooled, with stirring, and the co-crystal precipitates naturally or precipitates after taking up in a second solvent;
- the precipitate obtained is filtered and dried.

17. Process for the preparation of the co-crystal according to one of claims 1 to 15, characterised in that the two constituents are co-ground.

18. Process for the preparation of the co-crystal according to one of claims 1 to 15, characterised in that the two constituents are mixed in an organic or aqueous-organic solvent and then frozen and dried at a very low temperature.

19. Process for the preparation of the co-crystal according to one of claims 1 to 15, characterised in that powders of agomelatine and of the acid in question are mixed in a mixer and then the mixture is extruded by twin screw extrusion without a die in order to obtain a solid granular product directly at the extruder outlet.

20. Pharmaceutical compositions comprising as active ingredient a co-crystal according to one of claims 1 to 15, in combination with one or more pharmaceutically acceptable, inert, non-toxic carriers.

21. Pharmaceutical compositions according to claim 20 for use in the manufacture of medicaments for treating disorders of the melatoninergic system.

22. Pharmaceutical compositions according to claim 20 for use in the manufacture of medicaments for treating stress, sleep disorders, anxiety disorders and especially generalised anxiety disorder, obsessive-compulsive disorders, mood disorders and especially bipolar disorders, 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, and also in sexual dysfunctions, and as ovulation inhibitors and immunomodulators and in the treatment of cancers.

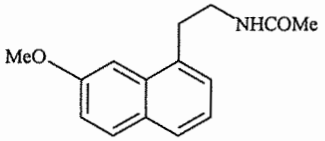
23. Co-crystal according to one of claims 1 to 15 for the treatment of disorders of the melatoninergic system.

24. Co-crystal according to one of claims 1 to 15 for treating stress, sleep disorders, anxiety disorders and especially generalised anxiety disorder, obsessive-compulsive disorders, mood disorders and especially bipolar disorders, 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, and also in sexual dysfunctions, and as ovulation inhibitors and immunomodulators and in the treatment of cancers.

The invention claimed is:

1. A co-crystal of agomelatine, comprising: agomelatine, or N-[2-(7-methoxy-1-naphthyl)ethyl]acetamide of formula (I)



(I),

and

an organic acid which is in a solid state at ambient temperature, wherein the co-crystal is selected from:

N-[2-(7-methoxy-1-naphthyl)ethyl]acetamide/para-hydroxybenzoic acid (2/1);

N-[2-(7-methoxy-1-naphthyl)ethyl]acetamide/para-hydroxybenzoic acid (1/2);

N-[2-(7-methoxy-1-naphthyl)ethyl]acetamide/citric acid (1/1);

N-[2-(7-methoxy-1-naphthyl)ethyl]acetamide/oxalic acid (2/1);

N-[2-(7-methoxy-1-naphthyl)ethyl]acetamide/gallic acid (2/1);

N-[2-(7-methoxy-1-naphthyl)ethyl]acetamide/maleic acid (1/1);

N-[2-(7-methoxy-1-naphthyl)ethyl]acetamide/malonic acid (1/1);

N-[2-(7-methoxy-1-naphthyl)ethyl]acetamide/glutaric acid (1/1);

N-[2-(7-methoxy-1-naphthyl)ethyl]acetamide/glycolic acid (1/1); and

N-[2-(7-methoxy-1-naphthyl)ethyl]acetamide/ketoglutaric acid (1/1).

2. The co-crystal according to claim 1, which is N-[2-(7-methoxy-1-naphthyl)ethyl]acetamide/para-hydroxybenzoic acid (2/1), having the following X-ray powder diffraction diagram (Bragg's angles 2 theta (expressed in °±0.2)): 13.16°, 14.91°, 17.37°, 18.39°, 18.93°, 19.04°, 19.65°, 19.96°, 20.25°, 21.49°, 25.00°.

3. The co-crystal according claim 1, which is N-[2-(7-methoxy-1-naphthyl)ethyl]acetamide/para-hydroxybenzoic acid (1/2), having the following X-ray powder diffraction diagram (Bragg's angles 2 theta (expressed in °±0.2)); 9.50°, 12.28°, 14.00°, 15.76°, 16.18°, 16.62°, 17.56°, 18.15°, 19.96°, 21.00°, 21.30°, 22.00°, 22.97°, 23.55°, 23.76°, 24.44°, 26.09°, 26.82°, 28.42°, 28.71°, 29.85°.

4. The co-crystal according to claim 1, which is N-[2-(7-methoxy-1-naphthyl)ethyl]acetamide/citric acid (1/1), having the following X-ray powder diffraction diagram (Bragg's angles 2 theta (expressed in °±0.2)): 5.21°, 12.24°, 17.07°, 19.38°, 20.69°, 21.90°, 22.81°, 27.30°.

5. The co-crystal according to claim 1, which is N-[2-(7-methoxy-1-naphthyl)ethyl]acetamide/oxalic acid (2/1), having the following X-ray powder diffraction diagram (Bragg's angles 2 theta (expressed in °±0.2)): 12.48°, 13.80°, 14.02°, 14.22°, 15.30°, 15.43°, 17.61°, 17.82°, 19.64°, 19.77°, 21.53°, 21.72°, 21.79°, 21.97°, 24.95°, 25.39°, 27.36°, 27.47°, 29.29°, 29.77°.

6. The co-crystal according to claim 1, which is N-[2-(7-methoxy-1-naphthyl)ethyl]acetamide/gallic acid (2/1), having the following X-ray powder diffraction diagram (Bragg's angles 2 theta (expressed in °±0.2)): 14.47°, 17.68°, 19.82°, 22.33°, 23.93°.

7. The co-crystal according to claim 1, which is N-[2-(7-methoxy-1-naphthyl)ethyl]acetamide/maleic acid (1/1), having the following X-ray powder diffraction diagram (Bragg's angles 2 theta (expressed in °±0.2)): 11.30°, 15.40°, 17.28°, 24.29°.

8. The co-crystal according to claim 1, which is N-[2-(7-methoxy-1-naphthyl)ethyl]acetamide/malonic acid (1/1), having the following X-ray powder diffraction diagram (Bragg's angles 2 theta (expressed in °±0.2)): 10.47°, 11.95°, 14.78°, 16.05°, 22.32°, 24.50°, 25.05°, 25.24°, 27.38°, 27.91°.

9. The co-crystal according to claim 1, which is N-[2-(7-methoxy-1-naphthyl)ethyl]acetamide/glutaric acid (1/1), having the following X-ray powder diffraction diagram (Bragg's angles 2 theta (expressed in °±0.2)): 9.59°, 10.35°, 11.96°, 20.57°, 21.65°, 23.34°.

10. The co-crystal according to claim 1, which is N-[2-(7-methoxy-1-naphthyl)ethyl]acetamide/glycolic acid (1/1), having the following X-ray powder diffraction

diagram (Bragg's angles 2 theta (expressed in °±0.2)): 14.11°, 14.23°, 17.98°, 18.83°, 19.51°, 20.61°, 23.96°, 24.39°, 26.44°, 28.11°, 29.52°.

11. The co-crystal according to claim 1, which is N-[2-(7-methoxy-1-naphthyl)ethyl]acetamide/ketoglutaric acid (1/1), having the following X-ray powder diffraction diagram (Bragg's angles 2 theta (expressed in °±0.2)): 15.36°, 16.34°, 16.54°, 19.24°, 23.57°, 23.90°, 24.41°<.

12. A process for obtaining the co-crystal according to claim 1, comprising:

mixing the agomelatine and the organic acid in an organic solvent in the desired proportions (1 equivalent of agomelatine per 0.25 to 4 molar equivalents of organic acid);

stirring the solution so obtained and optionally heating the solution at a temperature not greater than the boiling point of the selected solvent;

cooling the mixture, with stirring, and to precipitate the co-crystal naturally or adding a second solvent to precipitate the co-crystal;

filtering and drying the precipitate so obtained.

13. A process for the preparation of the co-crystal according to claim 1, wherein the agomelatine and the organic acid are co-ground.

14. A process for the preparation of the co-crystal according to claim 1, wherein the agomelatine and the organic acid are mixed in an organic or aqueous-organic solvent and then frozen and dried at a very low temperature.

15. A process for the preparation of the co-crystal according to claim 1, wherein powders of agomelatine and of the organic acid are mixed in a mixer and then the mixture is extruded by twin screw extrusion without a die in order to obtain a solid granular product directly at the extruder outlet.

16. A pharmaceutical composition comprising as active ingredient a co-crystal according to claim 1, in combination with one or more pharmaceutically acceptable, inert, non-toxic carriers.

17. A method of treating disorders of the melatoninergic system, in a subject in need thereof, comprising administration of an effective amount of the co-crystal according to claim 1.

18. A method of treating a condition selected from stress, sleep disorders, anxiety disorders, obsessive-compulsive disorders, mood disorders, 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, disorders associated with normal or pathological aging, migraine, memory loss, Alzheimer's disease, cerebral circulation disorders, sexual dysfunctions, conditions requiring an ovulation inhibitor, conditions requiring an immunomodulator, and cancer, in a subject in need thereof, comprising administration of an effective amount of the co-crystal according to claim 1.

19. The method of claim 18, wherein the condition is selected from generalised anxiety disorders and bipolar disorders.