PHARMACEUTICAL COMPOSITION

The invention relates to a pharmaceutical composition and in particular to a pharmaceutical composition comprising bitopertin or a salt thereof.

More particularly, the invention relates to a pharmaceutical composition comprising 5, 10 or 20 mg bitopertin in a 155 mg film-coated tablet, obtainable by

i. Mixing bitopertin with lactose monohydrate, maize starch, crosarmellose sodium and povidone,
ii. Granulating the mixed powder from step i using purified water,
iii. Drying and screen the granulate from step ii,
iv. Adding talc, magnesium stearate and microcrystalline cellulose to the granulate from step iii and mix,
v. Compressing the granulate into tablets,
vi. Preparing the film-coating suspension using a pre-mixture, containing polyvinylalcohol, titanium dioxide, macrogol 3350, talc and optionally yellow iron oxide and purified water, and
vii. Film-coating the tablets with the suspension from step vi.

The invention relates also to a pharmaceutical composition comprising 3, 30 and 60 mg bitopertin in a film-coated tablet.

Bitopertin ([4-(3-fluoro-5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-(5-methanesulfonyl-2-(S)-2,2,2-trifluoro-1-methyl-ethoxy)phenyl]-methanone) is described in WO2005/014563, and it can be used for the treatment of schizophrenia and other psychotic disorders by inhibition of the glycine transporter (GlyT1), the main glycine transporter in the forebrain. Thus, if a glutamate deficit is implicate in the pathophysiology of schizophrenia, enhancing glutamate transmission, in particular via NMDA receptor activation, would be predicted to produce both anti-psychotic and cognitive enhancing effects.

Thus, increasing activation of NMDA receptors via GlyT-1 inhibition may lead to agents that treat psychosis, schizophrenia, dementia and other diseases in which cognitive processes are impaired, such as attention deficit disorders or Alzheimer's disease.

Bitopertin is especially useful for the treatment of negative symptoms in schizophrenia, which are apathy, social withdrawal, emotional blunting, impaired ability to anticipate pleasure in everyday life and for the treatment of cognitive impairment such as for the treatment of difficulties with working memory, attention and planning.

It has now been found that a pharmaceutical composition comprising bitopertin in a dose of 3, 5, 10, 20, 30 or 60 mg is particularly efficient in treating negative or cognitive symptoms in schizophrenia. Furthermore, the tablet formulation in accordance with the invention may be suitable for the treatment of deficits in social communications and interactions in autism spectrum disorders (ASD), in the treatment of apathy in early Alzheimer's disease (AD), in the treatment of residual symptoms of motivation after a recent major depressive episode, in the treatment of post traumatic stress disorder (PTSD), for the prophylaxis for patients at high risk of schizophrenia and for the treatment of apathy and cognitive deficits in Parkinson's-disease (PD).

Bitopertin is practically insoluble in aqueous buffers and in water, but is freely soluble in polar organic solvents. Being a BCS 2 molecule (according to the Biopharmaceutics Classification System, wherein the molecule has high permeability and low solubility), the API particles size distribution has been identified as a major critical quality attribute of the drug substance. In vivo studies in both humans and cynomolgus monkeys showed a direct correlation between the particle size distribution of the API in tablets and the resulting bioavailability of the formulation. Thus, micronized API was selected for development of a suitable formulation.

In order to optimize the bioavailability and the dissolution performance, different excipients were tested as fillers, binder, disintegrant and lubricant. It has surprisingly been found that the dissolution behavior of the resulting tablets was dependent on the particle size distribution of the selected excipients. The dissolution was better, the finer the particle of the selected excipients was (see Figure 1) and a combination of corn starch and lactose provided the finest mean particle size distribution with the best tablet dissolution, which was also able to ensure suitable granulate particle size distribution, for appropriate flow of the final blend for tablet compression It. is hypothesized that micronized bitopertin could be optimally dispersed

finely within the tablet formulation only when using filler excipients with a fine mean particle size thus reducing the risk of API sintering during the compaction procedure.

API sintering would result in larger API particles and thus a decrease in dissolution and bioavailability.

Figure 1: Influence on particle size of excipients to tablet dissolution.

Table 1: Evaluation of different filler/ diluent combinations for 30 mg Bitopertin tablet

Filler	%	d50 [µm]	Diluent	%	d50 [µm]	Batch
D-Mannit	30	160	Avicel PH102	33.5	100	GLK0087/02
Lactose	30	30	Avicel PH102	33.5	100	GLK0088/01
Corn starch	30	10-25	Avicel PH102	33.5	100	GLK0095/01
Corn starch	30	10-25	lactose	33.5	30	GKS0001/01
Corn starch	30	10-25	Avicel PH101	35.5	50	GKS0004

With regard to patient compliance, an easy-to swallow solid dosage form is the preferred application. It has been found that a tablet formulation has a good performance of the desired dosage, robustness for transport and packaging. The present tablet performance was chosen to meet the criteria for an immediate release formulation and it was aimed at having more than 80% of the drug load dissolved within 15 minutes with a maximum amount liberated after 60 minutes. To cover the bitter taste, a film-coat was selected.

It was surprisingly found that a pharmaceutical composition comprising bitopertin in a tablet form with a dose range of 3, 5, 10, 20, 30 and 60 mg is particularly efficient in treating or preventing the above mentioned diseases. The preferred dosage range is 5, 10 and 20 mg of bitopertin.

In the present description the terms "diluent" and 'filler' refer to excipients which fills out the size of a tablet or capsule, making it practical to produce and convenient for the consumer to use. Suitable diluents and fillers include e.g. pharmaceutically acceptable inert fillers, such as microcrystalline cellulose, lactose monohydrate, dibasic calcium phosphate sugar, sugar alcohols, corn starch, sucrose, silicic anhydride, polysaccharides, N-methyl pyrrolidone (Pharmasolve (ISP)) and mixtures thereof. The term sugar and sugar alcohols comprises mannitol, lactose, fructose, sorbitol, xylitol, maltodextrin, dextrates, dextrins, lactitol and mixtures thereof.

Binders are added to tablet formulations to add cohesiveness to powders thereby providing the necessary bonding to form granules which under compaction form a compact mass as tablet. Methyl cellulose, carboxymethylcellulose, hydroxypropylcellulose, hydroxymethyl propylcellulose, polyvinylpyrrolidone, polyvinyl alcohol, povidone 30, starch and starch pregelatinized are suitable examples of binders. Individual binders, or Mixtures of two, three or more binders can be used in the formulation.

The term "disintegrant" refers to an excipient which expands and dissolve when wet causing the tablet to break apart in the digestive tract, and via the increase in surface area available for dissolution facilitation release of the active ingredients for absorption. Suitable disintegrants include e.g. lightly crosslinked polyvinyl pyrrolidone, corn starch, potato starch, maize starch, and modified starches, croscarmellose sodium, carboxymethylcellulose calcium, carboxymethylcellulose sodium, crossprovidone, sodium starch glycolate and mixtures thereof.

Suitable lubricants, including agents that act on the flowability of the powder by reducing interparticle friction and cohesion to be compressed, are colloidal silicon dioxide, such as aerosil, talc, stearic acid, magnesium stearate, calcium stearate, glyceryl behenate, sodium stearyl fumarate and silica gel.

As compression aid for the tablet is used microcrystalline cellulose,

The term "coating" refers to an excipient which is applied on the surface of a tablet and which protects tablet ingredients from deterioration by moisture in the air and make large or unpleasant-tasting tablets easier to swallow. Examples of coating agent include PVA (polyvinyl alcohol), HPMC (hydroxypropylmethyl cellulose) and PEG (polyethylene glycol).
In the film coating mixture are also included coloring agents, such as titanium dioxide and iron oxide yellow. A suitable plasticizer in the film coat is Macrogol 3350.

In accordance with the present invention, the formulation for bitopertin is intended to be an oval once-daily film-coated tablet with a size as small as possible (10 x 4.63 mm) with a tablet weight of 150 mg and 5 mg coat weight. All dose strengths have the same size, to be differentiated by engraving and different color shades. The tablet is an oval, biconvex film-coated tablet.

One object of the present invention is a film-coated tablet, comprising 3, 5, 10, 20, 30 and 60 mg bitopertin for 150 mg tablet weight and a coat weight of 5 mg.

A film-coated tablet contains:

Example 1: 5 mg bitopertin for 150 mg tablet weight (and 5 mg coat weight)

Component	**Weight (mg/tablet)**	**Function**
Bitopertin	5.00	Drug substance
Lactose monohydrate	78.75	diluent
Maize starch	37.50	filler
Croscarmellose sodium	3.75	disintegrant
Povidone 30	6.25	binder
Microcrystalline cellulose	15.00	Compression aid
Talc	3.00	lubricant
Magnesium stearate	0.75	lubricant
Total kernel weight	150.00	
Opadry II white 85F18422 (polyvinyl alcohol, titanium dioxide, macrogol 3350, talc	5.00	Film coat (coating agent, coloring agent, plasticizer, lubricant)
Total film-coat weight	5.0	
Total tablet weight	155.00	

Example 2: 10 mg bitopertin for 150 mg tablet weight

Component	**Weight (mg/tablet)**	**Function**
Bitopertin	10.00	Drug substance

Lactose monohydrate	73.75	diluent
Maize starch	37.50	filler
Croscarmellose sodium	3.75	disintegrant
Povidone 30	6.25	binder
Microcrystalline cellulose	15.00	Compression aid
Talc	3.00	lubricant
Magnesium stearate	0.75	lubricant
Total kernel weight	150.00	
Opadry II white 85F18422 (polyvinyl alcohol, titanium dioxide, macrogol 3350, talc, iron oxide yellow)	5.00	Film coat (coating agent, coloring agent, plasticizer, lubricant, coloring agent)
Total film-coat weight	5.0	
Total tablet weight	155.00	

Example 3: 20 mg bitopertin for 150 mg tablet weight

Component	**Weight (mg/tablet)**	**Function**
Bitopertin	20.00	Drug substance
Lactose monohydrate	63.75	diluent
Maize starch	37.50	filler
Croscarmellose sodium	3.75	disintegrant
Povidone 30	6.25	binder

Microcrystalline cellulose	15.00	Compression aid
Talc	3.00	lubricant
Magnesium stearate	0.75	lubricant
Total kernel weight	150.00	
Opadry II white 85F18422 (polyvinyl alcohol, titanium dioxide, macrogol 3350, talc, iron oxide yellow)	5.00	Film coat (coating agent, coloring agent, plasticizer, lubricant, coloring agent)
Total film-coat weight	5.0	
Total tablet weight	155.00	

Tablets containing 3, 30 and 60 mg bitopertin have the same consistence, wherein the weight of bitopertin and lactose monohydrate is always 83,75 mg in the tablet, that means that a tablet with 3 mg bitopertin contains 80.75 mg lactose monohydrate, or a tablet with 30 mg bitopertin contains 53.75 mg lactose monohydrate, or a tablet with 60 mg bitopertin contains 23.75 mg lactose monohydrate.

The invention also relates to a pharmaceutical composition as described above for use as medicament, and preferably for use as medicament for the treatment of schizophrenia and other psychotic disorders, especially for the treatment of negative or cognitive symptoms in schizophrenia, for the treatment of deficits in social communications and interactions in autism spectrum disorders (ASD), in the treatment of apathy in early Alzheimer's disease (AD), in the treatment of residual symptoms of motivation after a recent major depressive episode, in the treatment of post traumatic stress disorder (PTSD), for the prophylaxis for patients at high risk of schizophrenia and for the treatment of apathy and cognitive deficits in Parkinson's-disease (PD).

Furthermore, the invention also relates to the use of a pharmaceutical composition as described above for the treatment of the above-mentioned diseases.

The invention further relates to a method of treatment of schizophrenia and other psychotic disorders, especially for the treatment of negative or cognitive symptoms in

schizophrenia, for the treatment of deficits in social communications and interactions in autism spectrum disorders (ASD), in the treatment of apathy in early Alzheimer's disease (AD), in the treatment of residual symptoms of motivation after a recent major depressive episode, in the treatment of post traumatic stress disorder (PTSD), for the prophylaxis for patients at high risk of schizophrenia and for the treatment of apathy and cognitive deficits in Parkinson's-disease (PD).comprising the step of administering a pharmaceutical composition as described above to a patient in need thereof.

More particularly, the invention relates to a pharmaceutical composition comprising 3, 5, 10, 20 30 or 60 mg bitopertin in a 150 mg tablet size with 5 mg coat weight, obtainable by

i. Mixing bitopertin with a diluent, filler, desintegrant and binder,
ii. Granulating the mixed powder from step i using purified water,
iii. Drying and screen the granulate from step ii,
iv Adding lubricants and compression aid to the granulate from step iii and mix,
v. Compressing the granulate into tablets,
vi. Preparing the film-coating suspension using a pre-mixture, containing a coating agent, coloring agents, plasticizer, lubricant and purified water, and
vii. Film-coating the tablets with the suspension from step vi.

More specifically, the invention relates to a pharmaceutical composition comprising 3, 5, 10, 20, 30 or 60 mg bitopertin in a 150 mg tablet size with 5 mg coat weight, obtainable by

i. Mixing bitopertin with lactose monohydrate, maize starch, crosarmellose sodium and povidone,
ii. Granulating the mixed powder from step i using purified water,
iii. Drying and screen the granulate from step ii,
iv. Adding talc, magnesium stearate and microcrystalline cellulose to the granulate from step iii and mix,
v. Compressing the granulate into tablets,
vi. Preparing the film-coating suspension using a pre-mixture, containing polyvinylalcohol, titanium dioxide, macrogol 3350, talc and yellow iron oxide and purified water, and
vii. Film-coating the tablets with the suspension from step vi.

For the preparation of the tablet, the following procedure can be followed:

The tablets are manufactured using the conventional pharmaceutical operations of wet-high shear granulation, fluid bed drying, blending, compression, and film coating.

Detailed description of the manufacturing process:

1. Load bitopertin milled drug substance, lactose monohydrate, maize starch, croscarmellose sodium and Povidone 30 in a high shear mixer.
2. Blend for 5 to 10 min at suitable rpm.
3. Add water in the course of 10 min. and knead for further 5 to 10 min at suitable rpm.
4. The wet granules are transferred into the fluid bed dryer over a 5 mm sieve and dried under the following conditions: inlet air temperature: 50 to 70 °C, air flow: 300 to 600 m^3/h. Drying end point 4 % (range: 2.5 - 5.5 %) determined by LOD, Duration: 45 min.
5. Screen the granules through a 1.5 mm Frewitt cone sieve at suitable rotor speed.
6. Add microcrystalline cellulose as is and add talc and magnesium stearate through a hand sieve of 0.5 mm to the granules and blend with bin blender for 20 min at 6 rpm.
7. Compress the final blend from [step 6] into tablet core at suitable compression force and rotor speed to obtain tablets with hardness of 50-90N.
8. Prepare the coating suspension using purified water and the Opadry II Yellow 85F32645 film-coating mixture (Polyvinyl Alcohol partially hydrolyzed, titanium dioxide, Macrogol/PEG 3350, talc) and Iron oxide yellow) and stir for at least one hour.
9. Spray the coating suspension from [step 8] onto the tablet cores from [step 7].

Claims

1. A pharmaceutical composition in form of a film-coating tablet comprising bitopertin or a salt thereof.

2. A pharmaceutical composition according to claim 1 with a tablet weight of 150 mg and a film-coat weight of 5 mg.

3. A pharmaceutical composition according to any one of claims 1 and 2 for the treatment of negative or cognitive symptoms in schizophrenia, deficits in social communications and interactions in autism spectrum disorders (ASD), apathy in early Alzheimer's disease (AD), residual symptoms of motivation after a recent major depressive episode, post traumatic stress disorder (PTSD), for the prophylaxis for patients at high risk of schizophrenia and for the treatment of apathy and cognitive deficits in Parkinson's-disease.

4. A Pharmaceutical composition according to any one of claims 1, 2 and 3, comprising 3, 5, 10, 20, 30 or 60 mg of bitopertin or a salt thereof, obtainable by

i. Mixing bitopertin with a diluent, filler, desintegrant and binder,

ii. Granulating the mixed powder from step i using purified water,

iii. Drying and screen the granulate from step ii,

iv. Adding lubricants and compression aid to the granulate from step iii and mix,

v. Compressing the granulate into tablets,

vi. Preparing the film-coating suspension using a pre-mixture, containing a coating agent, coloring agents, plasticizer, lubricant and purified water, and

vii Film-coating the tablets with the suspension from step vi.

5. Pharmaceutical composition comprising 3, 5, 10, 20, 30 or 60 mg of bitopertin or a salt thereof according to claim 4, obtainable by

i. Mixing bitopertin with lactose monohydrate, maize starch, crosarmellose sodium and ovidone,

ii. Granulating the mixed powder from step i using purified water,

iii. Drying and screen the granulate from step ii,

iv. Adding talc, magnesium stearate and microcrystalline cellulose to the granulate from step iii and mix,

v. Compressing the granulate into tablets,

vi. Preparing the film-coating suspension using a pre-mixture, containing polyvinylalcohol, titanium dioxide, macrogol 3350, talc and yellow iron oxide and purified water, and

vii. Film-coating the tablets with the suspension from step vi.

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6. A pharmaceutical composition according to any one of claims 1 to 5, comprising:

Component	**Weight (mg/tablet)**
Bitopertin	5.00
Lactose monohydrate	78.75
Maize starch	37.50
Croscarmellose sodium	3.75
Povidone 30	6.25
Microcrystalline cellulose	15.00
Talc	3.00
Magnesium stearate	0.75
Opadry II white 85F18422 (polyvinyl alcohol, titanium dioxide, macrogol 3350, talc,	5.00

7 . A pharmaceutical composition according to any one of claims 1 to 5, comprising:

Component	**Weight (mg/tablet)**
Bitopertin	10.00
Lactose monohydrate	73.75
Maize starch	37.50

Croscarmellose sodium	3.75
Povidone 30	6.25
Microcrystalline cellulose	15.00
Talc	3.00
Magnesium stearate	0.75
Opadry II white 85F18422 (polyvinyl alcohol, titanium dioxide, macrogol 3350, talc, iron oxide yellow)	5.00

8. A pharmaceutical composition according to any one of claims 1 to 5, comprising

Component	**Weight (mg/tablet)**
Bitopertin	20.00
Lactose monohydrate	63.75
Maize starch	37.50
Croscarmellose sodium	3.75
Povidone 30	6.25
Microcrystalline cellulose	15.00
Talc	3.00
Magnesium stearate	0.75
Opadry II white 85F18422 (polyvinyl alcohol,	5.00

titanium dioxide, macrogol 3350, talc, iron oxide yellow)	

9. A pharmaceutical composition according to any one of claims 1 to 8 for use as medicament for the for the treatment of negative or cognitive symptoms in schizophrenia, deficits in social communications and interactions in autism spectrum disorders (ASD), apathy in early Alzheimer's disease (AD), residual symptoms of motivation after a recent major depressive episode, post traumatic stress disorder (PTSD), for the prophylaxis for patients at high risk of schizophrenia and for the treatment of apathy and cognitive deficits in Parkinson's-disease.

10. The use of a pharmaceutical composition according to any one of claims 1 to 8 for the treatment of negative or cognitive symptoms in schizophrenia, deficits in social communications and interactions in autism spectrum disorders (ASD), apathy in early Alzheimer's disease (AD), residual symptoms of motivation after a recent major depressive episode, post traumatic stress disorder (PTSD), for the prophylaxis for patients at high risk of schizophrenia and for the treatment of apathy and cognitive deficits in Parkinson's-disease.

11. A method for the treatment of negative or cognitive symptoms in schizophrenia, deficits in social communications and interactions in autism spectrum disorders (ASD), apathy in early Alzheimer's disease (AD), residual symptoms of motivation after a recent major depressive episode, post traumatic stress disorder (PTSD), for the prophylaxis for patients at high risk of schizophrenia and for the treatment of apathy and cognitive deficits in Parkinson's-disease, comprising the step of administering a pharmaceutical composition according to any one of claims 1 to 8 to a patient in need thereof.

12. A pharmaceutical composition according to any one of claims 1 to 8 which is administered once daily.

13. The invention as hereinbefore described.