very low doses; i.e. doses of buspirone which alone failed to produce a significant effect on LID (WO2012/048710).

In PCT/DK2012/050190 (filed 01.06.2012) and further provided herein, the present inventors have investigated administering zolmitriptan separately before administering buspirone and found additional beneficial effects by such sequential administration. In PCT/DK2012/050190 both compounds were administered by injections to achieve this further beneficial effect (s.c. or i.p.). However, repeated and timely separated injections are generally undesired especially for long-term treatments, and bolus injections may cause too-high plasma concentration doses which is a potential safety concern.

Summary

The present disclosure provides an orally available pharmaceutical formulation designed to obtain the beneficial synergistic effects of combining an agonist of two or more of the 5-HT1B, D and F receptors, exemplified by zolmitriptan, with a 5-HT1A agonist, exemplified by buspirone; surprisingly also achieving the additional beneficial effect of sequential administration of the two active ingredients, thus improving efficacy and reducing the risk of adverse effects while enabling ease of administration by eliminating the need for multiple administrations (such as injections or ingestions).

It is an aspect of the present disclosure to provide a pharmaceutical formulation comprising

a. a matrix constituent comprising an active pharmaceutical ingredient being an agonist of two or more of ~~the~~ 5-HT1B, 5-HT1D and 5-HT1F receptors selected from the group consisting of zolmitriptan, rizatriptan, sumatriptan, naratriptan, almotriptan, frovatriptan, avitriptan, imotriptan and eletriptan, and pharmaceutically acceptable derivatives thereof, said matrix constituent providing for extended release of said agonist of two or more of 5-HT1B, 5-HT1D and 5-HT1F receptors~~active pharmaceutical ingredient~~, and

b. a constituent comprising an active pharmaceutical ingredient being an agonist of the 5-HT1A receptor selected from the group consisting of buspirone, tandospirone, gepirone, alnespirone, binospirone, ipsapirone, perospirone, befiradol, repinotan, piclozotan, osemozotan, flesinoxan, flibanserin and sarizotan, and pharmaceutically acceptable derivatives thereof, said constituent providing for immediate release of said agonist of 5-HT1A receptor~~active pharmaceutical ingredient~~.

In one embodiment said pharmaceutical formulation is a dosage form, such as a solid dosage form, such as a tablet. In one embodiment said dosage form comprises constituents a. and b. in separate compartments or layers; such as an inner core matrix and an outer coating; or a bi-layered tablet. In another embodiment, each of said

bradykinesia, akinesia and dyskinesia, L-DOPA induced dyskinesia, and tardive dyskinesia.

It is another aspect of the present disclosure to provide the use of the pharmaceutical formulation as disclosed herein in the manufacture of a medicament for the treatment of a movement disorder.

Definitions

The term "agonist" in the present context refers to a substance capable of binding to and activating a (one or more) receptor(s). A 5-HT1A receptor agonist (5-HT1A agonist) is thus capable of binding to and activating the 5-HT1A receptor. An agonist of two or more the 5-HT1B, 5-HT1D and 5-HT1F receptors (5-HT1B/D/F agonist) is capable of binding to and activating two or three of the 5-HT1B, 5-HT1D and 5-HT1F receptor. The terms '5-HT1 agonist', '5-HT1 receptor agonist', and 'agonist of the 5-HT1 receptor' are used interchangeably herein.

The term "antagonist" in the present context refers to a substance capable of inhibiting the effect of a receptor agonist.

The terms "dopamine," "DA" and "4-(2-aminoethyl)benzene-1,2-diol," refer to a catecholamine neurotransmitter and hormone. Dopamine is a precursor of adrenaline (epinephrine) and noradrenaline (norepinephrine) and activates the five types of dopamine receptors—D1, D2, D3, D4, and D5—and their variants.

"L-DOPA" or "3,4-dihydroxyphenylalanine" is a precursor to the neurotransmitters dopamine, norepinephrine (noradrenaline), and epinephrine (adrenaline). L-DOPA is able to cross the blood-brain barrier, and is converted to dopamine by the enzyme aromatic L-amino acid decarboxylase (AADC), also known as DOPA decarboxylase (DDC). L-DOPA is used for treatment of Parkinson's disease.

The terms "Parkinson's disease," "Parkinson's" and "PD" refer to a neurological syndrome characterized by a dopamine deficiency, resulting from degenerative, vascular, or inflammatory changes in the basal ganglia of the substantia nigra. This term also refers to a syndrome which resembles Parkinson's disease, but which may or may not be caused by Parkinson's disease, such as Parkinsonian-like side effects caused by certain antipsychotic drugs. Parkinson's disease is also referred to as paralysis agitans and shaking palsy.

The term "synapse" refers to an area of a neuron that permits said neuron to pass an electrical or chemical signal to another cell. In a synapse, a plasma membrane of the signal-passing neuron (the *pre-synaptic* neuron) comes into close apposition with the membrane of the target (*post-synaptic*) cell.

Claims

1. A pharmaceutical formulation comprising
   a. a matrix constituent comprising an active pharmaceutical ingredient being an agonist of two or more of ~~the~~ 5-HT1B, 5-HT1D and 5-HT1F receptors selected from the group consisting of zolmitriptan, rizatriptan, sumatriptan, naratriptan, almotriptan, frovatriptan, avitriptan, imotriptan and eletriptan, and pharmaceutically acceptable derivatives thereof, said matrix constituent providing for extended release of said ~~active pharmaceutical ingredient~~ agonist of two or more of 5-HT1B, 5-HT1D and 5-HT1F receptors, and
   b. a constituent comprising an active pharmaceutical ingredient being an agonist of the 5-HT1A receptor selected from the group consisting of buspirone, tandospirone, gepirone, alnespirone, binospirone, ipsapirone, perospirone, befiradol, repinotan, piclozotan, osemozotan, flesinoxan, flibanserin and sarizotan, and pharmaceutically acceptable derivatives thereof, said constituent providing for immediate release of said ~~active pharmaceutical ingredient~~ agonist of 5-HT1A receptor.

~~2. The pharmaceutical formulation according to claim 1, wherein said agonist of two or more of the 5-HT1B, 5-HT1D and 5-HT1F receptors is a triptan.~~

~~3. The pharmaceutical formulation according to claim 2, wherein said triptan is selected from the group consisting of zolmitriptan, rizatriptan, sumatriptan, naratriptan, almotriptan, frovatriptan, avitriptan, imotriptan and eletriptan, and pharmaceutically acceptable derivatives thereof.~~

~~4.~~2. The pharmaceutical formulation according to claim ~~3~~1, wherein said ~~triptan~~ agonist of two or more of 5-HT1B, 5-HT1D and 5-HT1F receptors is zolmitriptan.

~~5. The pharmaceutical formulation according to claim 1, wherein said agonist of the 5-HT1A receptor is selected from the group consisting of buspirone, tandospirone, gepirone, alnespirone, binospirone, ipsapirone, perospirone, befiradol, repinotan piclozotan, osemozotan, flesinoxan, flibanserin and sarizotan, and pharmaceutically acceptable derivatives thereof.~~

~~6.~~3. The pharmaceutical formulation according to claim ~~5~~1, wherein said agonist of the 5-HT1A receptor is buspirone.

~~7.~~4. The pharmaceutical formulation according to any of the preceding claims, wherein said formulation is a solid dosage form, such as a tablet.

8.5. The pharmaceutical formulation according to any of the preceding claims, wherein said formulation comprises matrix constituent a. providing for extended release of an agonist of two or more of the 5-HT1B, 5-HT1D and 5-HT1F receptors, and constituent b. providing for immediate release of an agonist of the 5-HT1A receptor, in separate compartments or layers.

9.6. The pharmaceutical formulation according to any of the preceding claims, wherein said formulation comprises

a. an inner core matrix providing for extended release of an agonist of two or more of the 5-HT1B, 5-HT1D and 5-HT1F receptors, and
b. an outer coating providing for immediate release of an agonist of the 5-HT1A receptor.

10.7. The pharmaceutical formulation according to any of claims 1 to 85, wherein said formulation is a bi-layered tablet comprising

a. one layer providing for extended release of an agonist of two or more of the 5-HT1B, 5-HT1D and 5-HT1F receptors, and
b. another layer providing for immediate release of an agonist of the 5-HT1A receptor,

wherein each layer is present within the same tablet.

11.8. The pharmaceutical formulation according to any of the preceding claims, wherein each of said constituents a. and b. are provided together in a capsule, wherein said capsule comprises constituents a. and b. as separate granules or pellets.

12.9. The pharmaceutical formulation according to any of the preceding claims, wherein said matrix constituent a. and matrix constituent b. each comprises one or more excipients.

13.10. The pharmaceutical formulation according to any of the preceding claims, wherein said matrix constituent a. comprises one or more excipients, such as one or more release-controlling excipients.

~~14.~~11. The pharmaceutical formulation according to claims ~~12 to 13~~ 9 or 10, wherein said matrix constituent a. comprises the excipients hydroxypropylmethylcellulose (HPMC) and/or microcrystalline cellulose (MCC).

~~15. The pharmaceutical formulation according to claim 14, wherein said HPMC excipient is Methocel E4M and/or Methocel K100.~~

~~16.~~12. The pharmaceutical formulation according to ~~any of~~ claims ~~14 to 15~~ 11, wherein said HPMC excipient is present in an amount of from 20-50%, such as 20-25%, for example 25-30%, such as 30-35%, for example 35-40%, such as 40-45%, for example 45-50%.

~~17. The pharmaceutical formulation according to any of claims 14 to 16, wherein said MCC excipient is Avicel PH 101.~~

~~18.~~13. The pharmaceutical formulation according to ~~any of~~ claims ~~14 to 17~~ 11 or 12, wherein said MCC excipient is present in an amount of from 50 to 80%, such as 60-70%.

~~19.~~14. The pharmaceutical formulation according to any of the preceding claims, wherein said matrix constituent a. further comprises talc.

~~20.~~15. The pharmaceutical formulation according to claim ~~19~~14, wherein said talc is present in an amount of from 1-10%, such as about 5%.

~~21.~~16. The pharmaceutical formulation according to any of the preceding claims, wherein said matrix constituent a. is compressed to a hardness of from 50-70N.

~~22.~~17. The pharmaceutical formulation according to any of the preceding claims, wherein said matrix constituent a. provides for at least 80% release of the agonist of two or more of the 5-HT1B, 5-HT1D and 5-HT1F receptors after 12 hours.

~~23.~~18. The pharmaceutical formulation according to any of the preceding claims, wherein said formulation comprises said agonist of two or more of the 5-HT1B,

5-HT1D and 5-HT1F receptors in an amount of from 0.1 to 10 mg, such as from 0.5 to 5 mg, for example about 1 mg.

~~24.~~19. The pharmaceutical formulation according to any of the preceding claims, wherein said matrix constituent a. consists of one or more HPMCs, one or more MCCs, talc, and an agonist of two or more of the 5-HT1B, 5-HT1D and 5-HT1F receptors.

~~25.~~20. The pharmaceutical formulation according to any of the preceding claims, wherein said matrix constituent a. comprises ~~or consists essentially of~~

a. 10-50%, such as 20-40%, HPMC~~, such as Methocel E4M and/or Methocel K100~~
b. 40-80%, such as 55-75% MCC~~, such as Avicel PH 101~~
c. 1-10%, such as 2-8% talc
a. 0.1-5%, such as 0.5-2% of an agonist of two or more of the 5-HT1B, 5-HT1D and 5-HT1F receptors~~, preferably a triptan selected from the group consisting of zolmitriptan, rizatriptan, sumatriptan, naratriptan, almotriptan, frovatriptan and eletriptan~~.

~~26.~~21. The pharmaceutical formulation according to any of the preceding claims, wherein said formulation comprises said agonist of the 5-HT1A receptor in an amount of from 1 to 20 mg, such as from 5 to 15 mg, for example about 10 mg.

~~27.~~22. The pharmaceutical formulation according to any of the preceding claims, wherein said constituent b. comprises an excipient.

~~28.~~23. The pharmaceutical formulation according to any of the preceding claims, wherein said constituent b. comprises a film-forming excipient.

~~29.~~24. The pharmaceutical formulation according to ~~any of~~ claim~~s 27 to 28~~ 22 or 23, wherein said constituent b. excipient is a hydroxypropylmethylcellulose (HPMC).

~~30. The pharmaceutical formulation according to claim 29, wherein said HPMC is Pharmacoat 603.~~

~~31.~~25. The pharmaceutical formulation according to any of the preceding claims, wherein said constituent b. comprises or consists of at least one HPMC and an agonist of the 5-HT1A receptor.

~~32.~~26. The pharmaceutical formulation according to any of the preceding claims, wherein said constituent b. comprises or consists of

a. 25-40% HPMC~~, such as Pharmacoat 603~~
b. 60-75% of an agonist of the 5-HT1A receptor~~, preferably selected from the group consisting of buspirone, tandospirone, gepirone, alnespirone, binospirone, ipsapirone, perospirone, befiradol, repinotan piclozotan, osemozotan, flesinoxan, flibanserin and sarizotan~~.

~~33.~~27. The pharmaceutical formulation according to any of the preceding claims, wherein the formulation consisting of constituents a. and b. comprises ~~or consists essentially of~~

a. 20-40% HPMC~~, such as Methocel E4M and/or Methocel K100~~
b. 50-70% MCC~~, such as Avicel PH 101~~
c. 1-10% Talc
d. 0.1-10% of ~~a triptan selected from the group consisting of zolmitriptan, rizatriptan, sumatriptan, naratriptan, almotriptan, frovatriptan and eletriptan~~ an agonist of two or more of the 5-HT1B, 5-HT1D and 5-HT1F receptors,
e. 1-20% of an agonist of the 5-HT1A receptor ~~selected from the group consisting of buspirone, tandospirone, gepirone, alnespirone, binospirone, ipsapirone, perospirone, befiradol, repinotan piclozotan, osemozotan, flesinoxan, flibanserin and sarizotan,~~
f. 0.1-10% HPMC~~, such as Pharmacoat 603~~

wherein components a., b., c. and d. are comprised in matrix constituent a., and components e. and f. are comprised in constituent b.

~~34.~~28. The pharmaceutical formulation according to any of the preceding claims, wherein said formulation comprises one or more further active ingredients.

~~35.~~29. The pharmaceutical formulation according to claim ~~34~~28, wherein said further active ingredient is selected form the group consisting of dopamine; dopamine prodrugs such as L-DOPA or levodopa; carboxylase inhibitors such as

carbidopa or benserazide; dopamine receptor agonists such as bromocriptine, pergolide, pramipexole, ropinirole, piribedil, cabergoline, apomorphine, lisuride; NMDA antagonists such as for example amatidine; catechol-O-methyl transferases; COMT inhibitors such as tolcapone and entacapone; MAO-B inhibitors such as selegiline and rasagiline; serotonin receptor modulators; kappa opioid receptors agonists such as TRK-820; GABA modulators; modulators of neuronal potassium channels such as flupirtine and retigabine; and glutamate receptor modulators.

~~36.~~30. The pharmaceutical formulation according to claim ~~35~~29, wherein said further active ingredient is a dopamine prodrug such as L-DOPA.

~~37.~~31. The pharmaceutical formulation according to any of the preceding claims, wherein said formulation is for oral administration.

~~38.~~32. ~~The~~ Use of the pharmaceutical formulation according to any of the preceding claims~~, wherein said formulation is for use~~ in the manufacture of a medicament for the treatment of a movement disorder.

~~39.~~33. The ~~pharmaceutical formulation~~ use according to claim ~~38~~32, wherein said movement disorder is selected from the group of consisting of Parkinson's disease, movement disorders associated with Parkinson's disease such as bradykinesia, akinesia and dyskinesia, L-DOPA induced dyskinesia, tardive dyskinesia, ataxia, akathisia, dystonia, essential tremor, Huntington's disease, myoclonus, Rett syndrome, Tourette syndrome, Wilson's disease, dyskinesias, chorea, Machado-Joseph disease, restless leg syndrome, spasmodic torticollis, geniospasm or movement disorders associated therewith, movement disorders associated with use of drugs such as neuroleptic drugs, antipsychotics, antidepressants and anti-emetics, idiopathic disease, genetic dysfunctions, infections or other conditions which lead to dysfunction of the basal ganglia and/or lead to altered synaptic dopamine levels, and withdrawal of drugs.

~~40.~~34. The pharmaceutical formulation according to any of ~~the preceding~~ claims 1 to 31, wherein said agonist of two or more the 5-HT1B, 5-HT1D and 5-HT1F receptors is to be administered in a dosage of from 0.001 to 10 mg/kg bodyweight, such as 0.001 to 5 mg/kg bodyweight, such as 0.01 to 1 mg/kg bodyweight.

~~41.~~35. The pharmaceutical formulation according to any of ~~the preceding~~ claims 1 to 31 and 34, wherein said 5-HT1A agonist is to be administered in a dosage of from 0.01 to 10 mg/kg bodyweight, such as 0.01 to 5 mg/kg bodyweight, such as 0.1 to 1 mg/kg bodyweight.

~~42.~~36. The pharmaceutical formulation according to any of ~~the preceding~~ claims 1 to 31, 34 and 35, wherein said formulation is to be administered once daily.

~~43.~~37. The pharmaceutical formulation according to any of ~~the preceding~~ claims 1 to 31, 34 to 36, wherein said formulation is to be administered in combination with a separate dopamine prodrug, such as L-DOPA, sequentially or simultaneously.

~~44.~~38. The pharmaceutical formulation according to claim ~~43~~37, wherein said pharmaceutical formulation is administered before or simultaneously with a dopamine prodrug such as L-DOPA.

~~45.~~39. The pharmaceutical formulation according to ~~any of~~ claim~~s 43 and 44~~ 37 or 38, wherein said separate dopamine prodrug, such as L-DOPA, is administered in combination with benzerazide.

~~46.~~40. The pharmaceutical formulation according to any of ~~the preceding~~ claims 1 to 31 and 34 to 39, wherein said formulation is to be administered as long as a movement disorder or an increased risk of developing a movement disorder is present.

~~47.~~41. The pharmaceutical formulation according to any of ~~the preceding~~ claims 1 to 31, 34 to 40, wherein said formulation is manufactured by

1) preparing granules by mixing (MCC and HPMC) with (HPMC and the agonist of two or more of the 5-HT1B, 5-HT1D and 5-HT1F receptors, such as zolmitriptan),
2) blending the granules of step 1) with talc,
3) compressing the talc granules of step 2) into a matrix tablet,
4) coating the matrix tablet of step 3) with a solution of (HPMC and an agonist of the 5-HT1A receptor such as buspirone), and
5) drying the coated matrix tablet of step 4).