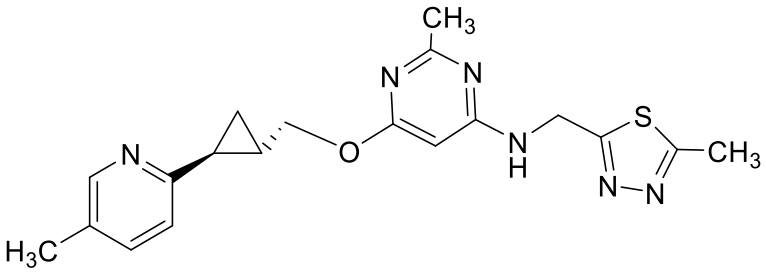
profiles and dose, the benefit of PDE10A inhibitors in the treatment of schizophrenia is confounded by insufficient target engagement and side effects. Understanding of the requirements for PDE10A inhibitors constitutes a challenging but promising field of drug discovery and development.

[0006] There remains a need for CR formulations of PDE10A inhibitors with an improved tolerability profile (reduced adverse events/side effects, e.g., dystonia, akathisia) and patient compliance.

SUMMARY

[0007] U.S. Patent 9,062,059 discloses potent PDE10A inhibitors, including 2-methyl-*N*-((5-methyl-1,3,4-thiadiazol-2-yl)methyl)-6-(((1*S*,2*S*)-2-(5-methylpyridin-2-yl)cyclopropyl)methoxy)pyrimidin-4-amine (Compound A), an ester derivative, geometric isomer, stereoisomer, or optical isomer thereof as therapeutics for neurological and psychiatric disorders. This disclosure provides CR formulations of Compound A and their use in the treatment of schizophrenia and other psychiatric disorders that improves the tolerability profile. In one aspect, this disclosure provides a controlled-release tablet formulation comprising a: 1) first layer having about 1%-25% by weight of pharmaceutically acceptable Compound A, represented by structural formula I:



I

or a pharmaceutically acceptable salt, ester derivative, geometric isomer, stereoisomer, or optical isomer thereof and about 60-90% by weight low viscosity polyethylene oxide (PEO) polymer; 2) second layer comprising about 50%-70% by weight high viscosity polyethylene oxide polymer, about 10%-40% by weight metal halide and about 5%-30% by weight tableting agent; and 3) semipermeable coating wherein the coating comprises about 1%-15% by weight of the tablet, said tablet having an orifice in the first layer, wherein said formulation induces no dystonia after administration. This disclosure also provides CR formulations of Compound A and their use in the treatment of schizophrenia and other psychiatric disorders that allows high peak concentrations (Cmax) with minimal or no incidence of dystonia.

This disclosure also provides CR formulations of Compound A wherein the excipients of the formulation are not dose dependent. This disclosure also provides CR formulations of Compound A and their use in the treatment of schizophrenia and other psychiatric disorders that can be dosed at high concentrations without titration. This disclosure also provides CR formulations of Compound A and their use in the treatment of schizophrenia and other psychiatric disorders that can be administered at doses that provide high peak concentrations (Cmax) with minimal or no incidence of dystonia. This disclosure also provides controlled-release formulations of Compound A that provide high peak concentrations (Cmax) and their use in the treatment of schizophrenia and other psychiatric disorders. In another aspect, this disclosure provides a controlled-release formulation of Compound A as defined herein for use in therapy.

[0008] This disclosure further provides CR formulations of Compound A and their use in the treatment of schizophrenia and other psychiatric disorders wherein the incidence of dystonia is reduced or eliminated. This disclosure further provides CR formulations of Compound A and their use in the treatment of schizophrenia and other psychiatric disorders wherein the incidence of dystonia is reduced or eliminated when administering escalated

doses (16 mg or higher) to ensure effective concentrations can be maintained for the duration of the dosing interval. In another aspect, this disclosure provides use of a controlled-release formulation of Compound A as defined herein in the manufacture of a medicament for the treatment of schizophrenia or other psychiatric disorders in a patient in need thereof, wherein the Compound A is to be administered at doses of 16mg or higher without inducing dystonia in the patient. The disclosure further provides CR formulations of Compound A having at or near zero-order release profiles, with pharmacokinetic profiles exhibiting minimal fluctuation between peak concentrations and trough concentrations which improves the tolerability profile. One example is CR formulations of Compound A with PTR from about 1.0 to about 3.5. An example of this disclosure is realized when PTR is from about 1.0 to about 2.0. Another example of this disclosure is realized when the peak concentration to trough concentration ratio is from about 1.0 to about 1.5. Another example of this disclosure is realized when the peak concentration to trough concentration ratio is from about 1.0 to about 1.3.

[0009] Another example of the disclosure is realized wherein patients are dosed with about 20mg to about 80mg, about 17 to about 47mg, 20mg to about 36mg, or about 17mg to about 24mg of CR formulations of Compound A with minimal or no dystonia. An example is realized when the CR formulation of Compound A is compared to an immediate-release (IR) formulation of Compound A having the same dose.

[0010] Another example of the disclosure is realized wherein dystonia is healthy participants and/or patients suffering with schizophrenia or other psychiatric disorders are dosed with CR formulations described herein of about 17mg to about 47mg, about 20mg to about 36, or about 20mg to about 24mg. An example is realized when the CR formulation of Compound A is compared to an IR formulation of Compound A having the same dose.

[0011] Another example of the disclosure is realized wherein healthy participants and patients suffering with schizophrenia or other psychiatric disorders are dosed with CR formulations described herein of about 20mg to about 36, about 20mg to about 24mg, or 24mg of the CR formulations of Compound A without titration wherein patients experience minimal or no observed dystonia. An example is realized when the CR formulation of Compound A is compared to an IR formulation of Compound A having the same dose.

[0012] An example of the disclosure are CR formulations comprising about 2mg to about 80mg of Compound A dosed once daily. Another example of the disclosure are CR formulations comprising from about 16mg to about 36, about 20mg to about 24mg, or 24mg of Compound A without titration. An example is realized when the release of Compound A is controlled and occurs over a period of about 12-24 hours. After repeat

administration of the composition into an in vivo environment, steady-state Cmax plasma concentrations are achieved by ~10 to 24 hours and are generally sustained over the dosing interval. Another example is realized when Compound A is dosed once daily with about 17mg to about 47mg, about 20mg to about 36mg or about 20mg to about 24mg, wherein the incidence of dystonia is mitigated. Another example is realized when the CR formulation of Compound A is administered once daily without incidence of dystonia. Another example is realized when the CR formulation of Compound A is administered at about 20mg to about 47mg once daily, without incidence of dystonia.

[0013] Another example of the disclosure is CR formulations wherein the amount of Compound A present in said formulation is estimated to produce generally sustained/constant enzyme occupancy (EO) levels at both the peak and trough of the 24 hr dosing interval (Table 2 – 5) in contrast to the IR formulation (Table 1). An example of the disclosure is realized when high levels of the estimated EO are sustained at both peak and trough at doses ranging from about 17mg to about 47mg, about 20mg to about 36mg, or about 20mg to 24mg. An example is realized when the estimated EO levels at both peak and trough are sustained above 75% at steady state. Another example is realized when the estimated EO levels at both peak and trough are sustained from about 65%-99%, 67%-99%, 70%-99%, 80-99%, 85%-99% at steady state. Another example is realized when the estimated EO levels at both peak and trough are sustained from about 70% to 99% at doses ranging from about 17mg to 47mg, or about 20mg to 36 mg in both the healthy population and population suffering from schizophrenia with no reported events of dystonia. Another example is realized when the estimated EO levels at both peak and trough are sustained from about 70% to 99% at doses ranging from about 17mg to 47mg or 20mg to 36 mg in patients suffering from schizophrenia with no reported events of dystonia. Another example is realized when the estimated EO levels are sustained from about 70% to 99% at doses ranging from about 17mg to 47mg or about 20mg to 36mg in healthy population with no reported events of dystonia.

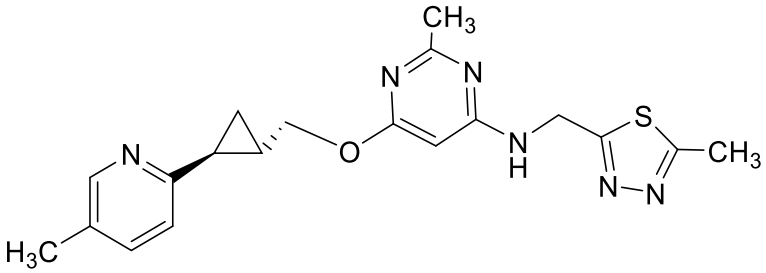
[0014] Other aspects of the disclosure can be realized upon review of the specification as a whole.

CLAIMS

What is claimed is:

1. A controlled-release tablet formulation comprising a:

1) first layer having about 1%-25% by weight of pharmaceutically acceptable Compound A, represented by structural formula I:



I

or a pharmaceutically acceptable salt, ester derivative, geometric isomer, stereoisomer, or optical isomer thereof and about 60-90% by weight low viscosity polyethylene oxide (PEO) polymer;

2) second layer comprising about 50%-70% by weight high viscosity polyethylene oxide polymer, about 10%-40% by weight metal halide and about 5%-30% by weight tableting agent; and

3) semipermeable coating wherein the coating comprises about 1%-15% by weight of the tablet, said tablet having an orifice in the first layer, wherein said formulation induces no dystonia after administration.

2. The formulation according to claim 1 wherein the low viscosity polyethylene oxide has a molecular weight range (g/mol) of about 100, 000 to 300,000 and is present in the first layer at about 65%-88% by weight.

3. The formulation of claims 1 or 2 wherein the high viscosity polyethylene oxide has a molecular weight range (g/mol) of about 4,000,000 to 7,000,000 and is present in the second layer at about 50%-70% by weight.

4. The formulation of any one of claims 1 to 3, wherein the tableting agent is selected from lactose, spray dried lactose, microcrystalline cellulose, mannitol, sorbitol, dibasic calcium phosphate dehydrate, and calcium sulphate dehydrate.

5. The formulation of claim 4 wherein the tableting agent is microcrystalline cellulose, present at about 10%-20% by weight.

6. The formulation of any one of claims 1 to 5, wherein the metal halide selected from sodium chloride, potassium chloride, calcium chloride, and potassium iodide, or a mixture thereof, and is present at about 15%-25% by weight.

7. The formulation any one of claims 1 to 6, wherein the semipermeable coating comprises cellulose acetate, ethyl cellulose, or a combination thereof and low molecular weight polyethylene glycol.

8. The formulation of any one of claims 1 to 7, wherein Compound A, or a pharmaceutically acceptable salt, ester derivative, geometric isomer, stereoisomer, or optical isomer thereof is present at about 4%-25% by weight, and low viscosity polyethylene oxide has a molecular weight range (g/mol) of about 100,000 to 300,000 and is present at about 65%-88% by weight of total first layer weight.

9. The formulation of any one of claims 1 to 8,

a) the high viscosity polyethylene oxide has a molecular weight range (g/mol) of about 4,000,000 to 7,000,000 and is present at about 60%-68% by weight,

b) the tableting agent is present up to10%-20% by weight, and

c) the metal halide is present at about 15%-25% by weight

of total weight of the second layer.

10. The formulation of any one of claims 1 to 9, wherein 5%-15% of the semipermeable coating comprises cellulose acetate, ethyl cellulose, or mixture thereof, wherein the cellulose acetate, ethyl cellulose, or mixture thereof contains about 5%-20%, by weight, of low molecular weight polyethylene glycol.

11. The formulation of any one of claims 1 to 10, further comprising a sugar alcohol selected from mannitol, sucrose, and lactose.

12. The formulation of any one of claims 1 to 11, that exhibits peak to trough concentration levels of Compound A from about 1.0 to about 3.5.

13. The formulation of any one of claims 1 to 12, comprising from about 17 mg to about 47 mg of Compound A which can be administered once daily with no incidence of dystonia.

14. The formulation of any one of claims 1 to 13, comprising Compound A at doses at 16mg or higher which exhibits sustained muscarinic enzyme occupancy at both peak and trough of about 65% or higher.

15. The formulation according to claim 14, wherein when administered in a patient population suffering from schizophrenia there are no reported incidents of dystonia.

16. Use of a controlled-release formulation of Compound A according to any one of claims 1 to 15 in the manufacture of a medicament for the treatment of schizophrenia or other psychiatric disorders in a patient in need thereof, wherein the Compound A is to be administered at doses of 16mg or higher without inducing dystonia in the patient.

17. A controlled-release formulation of Compound A according to any one of claims 1 to 15 for use in therapy.