

by CYP followed by a Roman or Arabic numeral, e.g., CYP3), and further divided into subfamilies (designated by a capital letter, e.g., CYP3A), which are comprised of those forms that are at least 55% related by their deduced amino acid sequences. Finally, the gene for each individual form of cytochrome P450 is assigned an Arabic number (e.g., CYP3A4).

[0007] CYP3A isoenzyme is a member of the cytochrome P450 superfamily which constitutes up to 60% of the total human liver microsomal cytochrome P450 and has been found in alimentary passage of stomach and intestines and livers. CYP3A has also been found in kidney epithelial cells, jejunal mucosa, and the lungs. CYP3A is one of the most abundant subfamilies in cytochrome P450 superfamily.

[0008] At least five (5) forms of CYPs are found in human CYP3A subfamily, and these forms are responsible for the metabolism of a large number of structurally diverse drugs. In non-induced individuals, CYP3A may constitute 15% of the P450 enzymes in the liver; in enterocytes, members of the CYP3A subfamily constitute greater than 70% of the CYP-containing enzymes.

[0009] CYP3A is responsible for metabolism of a large number of drugs including nifedipine, macrofide antibiotics including erythromycin and troleandomycin, cyclosporin, FK506, teffenedine, tamoxifen, lidocaine, midazolam, triazolam, dapsone, diltiazem, lovastatin, quinidine, ethylestradiol, testosterone, and alfentanil. CYP3A is involved in erythromycin N-demethylation, cyclosporine oxidation, nifedipine oxidation, midazolam hydroxylation, testosterone 6- β -hydroxylation, and cortisol 6- β -hydroxylation. CYP3A has also been shown to be involved in both bioactivation and detoxication pathways for several carcinogens *in vitro*.

[0010] There is a significant, unmet need for methods for administering a VMAT2 inhibitor, such as valbenazine or (+)- α -3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-ol, or a pharmaceutically acceptable salt and/or isotopic variant thereof, to a patient in need thereof, wherein the patient is also being treated with another substance which may interact with the VMAT2 inhibitor, such as a CYP3A4 inducer. The present disclosure fulfills these and other needs, as evident in reference to the following disclosure.

SUMMARY

[0010a] In one aspect, the present disclosure provides use of a therapeutically effective amount of a vesicular monoamine transport 2 (VMAT2) inhibitor chosen from valbenazine

and (+)- α -3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-ol, or a pharmaceutically acceptable salt and/or isotopic variant thereof, in the manufacture of a medicament for treating a patient in need of a vesicular monoamine transport 2 (VMAT2) inhibitor chosen from valbenazine and (+)- α -3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-ol, or a pharmaceutically acceptable salt and/or isotopic variant thereof, wherein:

the patient is to be administered a therapeutically effective amount of the VMAT2 inhibitor and

the patient or a medical care worker is to be informed that co-administration of a strong cytochrome P450 3A4 (CYP3A4) inducer is not recommended.

[0010b] In one aspect, the present disclosure provides use of a therapeutically effective amount of a vesicular monoamine transport 2 (VMAT2) inhibitor chosen from valbenazine and (+)- α -3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-ol, or a pharmaceutically acceptable salt and/or isotopic variant thereof, in the manufacture of a medicament for treating a patient in need of a vesicular monoamine transport 2 (VMAT2) inhibitor chosen from valbenazine and (+)- α -3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-ol, or a pharmaceutically acceptable salt and/or isotopic variant thereof, wherein the patient is being treated with a strong cytochrome P450 3A4 (CYP3A4) inducer, wherein:

treatment of the strong CYP3A4 inducer is to be discontinued and then

the VMAT2 inhibitor is to be administered to the patient, thereby avoiding the use of the VMAT2 inhibitor in combination with the strong CYP3A4 inducer.

[0011] Provided is a method of administering a vesicular monoamine transport 2 (VMAT2) inhibitor chosen from valbenazine and (+)- α -3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-ol, or a pharmaceutically acceptable

salt and/or isotopic variant thereof to a patient in need thereof, comprising: administering to the patient a therapeutically effective amount of the VMAT2 inhibitor and informing the patient or a medical care worker that co-administration of a strong cytochrome P450 3A4 (CYP3A4) inducer is not recommended.

[0012] Also provided is a method of administering a vesicular monoamine transport 2 (VMAT2) inhibitor chosen from valbenazine and (+)- α -3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-ol, or a pharmaceutically acceptable salt and/or isotopic variant thereof to a patient in need thereof wherein the patient is being treated with a strong cytochrome P450 3A4 (CYP3A4) inducer, comprising: discontinuing treatment of the strong CYP3A4 inducer and then administering the VMAT2 inhibitor to the patient, thereby avoiding the use of the VMAT2 inhibitor in combination with the strong CYP3A4 inducer.

[0013] These and other aspects of the disclosure will be apparent upon reference to the following detailed description. To this end, various references are set forth herein which describe in more detail certain background information, procedures, compounds, and/or compositions, and are each hereby incorporated by reference in their entirety.

DETAILED DESCRIPTION

[0014] In the following description, certain specific details are set forth in order to provide a thorough understanding of various embodiments. However, one skilled in the art will understand that the invention may be practiced without these details. In other instances, well-known structures have not been shown or described in detail to avoid unnecessarily obscuring descriptions of the embodiments. Unless the context requires otherwise, throughout the specification and claims which follow, the word “comprise” and variations thereof, such as, “comprises” and “comprising” are to be construed in an open, inclusive sense, that is, as “including, but not limited to.” Further, headings provided herein are for convenience only and do not interpret the scope or meaning of the claimed invention.

[0015] Reference throughout this specification to “one embodiment” or “an embodiment” or “some embodiments” or “a certain embodiment” means that a particular feature, structure or characteristic described in connection with the embodiment is included in at least one embodiment. Thus, the appearances of the phrases “in one embodiment” or “in an embodiment” or “in some embodiments” or “in a certain embodiment” in various places throughout this specification are not necessarily all referring to the same embodiment.

CLAIMS:

1. Use of a therapeutically effective amount of a vesicular monoamine transport 2 (VMAT2) inhibitor chosen from valbenazine and (+)- α -3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-ol, or a pharmaceutically acceptable salt and/or isotopic variant thereof, in the manufacture of a medicament for treating a patient in need of a vesicular monoamine transport 2 (VMAT2) inhibitor chosen from valbenazine and (+)- α -3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-ol, or a pharmaceutically acceptable salt and/or isotopic variant thereof, wherein:
the patient is to be administered a therapeutically effective amount of the VMAT2 inhibitor and
the patient or a medical care worker is to be informed that co-administration of a strong cytochrome P450 3A4 (CYP3A4) inducer is not recommended.
2. The use of claim 1, wherein the patient or medical care worker is to be informed that co-administration of the strong CYP3A4 inducer should be avoided or discontinued.
3. Use of a therapeutically effective amount of a vesicular monoamine transport 2 (VMAT2) inhibitor chosen from valbenazine and (+)- α -3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-ol, or a pharmaceutically acceptable salt and/or isotopic variant thereof, in the manufacture of a medicament for treating a patient in need of a vesicular monoamine transport 2 (VMAT2) inhibitor chosen from valbenazine and (+)- α -3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-ol, or a pharmaceutically acceptable salt and/or isotopic variant thereof, wherein the patient is being treated with a strong cytochrome P450 3A4 (CYP3A4) inducer, wherein:
treatment of the strong CYP3A4 inducer is to be discontinued and then
the VMAT2 inhibitor is to be administered to the patient, thereby avoiding the use of the VMAT2 inhibitor in combination with the strong CYP3A4 inducer.
4. The use of any one of claims 1 to 3, wherein the strong CYP3A4 inducer is chosen from nevirapine, pentobarbital, phenytoin, lumacaftor, rifabutin, rifampicin, carbamazepine, fosphenytoin, phenobarbital, primidone, primidone, enzalutamide, mitotane, and St. John's Wort.
5. The use of claim 4, wherein the strong CYP3A4 inducer is chosen from rifampicin, carbamazepine, phenytoin, and St. John's Wort.
6. The use of claim 5, wherein the strong CYP3A4 inducer is rifampicin.

7. The use of any one of claims 1 to 6, wherein the VMAT2 inhibitor is to be administered to the patient to treat a neurological or psychiatric disease or disorder.
8. The use of claim 7, wherein the neurological or psychiatric disease or disorder is a hyperkinetic movement disorder, mood disorder, bipolar disorder, schizophrenia, schizoaffective disorder, mania in mood disorder, depression in mood disorder, treatment-refractory obsessive compulsive disorder, neurological dysfunction associated with Lesch-Nyhan syndrome, agitation associated with Alzheimer's disease, Fragile X syndrome or Fragile X-associated tremor-ataxia syndrome, autism spectrum disorder, Rett syndrome, or chorea-acanthocytosis.
9. The use of claim 8, wherein the neurological or psychiatric disease or disorder is a hyperkinetic movement disorder.
10. The use of claim 9, wherein the hyperkinetic movement disorder is tardive dyskinesia.
11. The use of claim 9, wherein the hyperkinetic movement disorder is Tourette's syndrome.
12. The use of claim 9, wherein the hyperkinetic movement disorder is Huntington's disease.
13. The use of claim 9, wherein the hyperkinetic movement disorder is tics.
14. The use of claim 9, wherein the hyperkinetic movement disorder is chorea associated with Huntington's disease.
15. The use of claim 9, wherein the hyperkinetic movement disorder is ataxia, chorea, dystonia, Huntington's disease, myoclonus, restless leg syndrome, or tremors.

16. The use of any one of claims 1 to 15, wherein the VMAT2 inhibitor is to be administered orally.
17. The use of any one of claims 1 to 16, wherein the VMAT2 inhibitor is to be administered in the form of a tablet or capsule.
18. The use of any one of claims 1 to 17, wherein the VMAT2 inhibitor is to be administered with or without food.
19. The use of any one of claims 1 to 18, wherein the VMAT2 inhibitor is valbenazine or a pharmaceutically acceptable salt and/or isotopic variant thereof.
20. The use of claim 19, wherein the VMAT2 inhibitor is valbenazine or a pharmaceutically acceptable salt thereof.
21. The use of claim 20, wherein the VMAT2 inhibitor is a valbenazine tosylate salt.
22. The use of claim 21, wherein the VMAT2 inhibitor is a ditosylate salt of valbenazine.
23. The use of claim 19, wherein the VMAT2 inhibitor is an isotopic variant that is L-Valine, (2*R*,3*R*,11*bR*)-1,3,4,6,7,11*b*-hexahydro-9,10-di(methoxy- d_3)-3-(2-methylpropyl)-2*H*-benzo[*a*]quinolizin-2-yl ester or a pharmaceutically acceptable salt thereof.
24. The use of any one of claims 1 to 23, wherein the VMAT2 inhibitor is to be administered in an amount equivalent to between about 20 mg and about 160 mg of valbenazine free base.
25. The use of claim 24, wherein the VMAT2 inhibitor is to be administered in an amount equivalent to about 20 mg of valbenazine free base.

26. The use of claim 24, wherein the VMAT2 inhibitor is to be administered in an amount equivalent to about 40 mg of valbenazine free base.
27. The use of claim 24, wherein the VMAT2 inhibitor is to be administered in an amount equivalent to about 60 mg of valbenazine free base.
28. The use of claim 24, wherein the VMAT2 inhibitor is to be administered in an amount equivalent to about 80 mg of valbenazine free base.
29. The use of claim 24, wherein the VMAT2 inhibitor is to be administered in an amount equivalent to about 120 mg of valbenazine free base.
30. The use of any one of claims 1 to 23, wherein the VMAT2 inhibitor is to be administered for a first period of time in a first amount and then the amount is increased to a second amount.
31. The use of claim 30, wherein the first period of time is a week.
32. The use of claim 30 or 31 wherein the first amount is equivalent to about 40 mg of valbenazine free base.
33. The use of any one of claims 30 to 32, wherein the second amount is equivalent to about 80 mg of valbenazine free base.
34. The use of any one of claims 1 to 23, wherein the VMAT2 inhibitor is to be administered in an amount sufficient to achieve a maximal blood plasma concentration ($C_{\max}$) of (+)- α -DHTBZ of between about 15 ng to about 60 ng per mL plasma and a minimal blood plasma concentration ($C_{\min}$) of (+)- α -DHTBZ of at least 15 ng per mL plasma over an 8 hour period.
35. The use of any one of claims 1 to 23, wherein the VMAT2 inhibitor is to be administered in an amount sufficient to achieve a maximal blood plasma concentration ($C_{\max}$) of (+)- α -DHTBZ of between about 15 ng to about 60 ng per mL plasma and a minimal blood plasma concentration ($C_{\min}$) of approximately between about at least 33% -50% of the $C_{\max}$ over a 12 hour period.

36. The use of any one of claims 1 to 23, wherein the VMAT2 inhibitor is to be administered in an amount sufficient to achieve: (i) a therapeutic concentration range of about 15 ng to about 60 ng of (+)- α -DHTBZ per mL plasma; and (ii) a threshold concentration of at least 15 ng (+)- α -DHTBZ per mL plasma over a period of about 8 hours to about 24 hours.
37. The use of any one of claims 1 to 18, wherein the VMAT2 inhibitor is (+)- α -3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-ol, or a pharmaceutically acceptable salt and/or isotopic variant thereof.
38. The use of claim 37, wherein the VMAT2 inhibitor is (+)- α -3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-ol, or a pharmaceutically acceptable salt thereof.
39. The use of claim 37, wherein the VMAT2 inhibitor is an isotopic variant that is (+)- α -3-isobutyl-9,10-di(methoxy-d₃)-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-ol or a pharmaceutically acceptable salt thereof.