contraindications, warnings, and precautions for patients with cardiovascular risk factors and disease (See Alwhaibi M, et al. Pain Res Treat. 2016; 2016:8538101, and Gilmore B, Michael M. Am Fam Physician. 2011(83)271-280). Thus, for prior monotherapy or dual therapy migraine prevention and/or treatments, a substantial fraction of patients may fail to achieve headache relief and/or freedom from pain in response to treatment or preventative therapy. Further, some patients, referred to herein as therapy resistant migraine patients, will fail to successfully manage their migraine attacks and will suffer from migraines which are refractory to two or more prior monotherapy and/or dual therapy prevention or treatment regimens. These inadequately controlled migraine patients may have a number of migraine days per-month that continues to be significantly disabling.

There exists a need for more and different therapies that may prove to be effective in preventing migraine, and/or reducing the patients' susceptibility to migraine, and in particular for the prevention of therapy resistant migraines. Therapy resistant migraines is defined herein as migraine refractory to two or more prior monotherapy and/or dual therapy prevention and/or treatment regimens. Thus, there exists a need for new prevention options for patients who suffer from migraine attacks and have previously failed migraine preventative medications.

Summary

In one aspect, the present disclosure refers to a use of 2,4,6-trifluoro-N-[6-(1-methyl-piperidin-4-ylcarbonyl)-pyridin-2-yl]-benzamide, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the prevention of migraine in a patient, wherein the medicament is in a form for chronic nightly administration.

In another aspect, the present disclosure refers to a use of 2,4,6-trifluoro-N-[6-(1-methyl-piperidin-4-ylcarbonyl)-pyridin-2-yl]-benzamide, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the prevention of migraine, wherein the medicament is to be administered nightly at an oral dose of 25-200 mg of 2,4,6-trifluoro-N-[6-(1-methyl-piperidin-4-ylcarbonyl)-pyridin-2-yl]-benzamide, or a pharmaceutically acceptable salt thereof.

In yet another aspect, the present disclosure refers to a use of 2,4,6-trifluoro-N-[6-(1-methyl-piperidin-4-ylcarbonyl)-pyridin-2-yl]-benzamide, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the prevention of migraine, wherein the medicament is to be administered nightly at an oral dose of 25-200 mg of 2,4,6-trifluoro-N-[6-(1-methyl-piperidin-4-ylcarbonyl)-pyridin-2-yl]-benzamide, or a pharmaceutically acceptable salt thereof, for at least five consecutive nights.

In a further aspect, the present disclosure refers to a use of 2,4,6-trifluoro-N-[6-(1-methyl-piperidin-4-ylcarbonyl)-pyridin-2-yl]-benzamide, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the prevention of migraine, wherein the medicament is to be administered nightly at an oral dose of 25-200 mg of 2,4,6-trifluoro-N-[6-(1-methyl-piperidin-4-ylcarbonyl)-pyridin-2-yl]-benzamide, or a pharmaceutically acceptable salt thereof, for at least thirty consecutive nights.

In another aspect, the present disclosure refers to a use of 2,4,6-trifluoro-N-[6-(1-methyl-piperidin-4-ylcarbonyl)-pyridin-2-yl]-benzamide, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the prevention of migraine, wherein the medicament is to be administered at an oral dose of 25-200 mg of 2,4,6-trifluoro-N-[6-(1-methyl-piperidin-4-ylcarbonyl)-pyridin-2-yl]-benzamide, or a pharmaceutically acceptable salt thereof, every other night for at least ten consecutive nights.

In yet another aspect, the present disclosure refers to a use of 2,4,6-trifluoro-N-[6-(1-methyl-piperidin-4-ylcarbonyl)-pyridin-2-yl]-benzamide, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the prevention of migraine, wherein the medicament is to be administered at an oral dose of 25-200 mg of 2,4,6-trifluoro-N-[6-(1-methyl-piperidin-4-ylcarbonyl)-pyridin-2-yl]-benzamide, or a pharmaceutically acceptable salt thereof, every other night for at least thirty consecutive nights.

Description

The present invention provides for chronic nightly administration of lasmiditan and methods of preventing migraine. Chronic nightly administration of lasmiditan represents an innovative approach for prevention of migraine by selectively targeting 5-HT_{1F} with long-term nightly administration targeted to coincide with patients sleeping hours. Further, the

present invention provides for the use of chronic nightly administration of lasmiditan for reducing the patients' susceptibility to migraine. Further, the present invention provides for chronic nightly administration of lasmiditan and to methods of preventing therapy resistant migraine, which is defined herein as migraine refractory to two or more prior monotherapy and/or dual therapy treatment or prevention regimens.

Preclinical studies such as those described in Example 1 suggest that lasmiditan use can induce a surprisingly persistent improvement in a dysfunctional state of the trigeminal nervous system. Similarly, phase III clinical studies such as those described in Example 2 provide surprising and unexpected evidence that improvements in migraine patients

What is claimed:

1. Use of 2,4,6-trifluoro-N-[6-(1-methyl-piperidin-4-ylcarbonyl)-pyridin-2-yl]-benzamide, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the prevention of migraine in a patient, wherein the medicament is in a form for chronic nightly administration.

2. The use of claim 1, wherein the medicament is to be administered for at least five consecutive nights.

3. The use of claim 1, wherein the medicament is to be administered for at least thirty consecutive nights.

4. The use of claim 1, wherein the medicament is to be administered every other night, for at least ten consecutive nights.

5. The use of claim 1, wherein the medicament is to be administered every other night, for at least thirty consecutive nights.

6. The use of claim 1, wherein the patients' migraines have been refractory to two or more prior monotherapy and/or dual therapy treatment and/or prevention regimens.

7. The use of any one of claims 1 to 6, wherein the medicament is to be administered at a dose of 2,4,6-trifluoro-N-[6-(1-methyl-piperidin-4-ylcarbonyl)-pyridin-2-yl]-benzamide, or a pharmaceutically acceptable salt thereof, of 25 mg to 200 mg.

8. The use of any one of claims 1 to 6, wherein the medicament is to be administered at a dose of 2,4,6-trifluoro-N-[6-(1-methyl-piperidin-4-ylcarbonyl)-pyridin-2-yl]-benzamide, or a pharmaceutically acceptable salt thereof, of 25 mg.

9. The use of any one of claims 1 to 6, wherein the medicament is to be administered at a dose of 2,4,6-trifluoro-N-[6-(1-methyl-piperidin-4-

ylcarbonyl)-pyridin-2-yl]-benzamide, or a pharmaceutically acceptable salt thereof, of 50 mg.

10. The use of any one of claims 1 to 6, wherein the medicament is to be administered at a dose of 2,4,6-trifluoro-N-[6-(1-methyl-piperidin-4-ylcarbonyl)-pyridin-2-yl]-benzamide, or a pharmaceutically acceptable salt thereof, of 75 mg.

11. The use of any one of claims 1 to 6, wherein the medicament is to be administered at a dose of 2,4,6-trifluoro-N-[6-(1-methyl-piperidin-4-ylcarbonyl)-pyridin-2-yl]-benzamide, or a pharmaceutically acceptable salt thereof, of 100 mg.

12. The use of any one of claims 1 to 6, wherein the medicament is to be administered at a dose of 2,4,6-trifluoro-N-[6-(1-methyl-piperidin-4-ylcarbonyl)-pyridin-2-yl]-benzamide, or a pharmaceutically acceptable salt thereof, of 150 mg.

13. The use of any one of claims 1 to 6, wherein the medicament is to be administered at a dose of 2,4,6-trifluoro-N-[6-(1-methyl-piperidin-4-ylcarbonyl)-pyridin-2-yl]-benzamide, or a pharmaceutically acceptable salt thereof, of 200 mg.

14. Use of 2,4,6-trifluoro-N-[6-(1-methyl-piperidin-4-ylcarbonyl)-pyridin-2-yl]-benzamide, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the prevention of migraine, wherein the medicament is to be administered nightly at an oral dose of 25-200 mg of 2,4,6-trifluoro-N-[6-(1-methyl-piperidin-4-ylcarbonyl)-pyridin-2-yl]-benzamide, or a pharmaceutically acceptable salt thereof.

15. Use of 2,4,6-trifluoro-N-[6-(1-methyl-piperidin-4-ylcarbonyl)-pyridin-2-yl]-benzamide, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the prevention of migraine, wherein the medicament is to be administered nightly at an oral dose of 25-200 mg of 2,4,6-trifluoro-N-[6-(1-

methyl-piperidin-4-ylcarbonyl)-pyridin-2-yl]-benzamide, or a pharmaceutically acceptable salt thereof, for at least five consecutive nights.

16. Use of 2,4,6-trifluoro-N-[6-(1-methyl-piperidin-4-ylcarbonyl)-pyridin-2-yl]-benzamide, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the prevention of migraine, wherein the medicament is to be administered nightly at an oral dose of 25-200 mg of 2,4,6-trifluoro-N-[6-(1-methyl-piperidin-4-ylcarbonyl)-pyridin-2-yl]-benzamide, or a pharmaceutically acceptable salt thereof, for at least thirty consecutive nights.

17. Use of 2,4,6-trifluoro-N-[6-(1-methyl-piperidin-4-ylcarbonyl)-pyridin-2-yl]-benzamide, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the prevention of migraine, wherein the medicament is to be administered at an oral dose of 25-200 mg of 2,4,6-trifluoro-N-[6-(1-methyl-piperidin-4-ylcarbonyl)-pyridin-2-yl]-benzamide, or a pharmaceutically acceptable salt thereof, every other night for at least ten consecutive nights.

18. Use of 2,4,6-trifluoro-N-[6-(1-methyl-piperidin-4-ylcarbonyl)-pyridin-2-yl]-benzamide, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the prevention of migraine, wherein the medicament is to be administered at an oral dose of 25-200 mg of 2,4,6-trifluoro-N-[6-(1-methyl-piperidin-4-ylcarbonyl)-pyridin-2-yl]-benzamide, or a pharmaceutically acceptable salt thereof, every other night for at least thirty consecutive nights.

19. The use of claim 14, wherein the medicament is to be administered nightly at an oral dose of 25 mg of 2,4,6-trifluoro-N-[6-(1-methyl-piperidin-4-ylcarbonyl)-pyridin-2-yl]-benzamide, or a pharmaceutically acceptable salt thereof.

20. The use of claim 14, wherein the medicament is to be administered nightly at an oral dose of 50 mg of 2,4,6-trifluoro-N-[6-(1-methyl-piperidin-4-ylcarbonyl)-pyridin-2-yl]-benzamide, or a pharmaceutically acceptable salt thereof.

21. The use of claim 14, wherein the medicament is to be administered nightly at an oral dose of 75 mg of 2,4,6-trifluoro-N-[6-(1-methyl-piperidin-4-ylcarbonyl)-pyridin-2-yl]-benzamide, or a pharmaceutically acceptable salt thereof.

22. The use of claim 14, wherein the medicament is to be administered nightly at an oral dose of 100 mg of 2,4,6-trifluoro-N-[6-(1-methyl-piperidin-4-ylcarbonyl)-pyridin-2-yl]-benzamide, or a pharmaceutically acceptable salt thereof.

23. The use of claim 14, wherein the medicament is to be administered nightly at an oral dose of 150 mg of 2,4,6-trifluoro-N-[6-(1-methyl-piperidin-4-ylcarbonyl)-pyridin-2-yl]-benzamide, or a pharmaceutically acceptable salt thereof.

24. The use of claim 14, wherein the medicament is to be administered nightly at an oral dose of 200 mg of 2,4,6-trifluoro-N-[6-(1-methyl-piperidin-4-ylcarbonyl)-pyridin-2-yl]-benzamide, or a pharmaceutically acceptable salt thereof.

25. The use of any one of claims 1 to 24 substantially as herein described with reference to any example thereof and with or without reference to the accompanying drawings.