Despite considerable advances in drug treatment over the past two decades, patients receiving medication for the treatment of GERD continue to have a number of important needs for more effective control of their symptoms. In view of the importance of this unmet medical need, there is a great need for developing an effective treatment for the reduction of GERD symptoms in this difficult-to-treat population of patients with an insufficient response to a PPI.

Summary

In one aspect of the present disclosure, there is provided a use of a potassium-competitive acid blocker (P-CAB) in the manufacture of a medicament for the treatment, prevention and/or reduction of gastro-esophageal reflux disease (GERD) symptoms in patients who are partial responders to a proton pump inhibitor (PPI).

The present disclosure also provides a potassium-competitive acid blocker (P-CAB) for use in the treatment, prevention and/or reduction of GERD symptoms in patients with an insufficient response to a proton pump inhibitor (PPI) (i.e. PPI partial responders).

The present disclosure also provides a P-CAB for use in the treatment, prevention and/or reduction of symptoms of non-erosive reflux disease (NERD) or erosive esophagitis (EE) of Grade A as defined by the Los Angeles (LA) Classification.

The present disclosure further provides a pharmaceutical composition comprising the P-CAB for use according to the present disclosure.

The present disclosure also provides a method of treating, preventing and/or reducing GERD symptoms in a patient in need thereof, wherein the patient has an insufficient response to a proton pump inhibitor (PPI) (i.e. PPI partial responder), the method comprising administering to the patient a prophylactically or therapeutically effective amount of a potassium-competitive acid blocker (P-CAB).

The present disclosure also provides the use of a potassium-competitive acid blocker (P-CAB) for the manufacture of a medicament for use in the treatment, prevention and/or reduction of GERD symptoms in patients with an insufficient response to a proton pump inhibitor (PPI) (i.e. PPI partial responders).

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The present disclosure also provides the use of a P-CAB for the manufacture of a medicament for use in the treatment, prevention and/or reduction of symptoms of non-erosive reflux

disease (NERD) or erosive esophagitis (EE) of Grade A as defined by the Los Angeles (LA) Classification.

Preferably the P-CAB for use according to the present disclosure is for the treatment, prevention and/or reduction of symptoms of non-erosive reflux disease (NERD).

Preferably the P-CAB for use according to the present disclosure is for the treatment, prevention and/or reduction of symptoms of erosive esophagitis (EE) of Grade A as defined by the Los Angeles (LA) Classification.

Preferably the P-CAB for use according to the present disclosure is for the sustained reduction of GERD symptoms in patients with an insufficient response to a PPI.

Preferably the P-CAB for use according to the present disclosure is for the reduction in nighttime awakenings and insomnia associated with GERD.

Preferably the P-CAB for use according to the present disclosure is for the reduction in fatigue associated with sleep disturbance due to GERD.

Preferably the P-CAB for use according to the present disclosure is for the reduction in daytime sleepiness associated with sleep disturbance due to GERD.

Preferably the P-CAB for use according to the present disclosure is for the reduction in the patient's accidents associated with sleep disturbance due to GERD.

Preferably the P-CAB for use according to the present disclosure is for the reduction in the patient's physician visits and hospital admissions associated with GERD.

Preferably the P-CAB for use according to the present disclosure is for the improvement in physical and mental functioning, including concentration, in patients with GERD.

Preferably the P-CAB for use according to the present disclosure is for the reduction in anxiety associated with GERD.

Preferably the P-CAB for use according to the present disclosure is for the reduction in the patient's use of other medications for the treatment of GERD.

Preferably the P-CAB for use according to the present disclosure is for the improvement of general wellbeing and Quality of Life in patients with GERD.

Preferably the P-CAB for use according to the present disclosure is for the reduction of inflammation in patients with GERD.

For the avoidance of doubt, it should be noted that all particular and/or preferred embodiments identified herein are applicable to both the 'use' and 'method' as defined above. Moreover, it will be appreciated that the various additional applications/embodiments of the use and method of the present disclosure mentioned above (from reduction in nighttime awakenings and insomnia through to improvement of general wellbeing and Quality of Life, and the reduction of inflammation) can also be considered advantages of the present disclosure.

In an embodiment of the present disclosure, the method of treating, preventing and/or reducing GERD symptoms in a patient in need thereof comprises the step of:

a) identifying a patient suffering from GERD symptoms, wherein said patient has been administered, is being administered or is about to be administered a PPI.

In such an embodiment, the method may further comprise the step of:

b) preferentially selecting one or more particular P-CABs (preferably vonoprazan) from a group of treatment options for symptoms of GERD (such as P-CABs) to administer to the patient.

Furthermore, such an embodiment may additionally comprise the step of:

c) administering to said patient a therapeutically effective amount of the selected P-CAB(s) (preferably vonoprazan) to treat, prevent and/or reduce the GERD symptoms.

Preferably, the P-CAB for use according to the present disclosure is selected from 1-[5-(2-fluorophenyl)-1-(pyridin-3-ylsulfonyl)-1H-pyrrol-3-yl]-N-methylmethanamine (vonoprazan,

TAK-438), revaprazan (YH1855), YH4808 (Yuhan Corporation), RQ-4 (also known as RQ-00000004; RaQualia Pharma Inc.), RQ-774 (also known as RQ-00000774; RaQualia Pharma Inc.) and CS-526 (Daiichi Sankyo), and salts thereof (in particular, pharmaceutically acceptable salts). More preferably, the P-CAB is vonoprazan or a pharmaceutically acceptable salt thereof. A particularly preferred P-CAB is vonoprazan fumarate.

P-CABs suitable for use according to the present disclosure are also disclosed, for example, in EP-A-1784404, including the following:

1-benzyl-7-[N-(4-fluorobenzyl)-N-methyl]amino-2,3-dimethyl -1H- pyrrolo[2,3-c]pyridine hydrochloride;

1-(3-fluorobenzyl)-7-(4-fluorobenzylamino)-2,3-dimethyl-1H- pyrrolo[2,3-c]pyridine hydrochloride;

7-(4-fluorobenzylamino)-l-isobutyl-2,3-dimethyl-1H-pyrrolo[2,3-c] pyridine hydrochloride;

1l-isobutyl-2,3-dimethyl-7-(2-methylbenzylamino)-1H-pyrrolo[2,3-c] pyridine hydrochloride;

7-(4-chlorobenzylamino)-l-(4-fluorobenzyl)-2,3-dimethyl-1H- pyrrolo[2,3-c]pyridine hydrochloride;

7-(4-chlorobenzylamino)-2,3-dimethyl-l -propyl- 1H-pyrrolo[2,3-c] pyridine hydrochloride;

2,3-dimethyl-7-(naphthalen-2-yl)-1H-pyrrolo[2,3-c]pyridine hydrochloride;

7-(1,2,3,4-tetrahydroisoquinolin-2-yl)-2,3-dimethyl-1H- pyrrolo[2,3-c]pyridine hydrochloride;

1-benzyl-7-(1,2,3,4-tetrahydroisoquinolin-2-yl)-2,3-dimethyl-1H-pyrrolo[2,3-c]pyridine hydrochloride;

7-(1,2,3,4-tetrahydroisoquinolin-2-yl)-1,2,3-trimethyl-1H- pyrrolo[2,3-c]pyridine hydrochloride;

1-propyl-7-(1,2,3,4-tetrahydroisoquinolin-2-yl)-2,3-dimethyl-1H- pyrrolo[2,3-c]pyridine hydrochloride;

1-(2-methylthiazol-4-ylmethyl)-7-(1,2,3,4-tetrahydroisoquinolin-2-yl)-2,3-dimethyl -1 H-pyrrolo[2,3-c]pyridine hydrochloride;

1-(4-methylbenzyl)-7-(1,2,3,4-tetrahydroisoquinolin-2-yl)-2,3-dimethyl -1H- pyrrolo[2,3-c]pyridine hydrochloride;

1-(3-fluorobenzyl)-7-(1,2,3,4-tetrahydroisoquinolin-2-yl)-2,3-dimethyl -1H- pyrrolo[2,3-c]pyridine hydrochloride;

1-(4-methoxybenzyl)-7-(1,2,3,4-tetrahydroisoquinolin-2-yl)-2,3-dimethyl -1H- pyrrolo[2,3-c]pyridine hydrochloride;

1-allyl-7-(1,2,3,4-tetrahydroisoquinolin-2-yl)-2,3-dimethyl-1H- pyrrolo[2,3-c]pyridine hydrochloride;

1-(4-tert-butylbenzyl)-7-(1,2,3,4-tetrahydroisoquinolin-2-yl)-2,3-dimethyl -1H-pyrrolo[2,3-c] pyridine hydrochloride;

1-(2-vinyloxyethyl)-7-(1,2,3,4-tetrahydroisoquinolin-2-yl)-2,3-dimethyl -1H- pyrrolo[2,3-c]pyridine hydrochloride;

2-(1-allyl-2,3-dimethyl-1H-pyrrolo[2,3-c] pyridin-7-yl)-1-methyl-1,2,3,4-tetrahydroisoquinoline hydrochloride;

2-[1-(3-fluorobenzyl)-2,3-dimethyl-1H-pyrrolo[2,3-c]pyridin-7-yl]-1-methyl-1,2,3,4-tetrahydroisoquinoline hydrochloride; and

2-(1-allyl-2,3-dimethyl-1H-pyrrolo[2,3-c] pyridin-7-yl)-6-fluoro-1-methyl-1,2,3,4-tetrahydroisoquinoline hydrochloride,

and suitable alternative salts thereof.

In particular, 1-benzyl-7-(1,2,3,4-tetrahydroisoquinolin-2-yl)-2,3-dimethyl-1H-pyrrolo[2,3-c]pyridine hydrochloride; and 1-(3-fluorobenzyl)-7-(1,2,3,4-tetrahydroisoquinolin-2-yl)-2,3-dimethyl -1H- pyrrolo[2,3-c]pyridine hydrochloride (and suitable alternative salts thereof) may be mentioned.

In addition, P-CABs suitable for use according to the present disclosure are disclosed, for example, in US 8648080, including the following:

(S)-(−)-4-[(5,7-difluoro-3,4-dihydro-2H-chromen-4-yl)oxy]-N,N,2-trimethyl-1H-benzimidazole-6-carboxamide;

(S)-(−)-4-[(5,7-difluoro-3,4-dihydro-2H-chromen-4-yl)oxy]-2-methyl-6-(pyrrolidin-1-ylcarbonyl)-1H-benzimidazole;

(S)-(−)-4-[(5-fluoro-3,4-dihydro-2H-chromen-4-yl)oxy]-N,N,2-trimethyl-1H-benzimidazole-6-carboxamide;

(−)-1-(2-methoxyethyl)-N,N,2-trimethyl-8-phenyl-1,6,7,8-tetrahydrochromeno[7,8-d]imidazole-5-carboxamide;

(+8-(4-fluorophenyl)-1-(2-methoxyethyl)-N,N,2-trimethyl-1,6,7,8-tetrahydrochromeno[7,8-d]imidazole-5-carboxamide;

8-(4-fluorophenyl)-1-(3-hydroxypropyl)-N,N,2-trimethyl-1,6,7,8-tetrahydrochromeno[7,8-

d]imidazole-5-carboxamide;
8-(4-fluorophenyl)-1-(isoxazol-3-ylmethyl)-N,N,2-trimethyl-1,6,7,8-tetrahydrochromeno[7,8-d]imidazole-5-carboxamide;
8-(4-fluorophenyl)-N-(2-hydroxyethyl)-1-(2-methoxyethyl)-N,2-dimethyl-1,6,7,8-tetrahydrochromeno[8,7-d]imidazole-5-carboxamide;
(8-(4-fluorophenyl)-1-(2-methoxyethyl)-2-methyl-1,6,7,8-tetrahydrochromeno[8,7-d]imidazol-5-yl)(morpholino)methanone;
1-{5-(2-fluorophenyl)-1-[(6-methylpyridin-3-yl)sulfonyl]-1H-pyrrol-3-yl}-N-methylmethanamine;
1-[4-fluoro-5-phenyl-1-(pyridin-3-ylsulfonyl)-1H-pyrrol-3-yl]-N-methylmethanamine;
N-methyl-1-[5-(4-methyl-3-thienyl)-1-(pyridin-3-ylsulfonyl)-1H-pyrrol-3-yl]methanamine;
1-[5-(2-fluorophenyl)-1-(pyridin-3-ylsulfonyl)-1H-pyrrol-3-yl]-N-methylmethanamine;
N-Methyl-1-[5-(2-methylphenyl)-1-(pyridine-3-ylsulfonyl)-1H-pyrrol-3-yl]methanamine or;
8-[{2,6-dimethylbenzyl}amino]-N-[2-hydroxyethyl]-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxamide;
8R,9R)-7-(2-methoxyethoxy)-2,3-dimethyl-9-phenyl-7,8,9,10-tetrahydroimidazo[1,2-h][1,7]naphthyridine-8-ol;
5,6-dimethyl-2-(4-fluoro-phenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinoline-2-yl)pyrimidine;
(S)-(-)-N,N,2,3-tetramethyl-8-O-tolyl-3,6,7,8-tetrahydrochromeno[7,8-d]imidazole-5-carboxamide; and
7-(4-fluorobenzyloxy)-2,3-dimethyl-1-{[(1S,2S)-2-methyl cyclopropyl]methyl}-1H-pyrrolo[2,3-d]pyridazine,
and suitable salts thereof.

In particular, (S)-(-)-4-[(5,7-difluoro-3,4-dihydro-2H-chromen-4-yl)oxy]-N,N,2-trimethyl-1H-benzimidazole-6-carboxamide; (-)-1-(2-methoxyethyl)-N,N,2-trimethyl-8-phenyl-1,6,7,8-tetrahydrochromeno[7,8-d]imidazole-5-carboxamide; and 8-[{2,6-dimethylbenzyl}amino]-N-[2-hydroxyethyl]-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxamide (and suitable salts thereof) may be mentioned.

Preferably, the P-CAB for use according to the present disclosure is administered at a dose of the P-CAB of 0.5 mg to 500 mg per day. Preferably the dose is 10 mg to 200 mg per day and

12%, at least 13%, at least 14%, at least 15%, at least 16%, at least 17%, at least 18%, at least 19%, at least 20%, at least 25%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90% or 100%.

In yet another embodiment of the use and method of the invention, the P-CAB administration results in an improvement in regurgitation symptoms which is at least 1% greater than that achieved by PPI administration in subjects who are PPI partial responders. In another embodiment, the improvement in regurgitation symptoms is at least 2%, at least 3%, at least 4%, at least 5%, at least 6%, at least 7%, at least 8%, at least 9%, at least 10%, at least 11%, at least 12%, at least 13%, at least 14%, at least 15%, at least 16%, at least 17%, at least 18%, at least 19%, at least 20%, at least 25%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90% or 100%.

The pharmaceutical composition according to the present invention can be a solution or suspension, but is preferably a solid oral dosage form. Preferred solid oral dosage forms in accordance with the invention include tablets, capsules and the like which, optionally, may be coated if desired. Tablets can be prepared by conventional techniques, including direct compression, wet granulation and dry granulation. Capsules are generally formed from a gelatine material and can include a conventionally prepared granulate of excipients.

The pharmaceutical composition according to the present invention may typically comprise one or more conventional pharmaceutically acceptable excipient(s) selected from the group comprising a filler, a binder, a disintegrant, a lubricant and optionally further comprises at least one excipient selected from colouring agents, adsorbents, surfactants, film formers and plasticizers. A number of suitable compositions containing vonoprazan (TAK-438), as an exemplary P-CAB, are disclosed in WO 2010/013823.

The P-CAB for use according to the present invention can be appropriately administered orally or parenterally (e.g., topical, rectal, intravenous administrations and the like) as it is or as a pharmaceutical composition containing a pharmacologically acceptable carrier admixed according to a method known per se, such as tablets (including sugar-coated tablets and film-coated tablets), powder, granule, capsule (including soft capsule), orally disintegrating tablet, orally disintegrating film, liquid, injection, suppository, sustained- or (preferably)

Claims

1. Use of a potassium-competitive acid blocker (P-CAB) in the manufacture of a medicament for the treatment, prevention and/or reduction of gastro-esophageal reflux disease (GERD) symptoms in patients who are partial responders to a proton pump inhibitor (PPI).
2. The use according to claim 1, wherein the medicament is for the treatment, prevention and/or reduction of symptoms of non-erosive reflux disease (NERD) or erosive esophagitis (EE) of Grade A as defined by the Los Angeles (LA) Classification.
3. The use according to claim 1 or 2, wherein the medicament is for the treatment, prevention and/or reduction of symptoms of NERD.
4. The use according to claim 1 or 2, wherein the medicament is for the treatment, prevention and/or reduction of symptoms of EE of Grade A as defined by the LA Classification.
5. The use according to any preceding claim, wherein the PCAB is selected from 1-[5-(2-fluorophenyl)-1-(pyridin-3-ylsulfonyl)-1H-pyrrol-3-yl]-N-methylmethanamine (vonoprazan), revaprazan (YH1855), YH4808, RQ-4 and CS-526, or a salt thereof.
6. The use according to any preceding claim, wherein the PCAB is vonoprazan or a salt thereof.
7. The use according to claim 6, wherein the PCAB is vonoprazan fumarate.
8. The use according to any preceding claim wherein the dose of the P-CAB to be administered is 0.5 mg to 500 mg per day.
9. The use according to claim 8 wherein the dose of the P-CAB to be administered is 20 mg to 40 mg per day.
10. The use according to claim 9 wherein the dose of the P-CAB to be administered is selected from 20 or 40 mg per day.
11. The use according to any one of claims 1 to 10, wherein the PPI is selected from lansoprazole, pantoprazole, omeprazole and rabeprazole, or an optically active form thereof, or a salt thereof.
12. The use according to claim 11, wherein the PPI is dexlansoprazole or esomeprazole or a salt thereof.
13. The use according to claim 12, wherein the PPI is esomeprazole or a salt thereof.

14. The use according to any preceding claim, wherein the P-CAB is to be administered by once-daily dosing.

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