

SUMMARY

In one aspect, provided herein is use of a 1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid {(1S,3R,5R)-8-[(R)-2-hydroxy-3-(methanesulfonyl-methyl-amino)propyl]-8-azabicyclo[3.2.1]oct-3-yl}amide (velusetrag) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating idiopathic chronic intestinal pseudo-obstruction (CIPO), neuropathic chronic intestinal pseudo-obstruction, or chronic intestinal pseudo-obstruction being secondary to neurodegeneration or being secondary to autoimmune conditions or being secondary to connective tissue disorders or being secondary to demyelinating conditions.

The present disclosure relates to velusetrag or a pharmaceutically acceptable salt thereof for use in a method of treating idiopathic chronic intestinal pseudoobstruction (CIPO), neuropathic chronic intestinal pseudo-obstruction or chronic intestinal pseudo-obstruction being secondary to neurodegeneration or being secondary to autoimmune conditions or secondary to connective tissue disorders or being secondary to demyelinating conditions.

According to one example, the pharmaceutically acceptable salt is a hydrochloride salt. The disclosure moreover relates to the above use, wherein velusetrag is in crystalline form and/or hydrated form.

The disclosure, moreover, relates to the above use, wherein CIPO is the idiopathic CIPO, the neuropathic CIPO or the CIPO being secondary to neurodegeneration or being secondary to autoimmune conditions or secondary to connective tissue disorders or being secondary to demyelinating conditions, or any CIPO caused by diseases of the autonomic nervous system such as stroke, encephalitis, calcification of basal ganglia, orthostatic hypotension, one caused by diseases of intestinal wall nervous system such as paraneoplastic syndrome, viral infections, iatrogenic disorders, Hirschsprung's disease, Chagas' disease, Von Recklinghausen's disease, one caused by diseases of the intestinal wall muscle layer such as myotonic dystrophy, progressive systemic sclerosis or one caused by diseases of the mixed enteric nervous system and smooth muscle layer such as scleroderma, dermatomyositis, amyloidosis, Ehler-Danlos syndrome or one caused by an unknown mechanism such as hypothyroidism, hypoparathyroidism, pheochromocytoma, antidepressants drugs, antineoplastics or bronchodilators or one caused by immune-mediated and connective tissue disorder or disease such as paraneoplastic disease (CNS neoplasms, lung microstoma, bronchial carcinoid, leiomyosarcomas, systemic lupus erythematosus).

The disclosure moreover relates to the above use, wherein the patient is a subject with CIPO. Preferably the patient is an adult or a pediatric subject.

The disclosure moreover related to the above use, wherein the patient is one having a history of chronic CIPO or CIPO secondary to neurodegenerative disease or demyelinating disease.

Moreover, the disclosure relates to the above use, wherein at least one of the symptoms of CIPO (e.g. vomiting, bloating, abdominal pain) or disease exacerbations (e.g. pseudo-obstructive episodes) is alleviated or ameliorated. Moreover, the disclosure relates to the above use, wherein at least one of the symptoms of CIPO selected from abnormal gastrointestinal motility, increased dilatation of the proximal colon and/or of the distal small intestine, modified intestinal contractility, ulceration, inflammation of the proximal colon and/or of the distal small intestine, pseudo-obstructive episodes and lethality is alleviated or ameliorated and/or wherein the number and/or frequency of CIPO-related and/or CIPO-caused hospitalizations is reduced.

Further to this, the disclosure relates to the above use, wherein velusetrag is administered in a dose amount ranging from 0.5 mg to 30 mg, preferably from 5 mg to 15 mg, based on the weight of the free base. These dosages are meant to be daily doses, for an average adult human patient. However, dosages can be varied and/or adapted in function of the degree of severity of the disease, the specific patient conditions, the specific administration route chosen.

The disclosure moreover relates to the above use, wherein treatment duration can be varied and/or adapted in function of the degree of severity of the disease or the specific patient conditions. Preferably the treatment is administered for at least 1 to 24 weeks, preferably at least 24 weeks, preferably for at least 2 weeks or at least 4 weeks, preferably at least 6 weeks, preferably at least 12 weeks, or at least 14 weeks, preferably at least 16 weeks, preferably at least 18 weeks, 20 weeks, 22 weeks. Preferably 24 weeks or at least 24 weeks, preferably 26 weeks, 28 weeks, 30 weeks or longer. The treatment may also be administered at repeated cycle over at least at least 1 to 24 weeks, preferably at least 24 weeks, preferably for at least 2 weeks or at least 4 weeks, preferably at least 6 weeks, preferably at least 12 weeks, or at least 14 weeks, preferably at least 16 weeks, preferably at least 18 weeks, 20 weeks, 22

weeks. Preferably 24 weeks or at least 24 weeks, preferably 26 weeks, 28 weeks, 30 weeks or longer.

Velusetrag is preferably administered in a dose of 15 mg daily, wherein the dose is
5 taken once daily, preferably in the form of 3x5 mg tablets. The preferred administration route is oral administration.

In another example of the disclosure, pharmaceutical compositions with different routes of administration of velusetrag to the human patient are encompassed. The
10 routes of administration comprise, inter alia, oral, parenteral, buccal, sublingual, rectal, intraperitoneal, or endotracheal routes of administration. For example, parenteral administration may be by infusion, injection, or implantation. Parenteral may also include percutaneous administration via subcutaneous, intramuscular, intravenous, transdermal, or by implantation routes. If velusetrag is administered
15 parenterally, it may be in the form of a liquid, solid or gel. Similarly, if velusetrag is administered orally, it may be in the form of a liquid, capsule, tablet, chewable tablet or dissolvable film.

In one example, the product comprises velusetrag in an amount from about 0.5 mg to about 30 mg labeled for treatment of symptoms of CIPO. In yet another example,
20 the product comprises velusetrag in an amount from about 0.5 mg to about 15 mg, from about 0.5 mg to about 5 mg, from about 5 mg to about 15 mg, or about 5 mg, or about 15 mg labeled for treatment of symptoms of CIPO.

In one example, the disclosure provides a kit comprising using and dosing instructions on a package insert of a pharmaceutical product comprising velusetrag
25 according to the disclosure. In another example, the package insert instructs the patient to administer velusetrag for a period of treatment as indicated above.

Velusetrag may be administered in combination with other drugs not contraindicated with the administration of velusetrag. Preferably velusetrag is not
30 administered together with opioids and/or other 5-HT₄ receptor agonists (e.g., prucalopride, cisapride, clobopride, cinitapride).