SUMMARY

In one aspect of the present disclosure, there is provided a solid pharmaceutical composition comprising a pharmaceutically acceptable carrier, linaclotide, a cation selected from Mg^{2+}, Ca^{2+}, Zn^{2+}, Mn^{2+}, K^{+}, Na^{+} or Al^{3+}, and a sterically hindered primary amine.

In another aspect of the present disclosure, there is provided a solid pharmaceutical composition comprising:

linaclotide;

Ca^{2+};

leucine; and

hydroxypropyl methylcellulose,

wherein the molar ratio of Ca^{2+}:leucine:linaclotide is between 5-100:5-50:1.

In yet another aspect of the present disclosure, there is provided a solid pharmaceutical composition as defined herein for use in treating a gastrointestinal disorder selected from impaired intestinal motility, irritable bowel syndrome, constipation, pain associated with constipation, dyspepsia, gastroparesis, chronic intestinal pseudo obstruction, Crohn's disease, ulcerative colitis, or inflammatory bowel disease.

In a further aspect of the present disclosure, there is provided a use of linaclotide or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment of a gastrointestinal disorder selected from impaired intestinal motility, irritable bowel syndrome, constipation, pain associated with constipation, dyspepsia, gastroparesis, chronic intestinal pseudo obstruction, Crohn's disease, ulcerative colitis, or inflammatory bowel disease, said medicament comprising a solid pharmaceutical composition comprising a pharmaceutically acceptable carrier, linaclotide, a cation selected from Mg^{2+}, Ca^{2+}, Zn^{2+}, Mn^{2+}, K^{+}, Na^{+} or Al^{3+}, and a sterically hindered primary amine.

In another aspect of the present disclosure, there is provided a unit dosage form comprising a solid pharmaceutical composition as defined herein.

In yet another aspect of the present disclosure, there is provided a sealed container comprising a plurality of unit dosage forms as defined herein.

In a further aspect of the present disclosure, there is provided a method for preparing a solid pharmaceutical composition comprising linaclotide or a salt thereof, the method comprising:

(a) providing an aqueous solution comprising:

(i) linaclotide or a pharmaceutically acceptable salt thereof

(ii) one or more of a cation selected from Mg^{2+}, Ca^{2+}, Zn^{2+}, Mn^{2+}, K^{+}, Na^{+} or Al^{3+} or a sterically hindered primary amine; and,

(iii) optionally, a pharmaceutically acceptable binder; and

(b) applying the aqueous solution to a pharmaceutically acceptable filler to generate linaclotide-coated filler.

Solid, stable formulations of linaclotide suitable for oral administration are described herein as are methods for preparing such formulations. The formulations described herein contain a polypeptide consisting of the amino acid sequence Cys Cys Glu Tyr Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr ("linaclotide") or a pharmaceutically acceptable salt thereof.

The linaclotide formulations described herein are stable and have a sufficient shelf life for manufacturing, storing and distributing the drug. For example, formulations described herein are expected to have a shelf life of at least 12 months at room temperature storage conditions (e.g., 25°C/60% relative humidity (RH)). In further embodiments, the formulations described herein are expected to have a shelf life of at least 18 months or at least 24 months at room temperature storage conditions (e.g., 25°C/60% RH).

In some embodiments, formulations are described wherein ≥ 95% of the original amount of linaclotide in the composition remains after three months when packaged samples are stored at accelerated conditions (40°C/75% RH) when assessed in an assay on a weight/weight basis as determined by high pressure liquid chromatography (HPLC) against a linaclotide reference standard. In further embodiments, ≥ 90% of the original amount of linaclotide in the composition remains after at least 6 months when packaged samples are stored at accelerated conditions (40°C/75% RH). In other embodiments, formulations are described wherein chromatographic purity of the linaclotide as determined as area percent by HPLC remains at ≥ 95% over the course of at least three months when packaged samples are stored at accelerated conditions (40°C/75% RH). In further embodiments, the chromatographic purity of the linaclotide as determined by area percent by HPLC remains at ≥ 90% over the course of at least 6 months when packaged samples are stored at accelerated conditions (40 °C/75% RH). Thus, for example, no more than about 10% of the linaclotide undergoes degradation to other products such as an oxidation product of linaclotide, a hydrolysis product of linaclotide or a formaldehyde-mediated imine product of linaclotide ("formaldehyde imine product").

In one embodiment, the present disclosure comprises a pharmaceutical composition comprising linaclotide, wherein the chromatographic purity of the linaclotide decreases by

less than 10% after 18 months or 24 months of storage of the pharmaceutical composition at 25°C at 60% relative humidity in a sealed container containing a desiccant. In a further embodiment, the chromatographic purity of the linaclotide decreases by less than 9%, 8%, 7%, 6%, 5%, 4% or 2% after 18 months or 24 months of storage of the pharmaceutical

composition at 25°C at 60% relative humidity in a sealed container containing a desiccant. In another embodiment, the present disclosure comprises a pharmaceutical composition comprising linaclotide, wherein the chromatographic purity of the linaclotide decreases by less than 10% after 3 months or 6 months of storage of the pharmaceutical composition at 40°C at 75% relative humidity in a sealed container containing a desiccant. In a further embodiment, the chromatographic purity of the linaclotide decreases by less than 9%, 8%, 7%, 6%, 5%, 4% or 2% after 3 months or 6 months of storage of the pharmaceutical composition at 40°C at 75% relative humidity in a sealed container containing a desiccant.

In one embodiment, the present disclosure comprises a unit dosage form of a pharmaceutical composition comprising linaclotide, wherein the chromatographic purity of the linaclotide decreases by less than 10% after 18 months or 24 months of storage of the unit dosage form at 25°C at 60% relative humidity in a sealed container containing a desiccant. In a further embodiment, the chromatographic purity of the linaclotide decreases by less than 9%, 8%, 7%, 6%, 5%, 4% or 2% after 18 months or 24 months of storage of the unit dosage form at 25°C at 60% relative humidity in a sealed container containing a desiccant. In another embodiment, the present disclosure comprises a unit dosage form of a pharmaceutical composition comprising linaclotide, wherein the chromatographic purity of the linaclotide decreases by less than 10% after 3 months or 6 months of storage of the unit dosage form at 40°C at 75% relative humidity in a sealed container containing a desiccant. In a further embodiment, the chromatographic purity of the linaclotide decreases by less than 9%, 8%, 7%, 6%, 5%, 4% or 2% after 3 months or 6 months of storage of the unit dosage form at 40°C at 75% relative humidity in a sealed container containing a desiccant.

In one embodiment, the present disclosure comprises a sealed container comprising a plurality of unit dosage forms of a pharmaceutical composition comprising linaclotide, wherein the chromatographic purity of the linaclotide decreases by less than 10% after 18 months or 24 months of storage of the sealed container containing a desiccant at 25°C at 60% relative humidity. In a further embodiment, the chromatographic purity of the linaclotide decreases by less than 9%, 8%, 7%, 6%, 5%, 4% or 2% after 18 months or 24 months of storage of the sealed container containing a desiccant at 25°C at 60% relative humidity. In another embodiment, the present disclosure comprises a sealed container comprising a plurality of unit dosage forms of a pharmaceutical composition comprising linaclotide, wherein the chromatographic purity of the linaclotide decreases by less than 10% after 3 months or 6 months of storage of the sealed container containing a desiccant at 40°C at 75% relative humidity. In a further

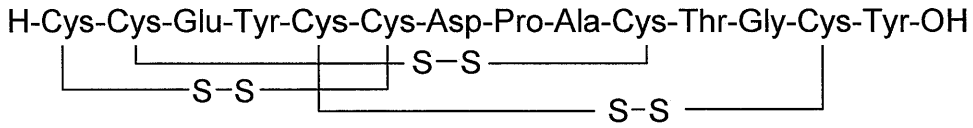
embodiment, the chromatographic purity of the linaclotide decreases by less than 9%, 8%, 7%, 6%, 5%, 4% or 2% after 3 months or 6 months of storage of the sealed container containing a desiccant at 40°C at 75% relative humidity.

In one embodiment, the present disclosure comprises a pharmaceutical composition comprising linaclotide, wherein the assay value for linaclotide determined on a weight/weight basis decreases by less than 10% after 18 months or 24 months of storage of the pharmaceutical composition at 25°C at 60% relative humidity in a sealed container containing a desiccant. In a further embodiment, the assay value for linaclotide determined on a weight/weight basis decreases by less than 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2% or 1% after 18 months or 24 months of storage of the pharmaceutical composition at 25°C at 60% relative humidity in a sealed container containing a desiccant. In another embodiment, the present disclosure comprises a pharmaceutical composition comprising linaclotide, wherein the assay value for linaclotide determined on a weight/weight basis decreases by less than 10% after 3 months or 6 months of storage of the pharmaceutical composition at 40°C at 75% relative humidity in a sealed container containing a desiccant. In a further embodiment, the chromatographic purity of the linaclotide decreases by less than 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2% or 1% after 3 months or 6 months of storage of the pharmaceutical composition at 40°C at 75% relative humidity in a sealed container containing a desiccant.

In one embodiment, the present disclosure comprises a unit dosage form of a pharmaceutical composition comprising linaclotide, wherein the assay value for linaclotide determined on a weight/weight basis decreases by less than 10% after 18 months or 24 months of storage of the unit dosage form at 25°C at 60% relative humidity in a sealed container containing a desiccant. In a further embodiment, the assay value for linaclotide determined on a weight/weight basis decreases by less than 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2% or 1% after 18 months or 24 months of storage of the unit dosage form at 25°C at 60% relative humidity in a sealed container containing a desiccant. In another embodiment, the present disclosure comprises a unit dosage form of a pharmaceutical composition comprising linaclotide, wherein the assay value for linaclotide determined on a weight/weight basis decreases by less than 10% after 3 months or 6 months of storage of the unit dosage form at 40°C at 75% relative humidity in a sealed container containing a desiccant. In a further embodiment, the assay value for linaclotide determined on a weight/weight basis decreases by less than 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2% or 1% after 3 months or 6 months of storage of the unit dosage form at 40°C at 75% relative humidity in a sealed container containing a desiccant.

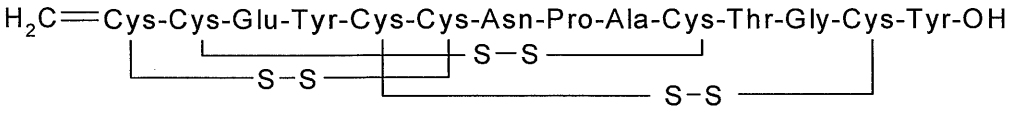
In one embodiment, the present disclosure comprises a sealed container comprising a plurality of unit dosage forms of a pharmaceutical composition comprising linaclotide, wherein the assay value for linaclotide determined on a weight/weight basis decreases by less than 10% after 18 months or 24 months of storage of the sealed container at 25°C at 60% relative humidity in a sealed container containing a desiccant. In a further embodiment, the assay value for linaclotide determined on a weight/weight basis decreases by less than 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2% or 1% after 18 months or 24 months of storage of the sealed container containing a desiccant at 25°C at 60% relative humidity. In another embodiment, the present disclosure comprises a sealed container comprising a plurality of unit dosage forms of a pharmaceutical composition comprising linaclotide, wherein the assay value for linaclotide determined on a weight/weight basis decreases by less than 10% after 3 months or 6 months of storage of the sealed container containing a desiccant at 40°C at 75% relative humidity. In a further embodiment, the assay value for linaclotide determined on a weight/weight basis decreases by less than 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2% or 1% after 3 months or 6 months of storage of the sealed container containing a desiccant at 40°C at 75% relative humidity.

In some embodiments, there is provided a pharmaceutical composition comprising linaclotide and a hydrolysis product comprising:



In some embodiments, the hydrolysis product comprises less than about 15% by weight of the composition, less than about 10% by weight of the composition, less than about 7% by weight of the composition or less than about 5% by weight of the composition. In other embodiments, the hydrolysis product comprises from about 0.01% to about 15% by weight of the composition, about 0.05% to about 10% by weight of the composition, about 0.05% to about 7% by weight of the composition or about 0.05% to about 5% by weight of the composition. In further embodiments, there is provided a method of treating a gastrointestinal disorder in a patient in need thereof comprising administering a pharmaceutical composition comprising linaclotide and a hydrolysis product.

In some embodiments, there is provided a pharmaceutical composition comprising linaclotide and a formaldehyde imine product comprising:



xylitol, sucrose and lactose); the filler comprises particles having an average diameter between 50 μm and 1000 μm; the lubricant and/or glidant is selected from: talc, leucine, magnesium stearate, stearic acid and polyvinyl alcohol; and the lubricant and/or glidant is selected from: calcium stearate, mineral oil, vegetable oil, polyethylene glycol (PEG ; e.g., PEG that is liquid or solid at room temperature), sodium benzoate, and sodium lauryl sulfate.

In some cases, the linaclotide solution used in a method for preparing the formulation has a pH below 7 (e.g., a pH between 1 and 3 or a pH between about 1.5 and about 2.5). The pH can be adjusted with, e.g., phosphoric acid. In some cases, the solution is buffered. Various pharmaceutically acceptable buffers can be used (e.g., phosphate buffer).

In some cases, the linaclotide solution used in a method for preparing the formulation comprises both a cation (e.g., $CaCl_2$) and a sterically hindered primary amine (e.g., leucine).

In some cases the linaclotide solution comprises $CaCl_2$ and leucine; the binder is methylcellulose; the filler is microcrystalline cellulose; the glidant and/or lubricant comprises talc or leucine.

Also provided is a pharmaceutical composition prepared by any of the methods described herein.

In another embodiment, a pharmaceutical composition is disclosed that comprises a pharmaceutically acceptable carrier, linaclotide and one or more agents selected from (i) a cation selected from Mg^{2+}, Ca^{2+}, Zn^{2+}, Mn^{2+}, K^{+}, Na^{+} or Al^{3+}, or (ii) a sterically hindered primary amine. In some embodiments, the pharmaceutical composition comprises at least one cation and at least one sterically hindered primary amine.

Methods of using the pharmaceutical compositions to treat a variety of gastrointestinal disorders are also described.

BRIEF DESCRIPTION OF THE FIGURE

Figure 1 demonstrates an example of an analysis of linaclotide by HPLC, wherein "Oxidation" refers to the linaclotide oxidation product, "Formaldehyde Imine" refers to the linaclotide formaldehyde imine product and "Hydrolysis" refers to the linaclotide hydrolysis product.

This figure is provided by way of example and is not intended to limit the scope of the present invention.

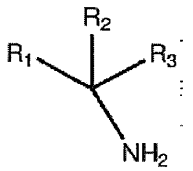
DETAILED DESCRIPTION

CLAIMS

1. A solid pharmaceutical composition comprising a pharmaceutically acceptable carrier, linaclotide, a cation selected from Mg^{2+}, Ca^{2+}, Zn^{2+}, Mn^{2+}, K^{+}, Na^{+} or Al^{3+}, and a sterically hindered primary amine.

2. The solid pharmaceutical composition according to claim 1, wherein said Mg^{2+}, Ca^{2+}, Zn^{2+}, Mn^{2+}, K^{+}, Na^{+} or Al^{3+} is provided as magnesium chloride, calcium chloride, calcium phosphate, calcium sulfate, zinc acetate, manganese chloride, potassium chloride, sodium chloride or aluminum chloride.

3. The solid pharmaceutical composition according to claim 1 or claim 2, wherein said cation is Ca^{2+} and is provided as calcium chloride.

4. The solid pharmaceutical composition according to any one of claims 1-3, wherein the sterically hindered primary amine is selected from an amino acid, a polymeric amine, or a compound of the formula: 

, wherein R_1, R_2 and R_3 are independently selected from: H;
-C(O)OH; C_1-C_6 alkyl, optionally substituted by $-CO_2H$, $-CONH_2$, or a 5-10 membered aryl or heteroaryl; C_1-C_6 alkoxyalkyl; or C_1-C_6 thioalkoxyalkyl, wherein any of the alkyl or aryl groups above can be singly or multiply substituted with halogen or $-NH_2$, and provided that no more than two of R_1, R_2 and R_3 are H.

5. The solid pharmaceutical composition according to claim 4, wherein the sterically hindered primary amine is a naturally-occurring amino acid selected from the group consisting of histidine, phenylalanine, alanine, glutamic acid, aspartic acid, glutamine, leucine, methionine, asparagine, tyrosine, threonine, isoleucine, tryptophan and valine.

6. The solid pharmaceutical composition according to claim *5,* wherein the naturally-occurring amino acid is leucine.

7. The solid pharmaceutical composition according to any one of claims 1-6 further comprising a pharmaceutically acceptable glidant, lubricant or additive that acts as both a glidant and lubricant.

8. The solid pharmaceutical composition according to any one of claims 1-7 further comprising one or more of an antioxidant; a pharmaceutically acceptable binder; or a pharmaceutically acceptable filler.

9. The solid pharmaceutical composition according to claim 8, wherein the pharmaceutically acceptable binder is selected from polyvinyl alcohol, polyvinylpyrrolidone (povidone), a starch, maltodextrin or a cellulose ether.

10. The solid pharmaceutical composition of claim 9, wherein the pharmaceutically acceptable binder is a cellulose ether selected from methylcellulose, ethylcellulose, carboxymethylcellulose, hydroxyethyl cellulose, hydroxyethyl methylcellulose, hydroxypropyl cellulose and hydroxypropyl methylcellulose.

11. The solid pharmaceutical composition according to any one of claims 8-10, wherein the pharmaceutically acceptable filler is cellulose, isomalt, mannitol or dibasic calcium phosphate.

12. The solid pharmaceutical composition according to claim 11, wherein the cellulose is selected from microfine cellulose and microcrystalline cellulose.

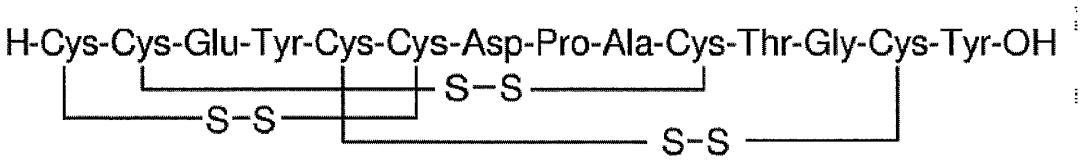
13. The solid pharmaceutical composition according to any one of claims 1-12, wherein the amine is leucine and the molar ratio of leucine to linaclotide is at least 10:1.

14. The solid pharmaceutical composition according to any one of claims 1-13, wherein the cation is Ca^{2+}, the amine is leucine and the molar ratio of Ca^{2+} to leucine is at least 1:1.

15. The solid pharmaceutical composition according to any one of claims 1-14, wherein the molar ratio of the cation: sterically hindered primary amine: linaclotide is 40-100:20-50:1.

16. The solid pharmaceutical composition according to any one of claims 1-15, wherein the cation is Ca^{2+}, the sterically hindered primary amine is leucine and the molar ratio of Ca^{2+}:leucine:linaclotide is 60:30:1.

17. The solid pharmaceutical composition according to any one of claims 1-16, further comprising: (i) a hydrolysis product having a structure of



comprising less than 2% by weight compared to the weight of the linaclotide; or

(ii) a linaclotide oxidation product having a molecular weight of 1542.8 comprising less than 2% by weight compared to the weight of the linaclotide.

18. A solid pharmaceutical composition comprising:
linaclotide;
Ca^{2+};
leucine; and
hydroxypropyl methylcellulose,
wherein the molar ratio of Ca^{2+}:leucine:linaclotide is between 5-100:5-50:1.

19. The solid pharmaceutical composition of claim 18, wherein the Ca^{2+} is provided as $CaCl_2$.

20. A solid pharmaceutical composition of any one of claims 1 -19 for use in treating a gastrointestinal disorder selected from impaired intestinal motility, irritable bowel syndrome, constipation, pain associated with constipation, dyspepsia, gastroparesis, chronic intestinal pseudo obstruction, Crohn's disease, ulcerative colitis, or inflammatory bowel disease.

21. Use of linaclotide or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment of a gastrointestinal disorder selected from impaired intestinal motility, irritable bowel syndrome, constipation, pain associated with constipation, dyspepsia, gastroparesis, chronic intestinal pseudo obstruction, Crohn's disease, ulcerative colitis, or inflammatory bowel disease, said medicament comprising a solid pharmaceutical composition comprising a pharmaceutically acceptable carrier, linaclotide, a cation selected from Mg^{2+}, Ca^{2+}, Zn^{2+}, Mn^{2+}, K^{+}, Na^{+} or Al^{3+}, and a sterically hindered primary amine.

22. The solid pharmaceutical composition of claim 20 or use of claim 21, wherein said irritable bowel syndrome is constipation-predominant irritable bowel syndrome or alternating irritable bowel syndrome.

23. The solid pharmaceutical composition of claim 20 or use of claim 21, wherein said irritable bowel syndrome is constipation-predominant irritable bowel syndrome.

24. The solid pharmaceutical composition of claim 20 or use of claim 21, wherein said constipation is chronic constipation, idiopathic constipation, post-operative ileus, or constipation caused by opiate use.

25. The solid pharmaceutical composition of claim 20 or use of claim 21, wherein said constipation is chronic constipation.

26. The solid pharmaceutical composition or use of any one of claims 20-25, wherein said pharmaceutical composition comprises 50 µg to 1 mg of linaclotide.

27. The solid pharmaceutical composition or use of claim 26, wherein said pharmaceutical composition comprises 67.5 µg, 133 µg, 150 µg, 266 µg or 300 µg of linaclotide.

28. The solid pharmaceutical composition or use of any one of claims 20-27, wherein said pharmaceutical composition is to be administered once daily or twice daily.

29. The solid pharmaceutical composition or use of any one of claims 20-28, wherein the pharmaceutical composition is to be administered once daily as one or two tablets or capsules.

30. The solid pharmaceutical composition or use of any one of claims 20-29, wherein said pharmaceutical composition comprises 266 μg of linaclotide.

31. The solid pharmaceutical composition or use of any one of claims 20-29, wherein said pharmaceutical composition comprises 133 μg of linaclotide.

32. The solid pharmaceutical composition or use of any one of claims 20-31, wherein said treatment is for a period of at least four weeks.

33. The solid pharmaceutical composition or use of any one of claims 20-32, wherein said treatment improves at least one symptom selected from reduced abdominal pain, an increase in the number of complete spontaneous bowel movements (CSBM) in a week, an increase in the number of spontaneous bowel movements (SBM) in a week, improved stool consistency, reduced straining, reduced abdominal discomfort, reduced bloating or reduced IBS-c symptom severity.

34. The solid pharmaceutical composition or use according to any one of claims 1-33, said composition further comprising coated beads, wherein the beads are coated with a coating solution comprising linaclotide.

35. The solid pharmaceutical composition, or use of claim 34, wherein the coating solution comprises:

linaclotide;
Ca^{2+};
leucine; and
hydroxypropyl methylcellulose,

wherein the molar ratio of Ca^{2+}:leucine:linaclotide is between 5-100:5-50:1.

36. The solid pharmaceutical composition, or use of claim 35, wherein the beads comprise microcrystalline cellulose.

37. A unit dosage form comprising a solid pharmaceutical composition according to any one of claims 1-19 or 34-36.

38. A sealed container comprising a plurality of unit dosage forms according to claim 37.

39. A method for preparing a solid pharmaceutical composition comprising linaclotide or a salt thereof, the method comprising:

(a) providing an aqueous solution comprising:

(i) linaclotide or a pharmaceutically acceptable salt thereof

(ii) one or more of a cation selected from Mg^{2+}, Ca^{2+}, Zn^{2+}, Mn^{2+}, K^{+}, Na^{+} or Al^{3+} or a sterically hindered primary amine; and,

(iii) optionally, a pharmaceutically acceptable binder; and

(b) applying the aqueous solution to a pharmaceutically acceptable filler to generate linaclotide-coated filler.

40. The method of claim 39, wherein the aqueous solution is applied to the filler by spray drying.