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(54) **Title**: STABLE SOLID FORMULATION OF A GC-C RECEPTOR AGONIST POLYPEPTIDE SUITABLE FOR ORAL ADMINISTRATION

(57) **Abstract**: 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

STABLE SOLID FORMULATION OF A GC-C RECEPTOR AGONIST POLYPEPTIDE SUITABLE FOR ORAL ADMINISTRATION

FIELD

This disclosure concerns solid formulations of a guanylate cyclase-C receptor agonist polypeptide suitable for oral administration and methods for preparing such formulations.

PRIORITY CLAIM

This application claims priortiy to United States Application Serial No. 61/089,422, filed August 15, 2008 and to the United States Provisional Application filed August 03, 2009 and entitled, "Stable Solid Formulation of a GC-C Receptor Agonist Polypeptide Suitable for Oral Administration". The entire contents of the aforementioned applications are incorporated herein by reference.

BACKGROUND

Many therapeutic polypeptides are formulated in aqueous solution because they are most active in this form. However, most polypeptides are not particularly stable in aqueous solution, such that the formulations often have a short half-life and require refrigeration. Although aqueous solutions of polypeptides can be dried by freeze-drying, spray-drying or other methods, such dried formulations may also be unstable and have reduced activity relative to an aqueous solution of the polypeptide. Typical break-down mechanisms that occur both in aqueous solution and in dried formulations include aggregation and oxidative or hydrolytic degradation. Thus, the majority of therapeutic polypeptides, whether in aqueous solution or dried, are stored under refrigerated conditions due to their limited stability.

Linaclotide is a peptide having the amino acid sequence Cys Cys Glu Tyr Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr that activates the guanylate cyclase-C (GC-C) receptor. Linaclotide, which may be administered orally, is useful for the treatment of gastrointestinal disorders and conditions, including irritable bowel syndrome (IBS) and chronic constipation (CC). Formulations comprising linaclotide have needed to be refrigerated in order to avoid degradation over time. However, refrigeration is inconvenient both for commercial distribution of the drug and for storage by patients. Thus, there is a need to have a solid linaclotide formulation that is stable at room temperature for at least 12 months.

SUMMARY

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 invention 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 invention 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 invention 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 invention 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 invention 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 invention 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 invention 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 invention 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 invention 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 invention 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.

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