SOLID DOSAGE FORMS OF (S)-ETHYL 2-AMINO-3-(4-(2-AMINO-6-((R)-1-(4-CHLORO-2-(3-METHYL-1H-PYRAZOL-1-YL)PHENYL)-2,2,2-TRIFLUOROETHOXY)PYRIMIDIN-4-YL)PHENYL)PROPANOATE

This application claims priority to U.S. provisional patent application no. 61/547,894, filed October 17, 2011, the entirety of which is incorporated herein by reference.

1. FIELD OF THE INVENTION

This invention relates to solid pharmaceutical dosage forms of (S)-ethyl 2-amino-3-(4-(2-amino-6-((R)-1-(4-chloro-2-(3-methyl-1H-pyrazol-1-yl)phenyl)-2,2,2-trifluoroethoxy)pyrimidin-4-yl)phenyl)propanoate (telotristat).

2. BACKGROUND OF THE INVENTION

The compound (S)-ethyl 2-amino-3-(4-(2-amino-6-((R)-1-(4-chloro-2-(3-methyl-1H-pyrazol-1-yl)phenyl)-2,2,2-trifluoroethoxy)pyrimidin-4-yl)phenyl)propanoate (telotristat) is an inhibitor of tryptophan hydroxylase, the enzyme responsible for the rate-limiting step in biosynthesis of 5-hydroxytryptamine (serotonin). *See, e.g.*, U.S. patent no. 7,709,493. The compound is believed to be useful in the treatment of diseases and disorders associated with abnormal levels of serotonin, such as diarrhea-predominant irritable bowel syndrome and carcinoid syndrome. Unfortunately, telotristat's physicochemical properties make its incorporation into a commercially viable dosage form difficult.

Telotristat hydrolyzes when contacted with water. Dosage forms comprising it must, therefore, limit this degradation as much as possible, and must be made using methods that limit the compound's exposure to moisture. The poor flowability of telotristat's crystalline hippurate salt (telotristat etiprate) further complicates the manufacture of dosage forms comprising it. Further adding to the problem is the desire to provide single unit dosage forms that contain at least 100 mg of the compound, and that rapidly release it upon oral administration.

In view of these factors, a need exists for solid dosage forms of telotristat that can be stored at typical temperatures and humidity levels for a commercially viable period of time, and for methods of their manufacture. Preferred dosage forms should be capable of rapidly delivering the compound upon oral administration. A particular need exists for a rapid release tablet formulation of telotristat with good chemical stability, satisfactory oral bioavailability, good processability, and high drug loading.

3. SUMMARY ~~OF THE INVENTION~~

This ~~invention~~ disclosure is directed to solid dosage forms of telotristat. Particular dosage forms are tablets made with the hippurate salt of telotristat (telotristat etiprate).

One embodiment of the ~~invention~~ disclosure encompasses a tablet suitable for administration to a patient comprising at least 100, 200, or 300 mg of an active pharmaceutical ingredient (API), which tablet has a disintegration time of less than 10, 5.0, 2.3, 2.0, or 1.8 minutes in water, wherein the API is telotristat or a pharmaceutically acceptable salt thereof.

Another embodiment encompasses a tablet suitable for administration to a patient comprising at least 100, 200, or 300 mg of an API based on free base, which tablet comprises acoating and has a disintegration time of less than 5.5, 4.5, or 4.0 minutes in water, wherein the API is telotristat or a pharmaceutically acceptable salt thereof.

Another embodiment encompasses a tablet having a core consisting essentially of telotristat hippurate, lactose, hyrdroxy propyl cellulose, croscarmellose sodium, magnesium stearate, and silicon dioxide.

~~Another embodiment encompasses~~ In one aspect, there is provided a tablet comprising telotristat or a pharmaceutically acceptable salt thereof, which forms less than 1.0, 0.8 or 0.5 percent (S)-2-amino-3-(4-(2-amino-6-((R)-1-(4-chloro-2-(3-methyl-1H-pyrazol-1-yl)phenyl)-2,2,2-trifluoroethoxy)pyrimidin-4-yl)phenyl)propanoic acid when stored at about 40 °C and about 75% relative humidity for six months.

Another embodiment encompasses a tablet comprising telotristat or a pharmaceutically acceptable salt thereof, which forms less than 0.5 or 0.4 percent (S)-2-amino-3-(4-(2-amino-6-((R)-1-(4-chloro-2-(3-methyl-1H-pyrazol-1-yl)phenyl)-2,2,2-trifluoroethoxy)pyrimidin-4-yl)phenyl)propanoic acid when stored at about 40 °C and about 75% relative humidity for three months.

In one aspect, there is provided a tablet having a core consisting essentially of telotristat etiprate, lactose, hyrdroxy propyl cellulose, croscarmellose sodium, magnesium stearate, and silicon dioxide.

In one aspect, there is provided a bottle comprising a tablet as defined above and a desiccant.

~~Another embodiment encompasses~~ In one aspect, there is provided a granule comprising telotristat etiprate, lactose, hydroxyl propyl cellulose, croscarmellose sodium, magnesium stearate, and silicon dioxide.

In one aspect, there is provided a granulate comprising granules as defined above, which has an average flow rate index of greater than about 0.3, 0.35, or 0.4 kg/sec.

~~Another embodiment encompasses~~ In one aspect, there is provided a method of making a tablet, which comprises: combining granules comprising intragranular ingredients with at least one extragranular ingredient, and compressing the granules to provide a tablet; wherein the intragranular ingredients comprise telotristat or a pharmaceutically acceptable

salt thereof, magnesium stearate, and lactose; and the at least one extragranular ingredient is lactose.

4. BRIEF DESCRIPTION OF THE FIGURES

Certain aspects of the invention can be understood with reference to the appended figures.

Figure 1 shows an X-ray powder diffraction (XRPD) pattern of a crystalline form of telotristat. The diffractogram was obtained using a Rigaku MiniFlex diffractometer (copper Kα radiation).

Figure 2 provides an XRPD pattern of a crystalline form of telotristat etiprate. The diffractogram was obtained using a Bruker D8 Advance (copper Kα radiation).