FORMULATIONS OF 4-AMINO-2-(2,6-DIOXOPIPERIDINE-3-YL)ISOINDOLINE-1,3-DIONE

1. FIELD

Provided herein are formulations and dosage forms of pomolidomide, *i.e.*, 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione or CC-4047. Methods of using the formulations and dosage forms are also provided herein.

2. BACKGROUND

Drug substances are usually administered as part of a formulation in combination with one or more other agents that serve varied and specialized pharmaceutical functions. Dosage forms of various types may be made through selective use of pharmaceutical excipients. As pharmaceutical excipients have various functions and contribute to the pharmaceutical formulations in many different ways, *e.g.*, solubilization, dilution, thickening, stabilization, preservation, coloring, flavoring, etc. The properties that are commonly considered when formulating an active drug substance include bioavailability, ease of manufacture, ease of administration, and stability of the dosage form. Due to the varying properties of the active drug substance to be formulated, dosage forms typically require pharmaceutical excipients that are uniquely tailored to the active drug substance in order to achieve advantageous physical and pharmaceutical properties.

Pomolidomide, which is also known as CC-4047, is chemically named 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione. Pomolidomide is an immunomodulatory compound that inhibits, for example, LPS induced monocyte TNFα, IL-1ß, IL-12, IL-6, MIP-1, MCP-1, GM-CSF, G-CSF, and COX-2 production. The compound is also known to co-stimulate the activation of T-cells. Pomolidomide and method of synthesizing the compound are described, e.g., in U.S. Patent No. 5,635,517, the entirety of which is incorporated herein by reference.

Pharmaceutical compositions and dosage forms comprising pomalidomide are generally known in the art. For example, U.S. Patent Application No. 2007/0155791 provides a general description of various dosage forms (i.e., oral, topical, parenternal, mucosal) comprising pomalidomide in combination with other active agents, carriers or excipients.

Due to its diversified pharmacological properties, pomolidomide is useful in treating, preventing, and/or managing various diseases or disorders. Thus, a need exists as to dosage forms of pomolidomide having advantageous physical and pharmaceutical properties.

3. SUMMARY

In a first aspect, the present invention refers to an oral dosage form in the form of a capsule which comprises: 1) 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione at an amount of 0.1 to 3 weight percent of the total weight of the composition; 2) a binder or filler at an amount of 90 to 99 weight percent of total weight of the composition; wherein the binder or filler is starch, mannitol or mixture thereof.

In a second aspect, the present invention refers to an oral dosage form which weighs 62.5 mg and comprises: 1) 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione, or a pharmaceutically acceptable salt or solvate thereof, at an amount that provides 0.5 mg potency of 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione; 2) pregelatinized starch at an amount of 35 mg; 3) sodium stearyl fumarate at an amount of 0.16 mg; and 4) spray dried mannitol at an amount that brings the total weight of the composition to 62.5 mg.

In a third aspect, the present invention refers to an oral dosage form which weighs 125 mg and comprises: 1) 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione or a pharmaceutically acceptable salt or solvate thereof, at an amount that provides 1 mg potency of 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione; 2) pregelatinized starch at an amount of 70 mg; 3) sodium stearyl fumarate at an amount of 0.32 mg; and 4) spray dried mannitol at an amount that brings the total weight of the composition to 125 mg.

In a fourth aspect, the present invention refers to an oral dosage form which weighs 250 mg and comprises: 1) 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione, or a pharmaceutically acceptable salt or solvate thereof, at an amount that provides 2 mg potency of 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione; 2) pregelatinized starch at an amount of 140 mg; 3) sodium stearyl fumarate at an amount of 0.64 mg; and 4) spray dried mannitol at an amount that brings the total weight of the composition to 250 mg.

In a fifth aspect, the present invention refers to an oral dosage form which weighs 180 mg and comprises: 1) 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione, or a pharmaceutically acceptable salt or solvate thereof, at an amount that provides 3 mg potency of 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione; 2) pregelatinized starch at an amount of 100.8 mg; 3) sodium stearyl fumarate at an amount of 0.45 mg; and 4) spray dried mannitol at an amount that brings the total weight of the composition to 180 mg.

In a sixth aspect, the present invention refers to an oral dosage form which weighs 240 mg and comprises: 1) 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione, or a pharmaceutically acceptable salt or solvate thereof, at an amount that provides 4 mg potency of 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione; 2) pregelatinized starch at an amount of 134.4 mg; 3) sodium stearyl fumarate at an amount of 0.6 mg; 4) spray dried mannitol at an amount of 0.6 mg; and 4) spray dried mannitol at an amount that brings the total weight of the composition to 240 mg.

In a seventh aspect, the present invention refers to an oral dosage form which weighs 300 mg and comprises: 1) 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione, or a pharmaceutically acceptable salt or solvate thereof, at an amount that provides 5 mg potency of 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione; 2) pregelatinized starch at an amount of 168 mg; 3) sodium stearyl fumarate at an amount of 0.75 mg; and 4) spray dried mannitol at an amount that brings the total weight of the composition to 300 mg.

In an eighth aspect, the present invention refers to the use of an oral dosage form as defined above in the manufacture of a medicament for treating, preventing, or managing cancer, pain, Macular Degeneration , a skin disease, a pulmonary disorder, an asbestos-related disorder, a parasitic disease, an immunodeficiency disorder, a CNS disorder, CNS injury, atherosclerosis, a sleep disorder, hemoglobinopathy, anemia, an inflammatory disease, an autoimmune disease, a viral disease, a genetic disease, an allergic disease, a bacterial disease, an ocular neovascular disease , a choroidal neovascular disease, a retina neovascular disease, or rubeosis in a patient wherein the medicament is to be administered to the patient.

Described~~Provided~~ herein are pharmaceutical dosage forms of pomolidomide, or a pharmaceutically acceptable stereoisomer, prodrug, salt, solvate, hydrate, or clathrate

thereof. Also described~~provided~~ herein are methods of treating, managing, or preventing diseases and conditions such as, but not limited to, cancer, pain, Macular Degeneration, a skin disease, a pulmonary disorder, an asbestos-related disorder, a parasitic disease, an immunodeficiency disorder, a CNS disorder, CNS injury, atherosclerosis, a sleep disorder, hemoglobinopathy, anemia, an inflammatory disease, an autoimmune disease, a viral disease, a genetic disease, an allergic disease, a bacterial disease, an ocular neovascular disease, a choroidal neovascular disease, a retina neovascular disease, and rubeosis, using pomolidomide, or a pharmaceutically acceptable stereoisomer, prodrug, salt, solvate, hydrate, or clathrate thereof, in the dosage forms described herein.

3.1. DEFINITIONS

As used herein and unless otherwise indicated, a composition that is "substantially free" of a compound means that the composition contains less than about 20 percent by weight, more preferably less than about 10 percent by weight, even more preferably less than about 5 percent by weight, and most preferably less than about 3 percent by weight of the compound.

As used herein and unless otherwise indicated, the term "stereomerically pure" means a composition that comprises one stereoisomer of a compound and is substantially free of other stereoisomers of that compound. For example, a stereomerically pure composition of a compound having one chiral center will be substantially free of the opposite enantiomer of the compound. A stereomerically pure composition of a compound having two chiral centers will be substantially free of other diastereomers of the compound. A typical stereomerically pure compound comprises greater than about 80 percent by weight of one stereoisomer of the compound and less than about 20 percent by weight of other stereoisomers of the compound, more preferably greater than about 90 percent by weight of one stereoisomer of the compound and less than about 10 percent by weight of the other stereoisomers of the compound, even more preferably greater than about 95 percent by weight of one stereoisomer of the compound and less than about 5 percent by weight of the other stereoisomers of the compound, and most preferably greater than about 97 percent by weight of one stereoisomer of the compound and less than about 3 percent by weight of the other stereoisomers of the compound.

As used herein and unless otherwise indicated, the term "enantiomerically pure" means a stereomerically pure composition of a compound having one chiral center.

As used herein, unless otherwise specified, the term "pharmaceutically acceptable salt(s)," as used herein includes, but is not limited to, salts of acidic or basic moieties of