PHARMACEUTICAL FORMULATIONS OF A HIF HYDROXYLASE INHIBITOR

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit under 35 U.S.C. § 119(e) of United States Provisional Application 61/831,909 filed June 6, 2013 and is hereby incorporated by reference in its entirety.

BACKGROUND

[0002] The present invention relates generally to pharmaceutical formulations of [(4-hydroxy-1-methyl-7-phenoxy-isoquinoline-3-carbonyl)-amino]-acetic acid.

[0003] [(4-Hydroxy-1-methyl-7-phenoxy-isoquinoline-3-carbonyl)-amino]-acetic acid (alternatively referred to herein as Compound A) is a potent inhibitor of hypoxia inducible factor (HIF) prolyl hydroxylase, as described in U.S. Patent No. 7,323,475. HIF prolyl hydroxylase inhibitors are useful for increasing the stability and/or activity of HIF, and useful for, inter alia, treating and preventing disorders associated with HIF, including anemia, and ischemia- and hypoxia-related disorders.

[0004] It has recently been discovered that Compound A undergoes decomposition after exposure to light. Heretofore, pharmaceutical formulations of Compound A which provide the necessary photostability of the compound have not yet been taught.

SUMMARY

[0005] The present disclosure fulfills the need of providing photostability of Compound A and others by providing a pharmaceutical formulation comprising [(4-hydroxy-1-methyl-7-phenoxy-isoquinoline-3-carbonyl)-amino]-acetic acid, a pharmaceutically acceptable excipient and an effective amount of a photostabilizing agent. In one embodiment, the pharmaceutical formulation comprises less than about 0.2% w/w (based on the amount of active pharmaceutical ingredient ("API")) photodegradation product of [(4-hydroxy-1-methyl-7-phenoxy-isoquinoline-3-carbonyl)-amino]-acetic acid. In another embodiment, the photostabilizing agent blocks light at a wavelength range of between about 200 and about 550 nm.

[0005a] In an aspect, there is provided a pharmaceutical formulation comprising [(4-hydroxy-1-methyl-7-phenoxy-isoquinoline-3-carbonyl)-amino]-acetic acid, a pharmaceutically acceptable excipient, and an

effective amount of a photostabilizing agent, wherein the pharmaceutical formulation comprises less than about 0.2% w/w (based on the amount of [(4-hydroxy-1-methyl-7-phenoxy-isoquinoline-3-carbonyl)-amino]-acetic acid) photodegradation product of [(4-hydroxy-1-methyl-7-phenoxy-isoquinoline-3-carbonyl)-amino]-acetic acid.

[0005b] In another aspect, there is provided a pharmaceutical formulation comprising [(4-hydroxy-1-methyl-7-phenoxy-isoquinoline-3-carbonyl)-amino]-acetic acid, a pharmaceutically acceptable excipient, and an effective amount of a photostabilizing agent, wherein the photostabilizing agent comprises titanium dioxide and at least one additional dye.

[0006] In one embodiment, the photostabilizing agent comprises titanium dioxide and at least one additional dye. In one embodiment, the photostabilizing agent blocks light at a wavelength range of

between about 200 and about 550 nm. In one embodiment, the dye is selected from the group consisting of a black dye, a blue dye, a green dye, a red dye, an orange dye, a yellow dye, and combinations thereof. In another embodiment, the dye is selected from the group consisting of a red dye, an orange dye, a yellow dye, and combinations thereof.

[0007] In one embodiment, the dye is selected from the group consisting of Allura Red AC, Allura Red AC aluminum lake, iron oxide red, iron oxide yellow, Sunset Yellow FCF, Sunset Yellow FCF aluminum lake, Indigotine, Indigotine aluminum lake, and combinations thereof.

[0008] In one embodiment, the pharmaceutical formulation comprises from about 20 mg to about 200 mg of [(4-hydroxy-1-methyl-7-phenoxy-isoquinoline-3-carbonyl)-amino]-acetic acid. In another embodiment, the pharmaceutical formulation comprises about 20 mg, about 50 mg, or about 100 mg of [(4-hydroxy-1-methyl-7-phenoxy-isoquinoline-3-carbonyl)-amino]-acetic acid.

[0009] In one embodiment, a solid dosage form comprises the pharmaceutical formulation and the solid dosage form is selected from a capsule, tablet, bead, granule, pellet, lozenge, pill, or gum. In another embodiment, the solid dosage form is a tablet. In another embodiment, the solid dosage form is a capsule.

[0009a] In another aspect, there is provided a solid dosage form comprising the pharmaceutical formulation as defined above, wherein the solid dosage form is selected from capsule, tablet, bead, granule, pellet, lozenge, pill, or gum.

[0010] ~~The present disclosure~~In another aspect, there is provideds a tablet comprising [(4-hydroxy-1-methyl-7-phenoxy-isoquinoline-3-carbonyl)-amino]-acetic acid, a pharmaceutically acceptable excipient and an effective amount of a photostabilizing agent. In one embodiment, the tablet comprises a tablet core and a coating. In some embodiments, the photostabilizing agent is blended into the tablet or the tablet core. In other embodiments, the tablet core comprises [(4-hydroxy-1-methyl-7-phenoxy-isoquinoline-3-carbonyl)-amino]-acetic acid and the pharmaceutically acceptable excipient, and the coating comprises the photostabilizing agent.

[0011] In one embodiment, the coating is present in the tablet in an amount that is from about 3% to about 8% w/w based on the weight of the tablet core. In another embodiment, the tablet core comprises from about 22% to about 28% w/w [(4-hydroxy-1-methyl-7-phenoxy-isoquinoline-3-carbonyl)-amino]-acetic acid (based on the weight of the tablet core). In yet another embodiment, the pharmaceutically acceptable excipient comprises lactose monohydrate, microcrystalline cellulose, povidone, croscarmellose sodium, and magnesium stearate.

[0011a] In another aspect, there is provided a tablet comprising a tablet core and a coating, wherein the tablet core comprises [(4-hydroxy-1-methyl-7-phenoxy-isoquinoline-3-carbonyl)-amino]-acetic acid and a pharmaceutically acceptable excipient, and the coating comprises an effective amount of a photostabilizing agent, wherein the coating is present in an amount from about 3% to about 8% w/w (based on the weight of the tablet core).

[0012] In one embodiment, the coating comprises from about 0.1% to about 50% w/w photostabilizing agent (based on coating weight). In some embodiments, the photostabilizing agent

comprises titanium dioxide and at least one additional dye selected from the group consisting of Allura Red AC, Allura Red AC aluminum lake, iron oxide red, iron oxide yellow, Sunset Yellow FCF, Sunset Yellow FCF aluminum lake, Indigotine, Indigotine aluminum lake, and combinations thereof. In another embodiment, the photostabilizing agent comprises titanium dioxide and Allura Red AC aluminum lake.

[0013] ~~The present disclosure~~In another aspect, there is provided~~s~~ a capsule comprising [(4-hydroxy-1-methyl-7-phenoxy-isoquinoline-3-carbonyl)-amino]-acetic acid, a pharmaceutically acceptable excipient and an effective amount of a photostabilizing agent. In one embodiment, the capsule comprises a capsule fill and a capsule shell. In one embodiment, the capsule fill comprises [(4-hydroxy-1-methyl-7-phenoxy-isoquinoline-3-carbonyl)-amino]-acetic acid and the pharmaceutically acceptable excipient, and the capsule shell comprises the photostabilizing agent.

[0014] In one embodiment, the capsule fill comprises from about 12% to about 15% w/w [(4-hydroxy-1-methyl-7-phenoxy-isoquinoline-3-carbonyl)-amino]-acetic acid (based on the weight of the capsule fill). In another embodiment, the pharmaceutically acceptable excipient comprises lactose monohydrate, microcrystalline cellulose, povidone, croscarmellose sodium, and magnesium stearate.

[0014a] In another aspect, there is provided a capsule comprising a capsule fill and a capsule shell, wherein the capsule fill comprises from about 12% to about 15% w/w [(4-hydroxy-1-methyl-7-phenoxy-isoquinoline-3-carbonyl)-amino]-acetic acid (based on the weight of the capsule fill) and a pharmaceutically acceptable excipient, and wherein the capsule shell comprises an effective amount of a photostabilizing agent.

[0015] In one embodiment, the capsule shell comprises the photostabilizing agent in an amount of from about 1.8% to about 6% w/w (based on the weight of the capsule shell). In some embodiments, the photostabilizing agent comprises titanium dioxide and at least one additional dye selected from the group consisting of Allura Red AC, iron oxide red, iron oxide yellow, and combinations thereof.

[0016] In a separate embodiment, a method of inhibiting the photodegradation of [(4-hydroxy-1-methyl-7-phenoxy-isoquinoline-3-carbonyl)-amino]-acetic acid is provided. The method comprises formulating [(4-hydroxy-1-methyl-7-phenoxy-isoquinoline-3-carbonyl)-amino]-acetic acid with an effective amount of a photostabilizing agent. In another embodiment, the photostabilizing agent comprises titanium dioxide and at least one additional dye.

[0016a] In another aspect, there is provided a method of inhibiting the photodegradation of [(4-hydroxy-1-methyl-7-phenoxy-isoquinoline-3carbonyl)-amino]-acetic acid, said method comprising formulating [(4-hydroxy-1-methyl-7-phenoxy-isoquinoline-3-carbonyl)-amino]-acetic acid with an effective amount of a photostabilizing agent.

[0017] In yet another embodiment, a method for treating, pretreating, or delaying onset or progression of a condition mediated at least in part by hypoxia inducible factor (HIF) is provided. The method comprises administering to a patient in need thereof, a pharmaceutical formulation, a tablet, or a capsule as described herein.

[0017a] In another aspect, there is provided the use of a pharmaceutical formulation as defined above, a tablet as defined above, or a capsule as defined above in the manufacture of a medicament for treating, pretreating, or delaying onset or progression of a condition mediated at least in part by hypoxia inducible factor (HIF).

[0018] In still yet another embodiment, a method for treating, pretreating, or delaying onset or progression of anemia is provided. The method comprises administering to a patient in need thereof, a pharmaceutical formulation, a tablet, or a capsule as described herein.

[0018a] In another aspect, there is provided the use of a pharmaceutical formulation as defined above, a tablet as defined above, or a capsule as defined above in the manufacture of a medicament for treating, pretreating, or delaying onset or progression of anemia.

BRIEF DESCRIPTION OF THE DRAWINGS

[0019] FIG. 1 illustrates the HPLC chromatograms of Compound A powders before and after exposure to sunlight. See Example 1 for details.

[0020] FIG. 2A and 2B illustrates the amount of photodegradation product in tablets containing either 20 mg (FIG. 2A) or 100 mg (FIG. 2B) of Compound A upon light exposure. The tablets are coated with a coating formula containing Allura Red AC/Indigotine /titanium dioxide (labeled as Allura Red AC/Indigotine in figures), Allura Red AC/titanium dioxide (labeled as Allura Red AC in figures), or red iron oxide/titanium dioxide (labeled as Red Iron Oxide in figures). See Example 2 for details.

[0021] FIG. 3A and 3B illustrates the amount of photodegradation product in tablets containing either 20 mg (FIG. 3A) or 100 mg (FIG. 3B) of Compound A upon light exposure. The tablets are coated with a variety of pink/peach coating formulas. See Example 2 for details.

[0022] FIG. 4 demonstrates the amount of photodegradation product in capsules covered with gelatin films containing various photostabilizing agents upon light exposure. See Example 3 for details.

DETAILED DESCRIPTION

Definitions

[0023] As used herein, the following terms have the following meanings.

[0024] The singular forms "a," "an," and "the" and the like include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a compound" includes both a single compound and a plurality of different compounds.

acceptable excipients comprising lactose monohydrate, microcrystalline cellulose, povidone, croscarmellose sodium, and magnesium stearate; and wherein the capsule shell is a gelatin shell comprising about 2% w/w iron oxide yellow, and about 1% w/w titanium dioxide (based on the weight of the capsule shell).

58. A method of inhibiting the photodegradation of [(4-hydroxy-1-methyl-7-phenoxy-isoquinoline-3carbonyl)-amino]-acetic acid, said method comprising formulating [(4-hydroxy-1-methyl-7-phenoxy-isoquinoline-3-carbonyl)-amino]-acetic acid with an effective amount of a photostabilizing agent.

59. The method of claim 58, wherein the photostabilizing agent comprises titanium dioxide and at least one additional dye.

60. Use of ~~A method for treating, pretreating, or delaying onset or progression of a condition mediated at least in part by hypoxia inducible factor (HIF), comprising administering to a patient in need thereof,~~ a pharmaceutical formulation of any one of claims 1-15, a tablet of any one of claims 19-35, or a capsule of any one of claims 36-57 in the manufacture of a medicament for treating, pretreating, or delaying onset or progression of a condition mediated at least in part by hypoxia inducible factor (HIF).

61. Use of ~~A method for treating, pretreating, or delaying onset or progression of anemia, comprising administering to a patient in need thereof,~~ a pharmaceutical formulation of any one of claims 1-15, a tablet of any one of claims 19-35, or a capsule of any one of claims 36-57 in the manufacture of a medicament for treating, pretreating, or delaying onset or progression of anemia.