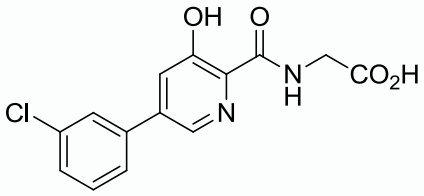
CLAIMS

1. An oral dosage formulation that is a tablet comprising an intra-granular component, an extra-granular component, and a film coating component,

wherein the intra-granular component comprises

55% to 75% by weight of {[5-(3-chlorophenyl)-3-hydroxypyridine-2-carbonyl]amino}acetic acid,



(Compound 1)

or a pharmaceutically acceptable salt thereof,

15% to 35% by weight of an insoluble diluent or carrier,

2.0% to 4.0% by weight of a disintegrant, and

1.8% to 3.8% by weight of a diluent or filler;

wherein the extra-granular component comprises

2.0% to 4.0% by weight of a disintegrant,

0.15% to 0.35% by weight of a glidant, and

0.35% to 1.15% by weight of a lubricant;

wherein the film coating component comprises 1.0% to 8% by weight of a tablet coating; and

wherein the weight is the total weight of all intra-granular and extra-granular components.

2. The formulation of claim 1

wherein the intra-granular component comprises

60% to 70% by weight of Compound 1,

20% to 30% by weight of an insoluble diluent or carrier,

2.5% to 3.5% by weight of a disintegrant, and

2.3% to 3.3% by weight of a diluent or filler;

wherein the extra-granular component comprises

2.5% to 3.5% by weight of a disintegrant,

0.2% to 0.3% by weight of a glidant, and

0.55% to 0.95% by weight of a lubricant;

wherein the film coating component comprises 1.0% to 8% by weight of a tablet coating; and

wherein the weight is the total weight of all intra-granular and extra-granular components.

3. The formulation of claim 1

wherein the intra-granular component comprises

60% by weight of Compound 1,

30% by weight of an insoluble diluent or carrier,

3% by weight of a disintegrant, and

2.8% by weight of a diluent or filler;

wherein the extra-granular component comprises

3% by weight of a disintegrant,

0.25% by weight of a glidant, and

0.75% by weight of a lubricant;

wherein the film coating component comprises 2.0% to 6.0% by weight of a tablet coating; and

wherein the weight is the total weight of all intra-granular and extra-granular components.

4. The formulation of claim 1

wherein the intra-granular component comprises

65% by weight of Compound 1,

25% by weight of an insoluble diluent or carrier,

3% by weight of a disintegrant, and

2.8% by weight of a diluent or filler;

wherein the extra-granular component comprises

3% by weight of a disintegrant,

0.25% by weight of a glidant, and

0.75% by weight of a lubricant;

wherein the film coating component comprises 2.0% to 6.0% by weight of a tablet coating; and

wherein the weight is the total weight of all intra-granular and extra-granular components.

5. The formulation of claim 1

wherein the intra-granular component comprises

70% by weight of Compound 1,

20% by weight of an insoluble diluent or carrier,

3% by weight of a disintegrant, and

2.8% by weight of a diluent or filler;

wherein the extra-granular component comprises

3% by weight of a disintegrant,

0.25% by weight of a glidant, and

0.75% by weight of a lubricant;

wherein the film coating component comprises 2.0% to 6.0% by weight of a tablet coating; and

wherein the weight is the total weight of all intra-granular and extra-granular components.

6. The formulation of claim 1

wherein the intra-granular component comprises

75% by weight of Compound 1,

15% by weight of an insoluble diluent or carrier,

3% by weight of a disintegrant, and

2.8% by weight of a diluent or filler;

wherein the extra-granular component comprises

3% by weight of a disintegrant,

0.25% by weight of a glidant, and

0.75% by weight of a lubricant;

wherein the film coating component comprises 2.0% to 6.0% by weight of a tablet coating; and

wherein the weight is the total weight of all intra-granular and extra-granular components.

7. The oral dosage formulation of claim 1, wherein the intra-granular components comprise Compound 1 , microcrystalline cellulose, sodium starch glycolate, and hydroxypropyl methylcellulose, wherein the extra-granular components comprise sodium starch glycolate, colloidal silicon dioxide, and magnesium stearate, and wherein the film-coating components comprise Opadry®.

8. The formulation of claim 7

wherein the intra-granular component comprises

55% to 75% by weight of Compound 1,

15% to 35% by weight of microcrystalline cellulose,

2.0% to 4.0% by weight of sodium starch glycolate, and

1.8% to 3.8% by weight of a hydroxypropyl methylcellulose;

wherein the extra-granular component comprises

2.0% to 4.0% by weight of a sodium starch glycolate,

0.15% to 0.35% by weight of colloidal silicon dioxide, and

0.35% to 1.15% by weight of magnesium stearate;

wherein the film coating component comprises 1.0% to 8% by weight of Opadry®; and

wherein the weight is the total weight of all intra-granular and extra-granular components.

9. The formulation of claim 7

wherein the intra-granular component comprises

60% to 70% by weight of Compound 1,

20% to 30% by weight of microcrystalline cellulose,

2.5% to 3.5% by weight of sodium starch glycolate, and

2.3% to 3.3% by weight of a hydroxypropyl methylcellulose;

wherein the extra-granular component comprises

2.5% to 3.5% by weight of a sodium starch glycolate,

0.2% to 0.3% by weight of colloidal silicon dioxide, and

0.55% to 0.95% by weight of magnesium stearate;

wherein the film coating component comprises 1.0% to 8% by weight of Opadry®; and

wherein the weight is the total weight of all intra-granular and extra-granular components.

10. The formulation of claim 7

wherein the intra-granular component comprises

60% by weight of Compound 1,

30% by weight of microcrystalline cellulose,

3% by weight of sodium starch glycolate, and

2.8% by weight of a hydroxypropyl methylcellulose;

wherein the extra-granular component comprises

3% by weight of a sodium starch glycolate,

0.25% by weight of colloidal silicon dioxide, and

0.75% by weight of magnesium stearate;

wherein the film coating component comprises 2.0% to 6.0% by weight of Opadry®; and

wherein the weight is the total weight of all intra-granular and extra-granular components.

11. The formulation of claim 7

wherein the intra-granular component comprises

65% by weight of Compound 1,

25% by weight of microcrystalline cellulose,

3% by weight of sodium starch glycolate, and

2.8% by weight of a hydroxypropyl methylcellulose;

wherein the extra-granular component comprises

3% by weight of a sodium starch glycolate,

0.25% by weight of colloidal silicon dioxide, and

0.75% by weight of magnesium stearate;

wherein the film coating component comprises 2.0% to 6.0% by weight of Opadry®; and

wherein the weight is the total weight of all intra-granular and extra-granular components.

12. The formulation of claim 7

wherein the intra-granular component comprises

70% by weight of Compound 1,

20% by weight of microcrystalline cellulose,

3% by weight of sodium starch glycolate, and

2.8% by weight of a hydroxypropyl methylcellulose;

wherein the extra-granular component comprises

3% by weight of a sodium starch glycolate,

0.25% by weight of colloidal silicon dioxide, and

0.75% by weight of magnesium stearate;

wherein the film coating component comprises 2.0% to 6.0% by weight of Opadry®; and

wherein the weight is the total weight of all intra-granular and extra-granular components.

13. The formulation of claim 7

wherein the intra-granular component comprises

75% by weight of Compound 1,

15% by weight of microcrystalline cellulose,

3% by weight of sodium starch glycolate, and

2.8% by weight of a hydroxypropyl methylcellulose;

wherein the extra-granular component comprises

3% by weight of a sodium starch glycolate,

0.25% by weight of colloidal silicon dioxide, and

0.75% by weight of magnesium stearate;

wherein the film coating component comprises 2.0% to 6.0% by weight of Opadry®; and wherein the weight is the total weight of all intra-granular and extra-granular components.

14. The formulation of any one of claims 1-13, wherein the intra-granular component comprises about 150 mg of Compound 1.

15. The formulation of any one of claims 1-14 for use in treating anemia comprising administering to a patient a formulation comprising intra-granular components, extra-granular components, and film coating components, wherein the intra-granular components comprise Compound 1, an insoluble diluent or carrier, a disintegrant, and a diluent or filler; wherein the extra-granular components comprise a disintegrant, a glidant, and/or a lubricant, and wherein the film coating components comprise a tablet coating.

16. The formulation for use of claim 15

wherein the intra-granular component comprises

55% to 75% by weight of Compound 1,

15% to 35% by weight of an insoluble diluent or carrier,

2.0% to 4.0% by weight of a disintegrant, and

1.8% to 3.8% by weight of a diluent or filler;

wherein the extra-granular component comprises

2.0% to 4.0% by weight of a disintegrant,

0.15% to 0.35% by weight of a glidant, and

0.35% to 1.15% by weight of a lubricant;

wherein the film coating component comprises 1.0% to 8% by weight of a tablet coating; and wherein the weight is the total weight of all intra-granular and extra-granular components.

17. The formulation for use of claim 15

wherein the intra-granular component comprises

60% to 70% by weight of Compound 1,

20% to 30% by weight of an insoluble diluent or carrier,

2.5% to 3.5% by weight of a disintegrant, and

2.3% to 3.3% by weight of a diluent or filler;

wherein the extra-granular component comprises

2.5% to 3.5% by weight of a disintegrant,

0.2% to 0.3% by weight of a glidant, and

0.55% to 0.95% by weight of a lubricant;

wherein the film coating component comprises 1.0% to 8% by weight of a tablet coating; and

wherein the weight is the total weight of all intra-granular and extra-granular components.

18. The formulation for use of claim 15

wherein the intra-granular component comprises

60% by weight of Compound 1,

30% by weight of an insoluble diluent or carrier,

3% by weight of a disintegrant, and

2.8% by weight of a diluent or filler;

wherein the extra-granular component comprises

3% by weight of a disintegrant,

0.25% by weight of a glidant, and

0.75% by weight of a lubricant;

wherein the film coating component comprises 2.0% to 6.0% by weight of a tablet coating; and

wherein the weight is the total weight of all intra-granular and extra-granular components.

19. The formulation for use of claim 15

wherein the intra-granular component comprises

65% by weight of Compound 1,

25% by weight of an insoluble diluent or carrier,

3% by weight of a disintegrant, and

2.8% by weight of a diluent or filler;

wherein the extra-granular component comprises

3% by weight of a disintegrant,

0.25% by weight of a glidant, and

0.75% by weight of a lubricant;

wherein the film coating component comprises 2.0% to 6.0% by weight of a tablet coating; and

wherein the weight is the total weight of all intra-granular and extra-granular components.

20. The formulation for use of claim 15

wherein the intra-granular component comprises

70% by weight of Compound 1,

20% by weight of an insoluble diluent or carrier,

3% by weight of a disintegrant, and

2.8% by weight of a diluent or filler;

wherein the extra-granular component comprises

3% by weight of a disintegrant,

0.25% by weight of a glidant, and

0.75% by weight of a lubricant;

wherein the film coating component comprises 2.0% to 6.0% by weight of a tablet coating; and

wherein the weight is the total weight of all intra-granular and extra-granular components.

21. The formulation for use of claim 15

wherein the intra-granular component comprises

75% by weight of Compound 1,

15% by weight of an insoluble diluent or carrier,

3% by weight of a disintegrant, and

2.8% by weight of a diluent or filler;

wherein the extra-granular component comprises

3% by weight of a disintegrant,

0.25% by weight of a glidant, and

0.75% by weight of a lubricant;

wherein the film coating component comprises 2.0% to 6.0% by weight of a tablet coating; and

wherein the weight is the total weight of all intra-granular and extra-granular components.

22. The formulation of any one of claims 1–14 for use in treating anemia secondary to non-dialysis dependent chronic kidney disease, comprising administering to a patient having

anemia secondary to non-dialysis dependent chronic kidney disease, wherein the formulation is suitable for administration of a daily dose of Compound 1 that is about 150 mg, about 300 mg, about 450 mg, about 600 mg, or about 750 mg of Compound 1.

23. The formulation of any one of claims 1–14 for use in treating anemia secondary to non-dialysis dependent chronic kidney disease, comprising administering a sufficient number of successive doses of a HIF prolyl hydroxylase inhibitor or a HIF-alpha stabilizer to a patient having anemia secondary to non-dialysis dependent chronic kidney disease wherein the patient has at least 2, 3, 4, 5 or all of (i) an estimated glomerular filtration rate (eGFR) of less than 60 mL/min/1.73m^2, wherein the subject is not on dialysis and not expected to start dialysis within 3 months of beginning of treatment, (ii) a hemoglobin level of less than 10.0 g/dL prior to commencement of treatment, (iii) a ferritin level equal to or above 100 ng/mL within 4 weeks of commencement of treatment, (iv) a transferrin saturation (TSAT) level equal to or above 20% within 4 weeks commencement of treatment, (v) a folate measurement equal to or above the lower limit of normal within 4 weeks commencement of treatment, (vi) a vitamin B12 measurement equal to or above the lower limit of normal within 4 weeks commencement of treatment, and (vii) an age of at least 18 years.

24. The formulation of any one of claims 1–14 for use in treating anemia secondary to non-dialysis dependent chronic kidney disease, comprising administering a sufficient number of successive doses of a HIF prolyl hydroxylase inhibitor or a HIF-alpha stabilizer to a patient having anemia secondary to non-dialysis dependent chronic kidney disease wherein the patient has at least 2, 3, 4, 5 or all of (i) an estimated glomerular filtration rate (eGFR) of less than 65 mL/min/1.73m^2, wherein the subject is not on dialysis and not expected to start dialysis within 3 months of beginning of treatment, (ii) a hemoglobin level of less than 10.0 g/dL prior to commencement of treatment, (iii) a ferritin level equal to or above 50 ng/mL within 4 weeks of commencement of treatment, (iv) a transferrin saturation (TSAT) level equal to or above 15% within 4 weeks commencement of treatment, (v) a folate measurement equal to or above the lower limit of normal within 4 weeks commencement of treatment, (vi) a vitamin B12 measurement equal to or above the lower limit of normal within 4 weeks commencement of treatment, and (vii) an age of at least 18 years.

25. The formulation of any one of claims 1–14 for use in treating anemia in a patient having non-dialysis dependent chronic kidney disease comprising:

administering to the patient an initial daily dose of Compound 1; if the Hgb has not increased by more than 0.5 g/dL above the baseline value after 4 weeks of daily administration at the initial daily dose of Compound 1, increasing the daily dose by 150 mg/day of Compound 1, and increasing the daily dose by 150 mg/day every 4 weeks until Hgb is above 10.0 g/dL;

if the Hgb rises rapidly during treatment, reducing the daily dose by 150 mg/day; if the Hgb falls below 10.0 g/dL, increasing the daily dose by 150 mg/day;

if the Hgb level exceeds 11.0 g/dL, interrupting treatment until the Hgb decreases to 10.5 g/dL or less, and thereafter resuming daily dosing with a daily dose reduced by 150 mg/day; and

if a dose adjustment is required to maintain Hgb at the desired level, adjusting the daily dose by 150 mg/day.

26. The formulation of any one of claims 1–14 for use in treating anemia in a patient having non-dialysis dependent chronic kidney disease comprising:

administering to the patient an initial daily dose of Compound 1; if the Hgb has not increased by more than 0.5 g/dL above the baseline value after 4 weeks of daily administration at the initial daily dose of Compound 1, increasing the daily dose by 150 mg/day of Compound 1, and increasing the daily dose by 150 mg/day every 4 weeks until Hgb is above 10.0 g/dL;

if the Hgb rises rapidly during treatment, reducing the daily dose by 150 mg/day; if the Hgb falls below 10.0 g/dL, increasing the daily dose by 150 mg/day;

if the Hgb level exceeds 12.0 g/dL, reducing the daily dose by 150 mg/day, and if Hgb level exceeds 13.0 g/dL, interrupting treatment until the Hgb decreases to 12.5 g/dL or less, and thereafter resuming daily dosing with a daily dose reduced by 150 mg/day; and

if a dose adjustment is required to maintain Hgb at the desired level, adjusting the daily dose by 150 mg/day.

27. The formulation of any one of claims 1–14 for use in treating anemia in a patient having non-dialysis dependent chronic kidney disease comprising:

administering to the patient an initial daily dose of Compound 1; if a dose adjustment is required to maintain Hgb at the desired level, adjusting the daily dose by 150 mg/day;

if the Hgb rises rapidly during treatment, reducing the daily dose by 150 mg/day; if the Hgb falls below 10.0 g/dL, increasing the daily dose by 150 mg/day; and if the Hgb level

exceeds 11.0 g/dL, interrupting treatment until the Hgb decreases to 10.5 g/dL or less, and thereafter resuming dosing with a daily dose reduced by 150 mg/day.

28. The formulation of any one of claims 1–14 for use in treating anemia in a patient having non-dialysis dependent chronic kidney disease comprising:

administering to the patient an initial daily dose of Compound 1; if a dose adjustment is required to maintain Hgb at the desired level, adjusting the daily dose by 150 mg/day;

if the Hgb rises rapidly during treatment, reducing the daily dose by 150 mg/day; if the Hgb falls below 10.0 g/dL, increasing the daily dose by 150 mg/day; and if the Hgb level exceeds 12.0 g/dL, reducing the daily dose by 150 mg/day, and if Hgb level exceeds 13.0 g/dL, interrupting treatment until the Hgb decreases to 12.5 g/dL or less, and thereafter resuming dosing with a daily dose reduced by 150 mg/day.

29. The formulation for use according to claim 25 or 26, wherein the baseline value is determined immediately prior to the first administration of Compound 1.

30. The formulation for use of any of claims 25–28, wherein the Hgb rises rapidly if the Hgb rises more than 1.0 g/dL in any 2-week period.

31. The formulation for use of any of claims 25–28, wherein the maximum daily dose is 600 mg/day.

32. The formulation for use of any of claims 25–28, wherein the daily dose is not increased more frequently than once every 4 weeks during the course of treatment.

33. The formulation for use of any of claims 25–28, wherein the daily dose is decreased more frequently than once every 4 weeks during the course of treatment.

34. The formulation for use of any of claims 25–28, wherein the initial daily dose is 300 mg/day.

35. The formulation for use of claim 34, wherein the initial daily dose is to be administered in form of two tablets of 150 mg of Compound 1 each.

36. The formulation for use of any of claims 25–28, wherein the initial daily dose is 450 mg/day.

37. The formulation for use of claim 36, wherein the initial daily dose is to be administered in form of three tablets of 150 mg of Compound 1 each.

38. The formulation for use of claim 35 or 37, wherein the initial daily dose is to be administered in the morning.

39. The formulation for use of claim 35 or 37, wherein the initial daily dose is to be administered between 7 am and 2 pm.

40. The formulation for use of any of claims 25–39, wherein Compound 1 is to be administered in the form of Formulation 2.

41. The formulation for use of any one of claims 25-40, wherein the intra-granular component comprises about 150 mg of Compound 1.