

Claims

1. An isolated crystalline form of compound 3, wherein the isolated crystalline form is Form 16, characterized by an X-ray powder diffraction pattern having peaks at 2θ angles of 6.8, 10.6, 13.6, 14.2, and $19.2^\circ \pm 0.2^\circ$.
2. The isolated crystalline form of claim 1, characterized by an X-ray powder diffraction pattern substantially similar to FIGURE 34.
3. An isolated crystalline form of compound 3, wherein the isolated crystalline form is Form 1, characterized by an X-ray powder diffraction pattern having peaks at 2θ angles of 8.9, 13.0, 18.9, 23.8, and $28.1^\circ \pm 0.2^\circ$.
4. The isolated crystalline form of claim 3, characterized by an X-ray powder diffraction pattern substantially similar to FIGURE 1.
5. An isolated crystalline form of compound 3, wherein the isolated crystalline form is Form 2, characterized by an X-ray powder diffraction pattern having peaks at 2θ angles of 12.7, 17.1, 19.2, 23.0, and $24.2^\circ \pm 0.2^\circ$.
6. The isolated crystalline form of claim 5, characterized by an X-ray powder diffraction pattern substantially similar to FIGURE 2.
7. An isolated crystalline form of compound 1, wherein the isolated crystalline form is Form 3, characterized by an X-ray powder diffraction pattern having peaks at 2θ angles of 7.5, 9.3, 14.5, 18.8, 21.3, and $24.8^\circ \pm 0.2^\circ$.
8. The isolated crystalline form of claim 7, characterized by an X-ray powder diffraction pattern substantially similar to FIGURE 5.

9. An isolated crystalline form of compound 1, wherein the isolated crystalline form is Form 7, characterized by an X-ray powder diffraction pattern having peaks at 2θ angles of 14.1, 19.1, 21.8, 23.5, and $25.7^\circ \pm 0.2^\circ$.

10. The isolated crystalline form of claim 9, characterized by an X-ray powder diffraction pattern substantially similar to FIGURE 15.

11. An isolated crystalline form of compound 1, wherein the isolated crystalline form is Form 8, characterized by an X-ray powder diffraction pattern having peaks at 2θ angles of 9.0, 9.2, 21.9, 22.1, 24.2, and $24.6^\circ \pm 0.2^\circ$.

12. The isolated crystalline form of claim 11, characterized by an X-ray powder diffraction pattern substantially similar to FIGURE 17.

13. An isolated crystalline form of compound 1, wherein the isolated crystalline form is Form 9, characterized by an X-ray powder diffraction pattern having peaks at 2θ angles of 6.5, 19.6, 20.1, and $21.6^\circ \pm 0.2^\circ$.

14. The isolated crystalline form of claim 13, characterized by an X-ray powder diffraction pattern substantially similar to FIGURE 19.

15. An isolated crystalline form of compound 3, wherein the isolated crystalline form is Form 17, characterized by an X-ray powder diffraction pattern having peaks at 2θ angles of 7.2, 13.6, 18.5, 19.3, 21.9, and $23.5^\circ \pm 0.2^\circ$.

16. The isolated crystalline form of claim 15, characterized by an X-ray powder diffraction pattern substantially similar to FIGURE 37.

17. An isolated crystalline form of compound 3, wherein the isolated crystalline form is Form 18, characterized by an X-ray powder diffraction pattern having peaks at 2θ angles of 6.4, 8.4, 9.8, 17.8, and $19.7^\circ \pm 0.2^\circ$.

18. The isolated crystalline form of claim 17, characterized by an X-ray powder diffraction pattern substantially similar to FIGURE 38.

19. An isolated crystalline form of compound 3, wherein the isolated crystalline form is Form 19, characterized by an X-ray powder diffraction pattern having peaks at 2θ angles of 8.1, 14.1, 16.4, 17.3, 20.5, and $24.1^\circ \pm 0.2^\circ$.

20. The isolated crystalline form of claim 19, characterized by an X-ray powder diffraction pattern substantially similar to FIGURE 39.

21. A method of treating an advanced hematologic malignancy selected from acute myelogenous leukemia (AML), myelodysplastic syndrome (MDS), chronic myelomonocytic leukemia (CMML), myeloid sarcoma, multiple myeloma, and lymphoma, each characterized by the presence of a mutant allele of IDH2, comprising administering to a subject in need thereof a therapeutically effective dose of compound 3, or a pharmaceutically acceptable salt thereof.

22. A method of treating an advanced hematologic malignancy selected from acute myelogenous leukemia (AML), myelodysplastic syndrome (MDS), chronic myelomonocytic leukemia (CMML), myeloid sarcoma, multiple myeloma, and lymphoma, each characterized by the presence of a mutant allele of IDH2, comprising administering to subject in need thereof a pharmaceutical composition comprising a therapeutically effective dose of compound 3, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carrier(s).

23. A method of treating an advanced hematologic malignancy selected from acute myelogenous leukemia (AML), myelodysplastic syndrome (MDS), chronic myelomonocytic leukemia (CMML), myeloid sarcoma, multiple myeloma, and lymphoma, each characterized by the presence of a mutant allele of IDH2, comprising administering to a subject in need thereof a pharmaceutically acceptable salt of compound 3 at a dose of from about 30 mg to about 300 mg free-base equivalent strength, once daily or twice daily.

24. The method of claim 23, wherein the dose is about 75 mg, once daily or twice daily.
25. The method of claim 23, wherein the dose is about 100 mg, once daily or twice daily.
26. The method of claim 23, wherein the dose is about 150 mg, once daily or twice daily.
27. The method of claim 23, wherein the dose is about 200 mg, once daily or twice daily.
28. The method of claim 23, wherein the dosage is an oral dosage form.
29. The method of claim 28, wherein the oral dosage form is a tablet.
30. The method of claim 23, wherein the dose is administered once daily.
31. The method of claim 23, wherein the dose is administered twice daily.
32. The method of claim 23, wherein the pharmaceutically acceptable salt of compound 3 is administered orally as any combination of 5, 10, 50, or 200 mg free-base equivalent strength tablets, twice daily or once daily.
33. The method of any one of claims 21 to 23, wherein the pharmaceutically acceptable salt of compound 3 is compound 1.
34. The method of any one of claims 21 to 23, wherein the advanced hematologic malignancy is selected from acute myelogenous leukemia (AML), myelodysplastic syndrome (MDS), chronic myelomonocytic leukemia (CMML), and lymphoma (e.g., T-cell lymphoma).

35. The method of claim 34, wherein the advanced hematologic malignancy is acute myelogenous leukemia (AML).

36. The method of claim 35, wherein the advanced hematologic malignancy is myelodysplastic syndrome (MDS).

37. The method of claim 35, wherein the advanced hematologic malignancy is chronic myelomonocytic leukemia (CMML).

38. The method of claim 35, wherein the advanced hematologic malignancy is lymphoma.

39. A method of treating an advanced hematologic malignancy selected from acute myelogenous leukemia (AML), myelodysplastic syndrome (MDS), chronic myelomonocytic leukemia (CMML), myeloid sarcoma, multiple myeloma, and lymphoma, each characterized by the presence of a mutant allele of IDH2, comprising administering to a subject in need thereof compound 1 at a dose of at least about 30 mg free-base equivalent strength twice daily.

40. The method of claim 39, wherein the dose is from about 75 mg to about 200 mg free-base equivalent strength.

41. A method of treating an advanced hematologic malignancy selected from acute myelogenous leukemia (AML), myelodysplastic syndrome (MDS), chronic myelomonocytic leukemia (CMML), and lymphoma, each characterized by the presence of a mutant allele of IDH2, comprising administering to subject in need thereof compound 1 at a dose of from about 75 mg to about 250 mg free-base equivalent strength once daily.

42. The method of claim 39 or 41, wherein the dose is about 75 mg.

43. The method of claim 39 or 41, wherein the dose is about 100 mg.

44. The method of claim 39 or 41, wherein the dose is about 150 mg.
45. The method of claim 39 or 41, wherein the dose is about 200 mg.
46. The method of claim 39 or 41, wherein the advanced hematologic malignancy is selected from acute myelogenous leukemia (AML), myelodysplastic syndrome (MDS), chronic myelomonocytic leukemia (CMML), and lymphoma.
47. The method of claim 39 or 41, wherein the dosage is an oral dosage form.
48. The method of claim 47, wherein the oral dosage form is a tablet.

Claims

1. An isolated crystalline form of compound 3, wherein the isolated crystalline form is Form 16, characterized by an X-ray powder diffraction pattern having peaks at 2Θ angles of 6.8, 10.6, 13.6, 14.2, and $19.2^\circ + 0.2^\circ$.
2. The isolated crystalline form of claim 1, characterized by an X-ray powder diffraction pattern substantially similar to FIGURE 34.
3. An isolated crystalline form of compound 3, wherein the isolated crystalline form is Form 1, characterized by an X-ray powder diffraction pattern having peaks at 2Θ angles of 8.9, 13.0, 18.9, 23.8, and $28.1^\circ + 0.2^\circ$.
4. The isolated crystalline form of claim 3, characterized by an X-ray powder diffraction pattern substantially similar to FIGURE 1.
5. An isolated crystalline form of compound 3, wherein the isolated crystalline form is Form 2, characterized by an X-ray powder diffraction pattern having peaks at 2Θ angles of 12.7, 17.1, 19.2, 23.0, and $24.2^\circ + 0.2^\circ$.
6. The isolated crystalline form of claim 5, characterized by an X-ray powder diffraction pattern substantially similar to FIGURE 2.
7. An isolated crystalline form of compound 1, wherein the isolated crystalline form is Form 3, characterized by an X-ray powder diffraction pattern having peaks at 2Θ angles of 7.5, 9.3, 14.5, 18.8, 21.3, and $24.8^\circ + 0.2^\circ$.
8. The isolated crystalline form of claim 7, characterized by an X-ray powder diffraction pattern substantially similar to FIGURE 5.
9. An isolated crystalline form of compound 1, wherein the isolated crystalline form is Form 7, characterized by an X-ray powder diffraction pattern having peaks at 2Θ angles of 14.1, 19.1, 21.8, 23.5, and $25.7^\circ + 0.2^\circ$.
10. The isolated crystalline form of claim 9, characterized by an X-ray powder diffraction pattern substantially similar to FIGURE 15.

11. An isolated crystalline form of compound 1, wherein the isolated crystalline form is Form 8, characterized by an X-ray powder diffraction pattern having peaks at 2Θ angles of 9.0, 9.2, 21.9, 22.1, 24.2, and $24.6^\circ \pm 0.2^\circ$.
12. The isolated crystalline form of claim 11, characterized by an X-ray powder diffraction pattern substantially similar to FIGURE 17.
13. An isolated crystalline form of compound 1, wherein the isolated crystalline form is Form 9, characterized by an X-ray powder diffraction pattern having peaks at 2Θ angles of 6.5, 19.6, 20.1, and $21.6^\circ \pm 0.2^\circ$.
14. The isolated crystalline form of claim 13, characterized by an X-ray powder diffraction pattern substantially similar to FIGURE 19.
15. An isolated crystalline form of compound 3, wherein the isolated crystalline form is Form 17, characterized by an X-ray powder diffraction pattern having peaks at 2Θ angles of 7.2, 13.6, 18.5, 19.3, 21.9, and $23.5^\circ \pm 0.2^\circ$.
16. The isolated crystalline form of claim 15, characterized by an X-ray powder diffraction pattern substantially similar to FIGURE 37.
17. An isolated crystalline form of compound 3, wherein the isolated crystalline form is Form 18, characterized by an X-ray powder diffraction pattern having peaks at 2Θ angles of 6.4, 8.4, 9.8, 17.8, and $19.7^\circ \pm 0.2^\circ$.
18. The isolated crystalline form of claim 17, characterized by an X-ray powder diffraction pattern substantially similar to FIGURE 38.
19. An isolated crystalline form of compound 3, wherein the isolated crystalline form is Form 19, characterized by an X-ray powder diffraction pattern having peaks at 2Θ angles of 8.1, 14.1, 16.4, 17.3, 20.5, and $24.1^\circ \pm 0.2^\circ$.
20. The isolated crystalline form of claim 19, characterized by an X-ray powder diffraction pattern substantially similar to FIGURE 39.
21. Use of a therapeutically effective dose of compound 3, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of an advanced hematologic malignancy selected from acute myelogenous leukemia (AML), myelodysplasia syndrome (MDS), chronic

myelomonocytic leukemia (CMML), myeloid sarcoma, multiple myeloma, and lymphoma, each characterized by the presence of a mutant allele of IDH2 .

22. Use of a therapeutically effective dose of compound 3, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carrier(s) in the manufacture of a medicament for the treatment of an advanced hematologic malignancy selected from acute myelogenous leukemia (AML), myelodysplasia syndrome (MDS), chronic myelomonocytic leukemia (CMML), myeloid sarcoma, multiple myeloma, and lymphoma, each characterized by the presence of a mutant allele of IDH2.

23. Use of a pharmaceutically acceptable salt of compound 3 in the manufacture of a medicament for the treatment of an advanced hematologic malignancy selected from acute myelogenous leukemia (AML), myelodysplasia syndrome (MDS), chronic myelomonocytic leukemia (CMML), myeloid sarcoma, multiple myeloma, and lymphoma, each characterized by the presence of a mutant allele of IDH2 wherein the dose is from 30 mg to 300 mg free-base equivalent strength, once daily or twice daily.

24. The use of claim 23, wherein the dose is 75 mg, once daily or twice daily.

25. The use of claim 23, wherein the dose is 100 mg, once daily or twice daily.

26. The use of claim 23, wherein the dose is 150 mg, once daily or twice daily.

27. The use of claim 23, wherein the dose is 200 mg, once daily or twice daily.

28. The use of claim 23, wherein the dosage is an oral dosage form.

29. The use of claim 28, wherein the oral dosage form is a tablet.

30. The use of claim 23, wherein the dose is administered once daily.

31. The use of claim 23, wherein the dose is administered twice daily.

32. The use of claim 23, wherein the pharmaceutically acceptable salt of compound 3 is administered orally as any combination of 5, 10, 50, or 200 mg free-base equivalent strength tablets, twice daily or once daily.

33. The use of any one of claims 21 to 23, wherein the pharmaceutically acceptable salt of compound 3 is compound 1.

34. The use of any one of claims 21 to 23, wherein the advanced hematologic malignancy is selected from acute myelogenous leukemia (AML), myelodysplasia syndrome (MDS), chronic myelomonocytic leukemia (CMML), and lymphoma (e.g., T-cell lymphoma).
35. The use of claim 34, wherein the advanced hematologic malignancy is acute myelogenous leukemia (AML).
36. The use of claim 35, wherein the advanced hematologic malignancy is myelodysplasia syndrome (MDS).
37. The use of claim 35, wherein the advanced hematologic malignancy is chronic myelomonocytic leukemia (CMML).
38. The use of claim 35, wherein the advanced hematologic malignancy is lymphoma.
39. Use of compound 1 in the manufacture of a medicament for the treatment of an advanced hematologic malignancy selected from acute myelogenous leukemia (AML), myelodysplasia syndrome (MDS), chronic myelomonocytic leukemia (CMML), myeloid sarcoma, multiple myeloma, and lymphoma, each characterized by the presence of a mutant allele of IDH2 wherein the dose is 30 mg free-base equivalent strength twice daily.
40. The use of claim 39, wherein the dose is from 75 mg to 200 mg free-base equivalent strength.
41. Use of compound 1 in the manufacture of a medicament for the treatment of an advanced hematologic malignancy selected from acute myelogenous leukemia (AML), myelodysplasia syndrome (MDS), chronic myelomonocytic leukemia (CMML), and lymphoma, each characterized by the presence of a mutant allele of IDH2 wherein the dose is from 75 mg to 250 mg free-base equivalent strength once daily.
42. The use of claim 39 or 41, wherein the dose is 75 mg.
43. The use of claim 39 or 41, wherein the dose is 100 mg.
44. The use of claim 39 or 41, wherein the dose is 150 mg.
45. The use of claim 39 or 41, wherein the dose is 200 mg.
46. The use of claim 39 or 41, wherein the advanced hematologic malignancy is selected from acute myelogenous leukemia (AML), myelodysplasia syndrome (MDS), chronic myelomonocytic leukemia (CMML), and lymphoma.

47. The use of claim 39 or 41, wherein the dosage is an oral dosage form.
48. The use of claim 47, wherein the oral dosage form is a tablet.