SOTORASIB FORMULATION

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Patent Application No. 63/184,941, filed May 6, 2021, and U.S. Provisional Patent Application No. 63/212,316, filed June 18, 2021, each of which is incorporated herein by reference in its entirety.

BACKGROUND

[0002] From its identification as one of the first human oncogenes in 1982 (Der *et al.*, 1982), KRAS (the Kirsten rat sarcoma viral oncogene homologue) has been the focus of extensive academic and industrial research, as a key node in the MAPK signal transduction pathway, as a transforming factor in a network of parallel effector pathways (*e.g.*, PI3K/AKT) (Vojtek *et al.*, 1998) and as a potential target for anti-cancer agents (Malumbres *et al.*, 2003). Despite progress in the development of inhibitors of upstream and downstream nodes in the MAPK pathway (*e.g.*, EGFR (Sridhar *et al.*, 2003), BRAF (Holderfield *et al.*, 2014), and MEK (Caunt *et al.*, 2015), the KRAS protein has historically proven resistant to direct inhibition.

[0003] KRAS is a G-protein that couples extracellular mitogenic signaling to intracellular, pro-proliferative responses. KRAS serves as an intracellular "on/off" switch. Mitogen stimulation induces the binding of GTP to KRAS, bringing about a conformational change which enables the interaction of KRAS with downstream effector proteins, leading to cellular proliferation. Normally, pro-proliferative signaling is regulated by the action of GTPase-activating proteins (GAPs), which return KRAS to its GDP-bound, non-proliferative state. Mutations in KRAS impair the regulated cycling of KRAS between these GDP- and GTP-bound states, leading to the accumulation of the GTP-bound active state and dysregulated cellular proliferation (Simanshu *et al.*, 2017).

[0004] Attempts to develop inhibitors of mutated KRAS proteins have historically been thwarted by the absence of druggable pockets on the surface of the protein (Cox *et al.*, 2014). Discoveries in the field that followed brought about significant new efforts in KRAS inhibitor research, which have recently culminated in the entry of KRAS inhibitors into human clinical trials. *See* https://clinicaltrials.gov/: *e.g.*, NCT03600883 & NCT04185883 (sotorasib, AMG 510) (last accessed April 23, 2021). These efforts have recently culminated in the submission of a new drug application to the United States Food and Drug Administration for sotorasib (Amgen Press Release, Dec. 16, 2020; https://wwwext.amgen.com/newsroom/press-releases/2020/12/amgen-submits-sotorasib-new-drug-application-to-u-s--fda-for-advanced-or-metastatic-non-small-cell-lung-cancer-with-kras-g12c-mutation, last accessed April 21, 2021).

[0005] Accordingly, there is a need for sotorasib formulations suitable for patients.

SUMMARY

[0006] Provided herein are formulations of sotorasib. In one example, described herein are formulations comprising sotorasib, a diluent in an amount of 40-95% (w/w), a disintegrant in an amount of 0.5-5% (w/w), and a lubricant in an amount of 0.25-5% (w/w). In another aspect, the diluent comprises a plastic diluent and optionally

a brittle diluent, and (a) provided that the brittle diluent is present, the formulation is characterized by (1) a first ratio by weight of the plastic diluent to the brittle diluent that is greater than or equal to 2.5:1; and (2) a second ratio by weight of the plastic diluent to sotorasib and the brittle diluent, taken together, is greater than or equal to 1.2:1 and less than the first ratio; or (b) provided that the brittle diluent is absent, the formulation is characterized by a ratio by weight of the plastic diluent to sotorasib that is greater than or equal to 1.2:1 and less than 3.5:1. In some examples, the formulations comprise sotorasib in an

amount of 1-20% (w/w). In some examples, the formulations comprise sotorasib in an amount of 20-45% (w/w). In some examples, the formulations comprise the diluent in an amount of 61-91% (w/w). In some examples, the formulations comprise the diluent in an amount of 51-77% (w/w).

[0007] In another example, the formulations described herein are for use as a medicament, or for treating cancer. In another example, the formulation described herein is for use in the manufacture of a medicament for treating cancer.

[0008] In another example, described herein is a method of treating cancer in a patient comprising administering to the patient a therapeutically effective amount of sotorasib provided as a formulation described herein, wherein the formulation provides the therapeutically effective amount in one or more dosage units. In another aspect, the formulation described herein is for use in the manufacture of a medicament for treating cancer, wherein the medicament provides a therapeutically effective amount of the formulation in one or more dosage units.

[0009] The terms “subject” and “patient” are used interchangeably herein.

BRIEF DESCRIPTION OF THE FIGURES

[0010] Figure 1 is a graph showing the dissolution profile (percent dissolved over time) of sotorasib provided in Formulation #1 (1% (w/w), 1 mg sotorasib).

[0011] Figure 2 is a graph showing the dissolution profile (percent dissolved over time) of sotorasib provided in Formulation #2 (37.5% (w/w), 240 mg sotorasib).

[0012] Figure 3 is a graph showing the dissolution profile (percent dissolved over time) of sotorasib provided in Formulation #3 (50% (w/w), 360 mg sotorasib).

[0013] Figure 4 is a graph showing the dissolution profile (percent dissolved over time) of sotorasib provided in Formulation #4 (30% (w/w), 180 mg sotorasib).

[0014] Figure 5 is a graph showing the dissolution profile (percent dissolved over time) of sotorasib provided in Formulation #5 (40% (w/w), 360 mg sotorasib).

[0015] Figure 6 is a graph showing the dissolution profile (percent dissolved over time) of sotorasib provided in Formulation #6 (20% (w/w), 30 mg sotorasib).

[0016] Figure 7 is a graph showing the dissolution profile (percent dissolved over time) of sotorasib provided in Formulation #7 (20% (w/w), 120 mg sotorasib).

[0017] Figure 8 is a graph showing the dissolution profile (percent dissolved over time) of sotorasib provided in Formulation #8 (20% (w/w), 120 mg sotorasib).

[0018] Figure 9A is a graph showing the dissolution profile (percent dissolved over time) of sotorasib provided in Formulation #9a (32% (w/w), 240 mg sotorasib).

[0019] Figure 9B is a graph showing the dissolution profile (percent dissolved over time) of sotorasib provided in Formulation #9b (32% (w/w), 240 mg sotorasib).

What is claimed is:

1. A formulation comprising

(a) sotorasib;

(b) a diluent in an amount of 40-95% (w/w);

(c) a disintegrant in an amount of 0.5-5% (w/w); and

(d) a lubricant in an amount of 0.25-5% (w/w);

wherein the diluent comprises a plastic diluent and optionally a brittle diluent, and

(a) provided that the brittle diluent is present, the formulation is characterized by

(1) a first ratio by weight of the plastic diluent to the brittle diluent that is greater than or equal to 2.5:1; and

(2) a second ratio by weight of the plastic diluent to sotorasib and the brittle diluent, taken together, is greater than or equal to 1.2:1 and less than the first ratio; or

(b) provided that the brittle diluent is absent, the formulation is characterized by a ratio by weight of the plastic diluent to sotorasib that is greater than or equal to 1.2:1 and less than 3.5:1.

2. The formulation of claim 1, wherein the diluent comprises a plastic diluent and a brittle diluent, and wherein the first ratio is greater than or equal to 3:1 and the second ratio is greater than or equal to 1.4:1 and less than 3:1.

3. The formulation of claim 1, wherein the diluent comprises a plastic diluent and no brittle diluent, and wherein the ratio by weight of the plastic diluent to sotorasib that is greater than or equal to 1.4:1 and less than 3:1.

4. The formulation of claim 1, comprising sotorasib in an amount of 1-20% (w/w).

5. The formulation of claim 4, comprising sotorasib in an amount of 20% (w/w).

6. The formulation of claim 4 or claim 5, wherein the diluent comprises a plastic diluent and a brittle diluent, wherein the ratio by weight of the plastic diluent to the brittle diluent ranges from 2.5:1 to 3.5:1.

7. The formulation of claim 4 or claim 5, wherein the diluent comprises a plastic diluent and a brittle diluent, wherein the ratio by weight of the plastic diluent to the brittle diluent is 3:1.

8. The formulation of claim 1, comprising sotorasib in an amount of 20-45% (w/w).

9. The formulation of claim 8, comprising sotorasib in an amount of 32% (w/w).

10. The formulation of claim 8 or claim 9, wherein the ratio by weight of the plastic diluent to sotorasib and the brittle diluent, if present, taken together, ranges from 1.2:1 to 1.7:1.

11. The formulation of claim 8 or claim 9, wherein the ratio by weight of the plastic diluent to sotorasib and the brittle diluent, if present, taken together, ranges from 1.4:1 to 1.5:1.

12. The formulation of any one of claims 1 to 11, wherein the diluent comprises one or more of lactose, dibasic calcium phosphate (DCP), mannitol, sorbitol, xylitol, calcium carbonate, magnesium carbonate, tribasic calcium phosphate, trehalose, microcrystalline cellulose, and starch.

13. The formulation of any one of claims 1 to 11, wherein the diluent comprises one or more of lactose, dibasic calcium phosphate (DCP), mannitol, microcrystalline cellulose, and starch.

14. The formulation of any one of claims 1 to 11, wherein the diluent comprises one or more of lactose and microcrystalline cellulose.

15. The formulation of any one of claims 12 to 14, wherein the lactose is lactose monohydrate.

16. The formulation of any one of claims 1 to 11, wherein the plastic diluent comprises one or more of microcrystalline cellulose and starch.

17. The formulation of claim 16, wherein the plastic diluent is microcrystalline cellulose.

18. The formulation of any one of claims 1 to 11, wherein the brittle diluent comprises one or more of lactose, dibasic calcium phosphate (DCP), mannitol, sorbitol, xylitol, calcium carbonate, magnesium carbonate, tribasic calcium phosphate, and trehalose.

19. The formulation of claim 18, wherein the brittle diluent is lactose.

20. The formulation of claim 19, wherein the lactose is lactose monohydrate.

21. The formulation of any one of claims 1 to 11, wherein the brittle excipient has an average Heckel yield pressure of greater than 125 MPa.

22. The formulation of any one of claims 1 to 11, where the plastic excipient has an average Heckel yield pressure of less than 125 MPa.

23. The formulation of any one of claims 1 to 22, comprising a disintegrant in an amount of 2-4% (w/w).

24. The formulation of any one of claims 1 to 22, comprising a disintegrant in an amount of 3% (w/w).

25. The formulation of any one of claims 1, 23, and 24, wherein the disintegrant comprises one or more of cross-linked sodium carboxy methyl cellulose (croscarmellose sodium), cross-linked polyvinylpyrrolidone (crospovidone), sodium starch glycolate, pregelatinized starch, calcium carboxymethyl cellulose, low substituted hydroxypropyl cellulose, and magnesium aluminum silicate.

26. The formulation of claim 25, wherein the disintegrant comprises one or more of croscarmellose sodium and sodium starch glycolate.

27. The formulation of claim 25, wherein the disintegrant is croscarmellose sodium.

28. The formulation of any one of claims 1 to 27, comprising a lubricant in an amount of 0.5-3% (w/w).

29. The formulation of any one of claims 1 to 27, comprising a lubricant in an amount of 0.5-1.5% (w/w).

30. The formulation of any one of claims 1 to 27, comprising a lubricant in an amount of 1% (w/w).

31. The formulation of any one of claims 28 to 30, wherein the lubricant comprises one or more of magnesium stearate, calcium stearate, oleic acid, caprylic acid, stearic acid, magnesium isovalerate, calcium laurate, magnesium palmitate, behenic acid, glyceryl behenate, glyceryl stearate, sodium stearyl fumarate, potassium stearyl fumarate, zinc stearate, sodium oleate, sodium stearate, sodium benzoate, sodium acetate, sodium chloride, talc, polyethylene glycol, and hydrogenated vegetable oil.

32. The formulation of claim 31, wherein the lubricant is magnesium stearate.

33. The formulation of any one of claims 1 to 32, comprising sotorasib in an amount of 120 mg.

34. The formulation of any one of claims 1 to 32, comprising sotorasib in an amount of 240 mg.

35. The formulation of any one of claims 1 to 32, comprising sotorasib in an amount of 320 mg.

36. The formulation of any one of claims 1 to 8, 12 to 23, 25 to 29, 31, and 32, comprising sotorasib in an amount of 16-24% (w/w), a diluent in an amount of 61-91% (w/w), a disintegrant in an amount of 2.4-3.6% (w/w), and a lubricant in an amount of 0.8-1.2% (w/w).

37. The formulation of any one of claims 1 to 8 and 12 to 32, comprising sotorasib in an amount of 20% (w/w), a diluent in an amount of 76% (w/w), a disintegrant in an amount of 3% (w/w), and a lubricant in an amount of 1% (w/w).

38. The formulation of claim 36 or claim 37, comprising sotorasib in an amount of 120 mg.

39. The formulation of claim 1, comprising sotorasib in an amount of 20% (w/w), microcrystalline cellulose in an amount of 57% (w/w), lactose monohydrate in an amount of 19 % (w/w), croscarmellose sodium an amount of 3% (w/w), and magnesium stearate in an amount of 1% (w/w).

40. The formulation of claim 1, comprising sotorasib in an amount of 120 mg, microcrystalline cellulose in an amount of 342 mg, lactose monohydrate in an amount of 114 mg, croscarmellose sodium an amount of 18 mg, and magnesium stearate in an amount of 6 mg.

41. The formulation of any one of claims 1 to 8, 12 to 23, 25 to 29, 31, and 32, comprising sotorasib in an amount of 26-38% (w/w), a diluent in an amount of 51-77% (w/w), a disintegrant in an amount of 2.4-3.6% (w/w), and a lubricant in an amount of 0.8-1.2% (w/w).

42. The formulation of any one of claims 1 to 8 and 12 to 32, comprising sotorasib in an amount of 32% (w/w), a diluent in an amount of 64% (w/w), a disintegrant in an amount of 3% (w/w), and a lubricant in an amount of 1% (w/w).

43. The formulation of claim 41 or claim 42, comprising sotorasib in an amount of 240 mg.

44. The formulation of claim 41 or claim 42, comprising sotorasib in an amount of 320 mg.

45. The formulation of claim 1, comprising sotorasib in an amount of 32% (w/w), microcrystalline cellulose in an amount of 57% (w/w), lactose monohydrate in an amount of 7 % (w/w), croscarmellose sodium an amount of 3% (w/w), and magnesium stearate in an amount of 1% (w/w).

46. The formulation of claim 1, comprising sotorasib in an amount of 240 mg, microcrystalline cellulose in an amount of 427.5 mg, lactose monohydrate in an amount of 52.5 mg, croscarmellose sodium an amount of 22.5 mg, and magnesium stearate in an amount of 7.5 mg.

47. The formulation of claim 1, comprising sotorasib in an amount of 320 mg, microcrystalline cellulose in an amount of 570 mg, lactose monohydrate in an amount of 70 mg, croscarmellose sodium in an amount of 30 mg, and magnesium stearate in an amount of 10 mg.

48. The formulation of any one of claims 1 to 47, wherein the formulation is a solid dosage form.

49. The formulation of claim 48, wherein the solid dosage form is for oral administration.

50. The formulation of claim 48 or claim 49, wherein the solid dosage form is a tablet.

51. The formulation of claim 50, wherein the tablet is coated with a coating composition.

52. The formulation of claim 51, wherein the coating composition comprises polyvinyl alcohol.

53. The formulation of claim 52, wherein the coating composition further comprises one or more of titanium dioxide, polyethylene glycol, talc, and a coloring agent.

54. The formulation of any one of claims 1 to 53, wherein at least 50% of the sotorasib in the formulation is released within 30 minutes as measured by a dissolution test using a USP <711> apparatus 2 with 75 rpm paddle speed, at 37 ºC in a dissolution medium of 900 ml of water at pH 6.7 comprising 50 mM sodium phosphate and a surfactant to maintain sink conditions.

55. The formulation of claim 54, wherein at least 80% of the sotorasib in the formulation is released within 30 minutes.

56. The formulation of claim 54, wherein at least 85% of the sotorasib in the formulation is released within 15 minutes.

57. The formulation of any one of claims 54 to 56, wherein the surfactant is 0.2-0.6% (w/v) sodium dodecyl sulfate (SDS).

58. A formulation of any one of claims 1 to 57 for use as a medicament.

59. Use of a formulation of any one of claims 1 to 57 in the manufacture of a medicament for treating cancer, wherein the medicament provides a therapeutically effective amount of the formulation in one or more dosage units.

60. Use of a formulation of any one of claims 1 to 57 in the manufacture of a medicament for treating cancer, wherein one or more cells of the cancer express a KRAS G12C mutant protein.

61. The use of claim 59 or claim 60, wherein the cancer is non-small cell lung cancer, small bowel cancer, appendiceal cancer, colorectal cancer, cancer of unknown primary, endometrial cancer, mixed cancer types, pancreatic cancer, hepatobiliary cancer, small cell lung cancer, cervical cancer, germ cell cancer, ovarian cancer, gastrointestinal neuroendocrine cancer, bladder cancer, myelodysplastic/myeloproliferative neoplasms, head

and neck cancer, esophagogastric cancer, soft tissue sarcoma, mesothelioma, thyroid cancer, leukemia, or melanoma.

62. The use of claim 59 or claim 60, wherein the cancer is non-small cell lung cancer, colorectal cancer, pancreatic cancer, appendiceal cancer, endometrial cancer, cancer of unknown primary, ampullary cancer, gastric cancer, small bowel cancer, sinonasal cancer, bile duct cancer, or melanoma.

63. The use of claim 62, wherein the cancer is non-small cell lung cancer.

64. The use of claim 62, wherein the cancer is colorectal cancer.

65. The use of claim 62, wherein the cancer is pancreatic cancer.

66. The use of any one of claims 59 to 65, wherein the medicament is for dispersing the therapeutically effective amount of the formulation provided as one or more dosage units in water by stirring before administration to the patient.

67. The use of claim 66, wherein the water is non-carbonated.

68. The use of claim 66 or claim 67, wherein the water has room-temperature.

69. The use of any one of claims 66 to 68, wherein the water has a volume of 120 mL.

70. The use of any one of claims 66 to 69, wherein the therapeutically effective amount is for dispersion in water immediately or within 2 hours before administration to the patient.

71. The use of any one of claims 66 to 70, wherein the patient has difficulty swallowing solids.