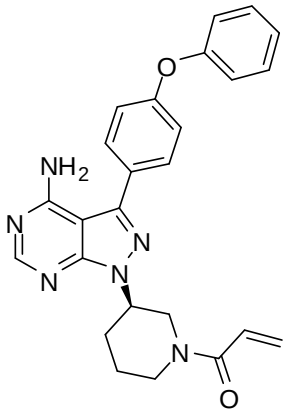
Claims

WHAT IS CLAIMED IS:

1. A stable pharmaceutical formulation comprising:

(i) ibrutinib, or a pharmaceutically acceptable salt/solvate thereof, wherein ibrutinib is a compound with the structure of Compound 1,



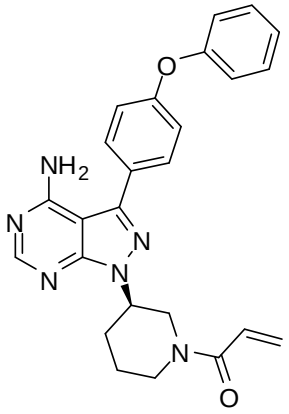
Compound 1,

and a suspending agent, optionally in the presence of a pharmaceutically acceptable carrier (e.g., aqueous carrier); and

(ii) one or more preservatives, wherein at least one preservative is benzyl alcohol; and, optionally, one or more other pharmaceutically acceptable excipients.

2. A pharmaceutical formulation as claimed in claim 1, in the form of a suspension comprising:

(i) ibrutinib, or a pharmaceutically acceptable salt/solvate thereof, wherein ibrutinib is a compound with the structure of Compound 1,



Compound 1,

suspended in a pharmaceutically acceptable carrier (e.g., aqueous carrier); and

(ii) at least one preservative that is benzyl alcohol;

and, optionally, one or more other pharmaceutically acceptable excipients.

3. A pharmaceutical formulation as claimed in claim 1 or claim 2, wherein the formulation also contains a preservative selected from one or more of antimicrobials, anti-oxidants, radical scavengers, oxygen scavengers and/or chelating agents, for instance selected from the group consisting of benzoic acid, parabens (methyl or ethyl paraben), butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), chlorbutol, a gallate, a hydroxybenzoate, EDTA, phenol, chlorocresol, metacresol, benzethonium chloride, myristyl-γ-piccolinium chloride, phenylmercuric acetate, thimerosal, sorbic acid, propionic acid, propylene glycol, Vitamin E, ascorbyl palmitate, sodium ascorbate, sodium sulfite, L-cysteine, acetylcysteine, methionine, thioglycerol, acetone sodium bisulfite, isoascorbic acid, hydroxypropyl cyclodextrin, sodium citrate, sodium EDTA, malic acid, acetic acid, and mixtures thereof.

4. A pharmaceutical formulation as claimed in claim 1, claim 2 or (where applicable) claim 3, wherein the preservative comprises greater than 50% (by weight) benzyl alcohol, for instance greater than 90% benzyl alcohol, e.g., the preservative consists essentially of benzyl alcohol.

5. A pharmaceutical formulation as claimed in any of the preceding claims, wherein pharmaceutical formulation comprises between 0.1% and 10% w/v, or, between 1 mg/ml and 50 mg/ml preservative.

6. A pharmaceutical formulation as claimed in claim 5, wherein the preservative is between 0.5% and 2% w/v, or, between 5 mg/ml and 20 mg/ml.

7. A pharmaceutical formulation as claimed in any of the preceding claims, wherein the pharmaceutical formulation comprises a suspending agent selected from alginates, a cellulose ether, methyl cellulose, hydroxyethylcellulose, carboxymethylcellulose, sodium carboxymethylcellulose, microcrystalline cellulose, acacia, tragacanth, xanthan gum, bentonite, carbomer, carrageenan, powdered cellulose and gelatin.

8. A pharmaceutical formulation as claimed in claim 7, wherein the suspending agent is a cellulose ether, such as microcrystalline cellulose (e.g., silicified microcrystalline cellulose SMCC).

9. A pharmaceutical formulation as claimed in any of the preceding claims, wherein the formulation contains a suspending agent in an amount that is between 0.1% and 10% w/v, or, between 1 mg/ml and 50 mg/ml.

10. A pharmaceutical formulation as claimed in claim 9, wherein the amount of the suspending agent is between 0.5% and 2% w/v, or, between 5 mg/ml and 20 mg/ml.

11. A pharmaceutical formulation as claimed in any of the preceding claims, wherein the pharmaceutical formulation further comprises one or more wetting agent (e.g., a cellulose ether such as hydroxypropylcellulose or hydroxypropylmethylcellulose), one or more buffering agent (e.g., containing citric acid.H_2O and/or sodium hydrogen phosphate), one or more pH adjusting agent (e.g., sodium hydroxide and/or hydrochloric acid) and/or (e.g., optionally) a sweetener (e.g., sucralose).

12. A pharmaceutical formulation as claimed in any of the preceding claims, wherein the pharmaceutical formulation, based on the pharmaceutical carrier being 1 ml of purified water, comprises:
ibrutinib 20-200 mg/ml; benzyl alcohol preservative 2.5-25 mg/ml; suspending agent 2-24 mg/ml; optionally, wetting agent e.g., 0.5-10 mg/ml; optionally, buffers e.g., 0.5-10 mg/ml; optionally, sweetener e.g., 0.1-5 mg/ml; and, optionally, pH adjusting agents (q.s.).

13. A pharmaceutical formulation as claimed in Claim 12, wherein the pharmaceutical formulation, based on the pharmaceutical carrier being 1 ml of purified water, comprises:
ibrutinib 60-80 mg/ml; benzyl alcohol preservative 8-12 mg/ml; suspending agent 10-14 mg/ml; optionally, wetting agent e.g., 2-3 mg/ml; optionally, buffers e.g., 1.5-2.5 mg/ml; optionally, sweetener e.g., 0.5-1.5 mg/ml; and, optionally, pH adjusting agents (q.s.).

14. A pharmaceutical formulation as claimed in any of claims 1-11, wherein the pharmaceutical formulation comprises the following relative quantities (w/w) of the components (in relation to each other) and compared to 70 mg of ibrutinib:
benzyl alcohol preservative 5-15 mg; suspending agent 6-18 mg; optionally, wetting agent e.g., 1-5 mg; optionally, buffers e.g., 1-3 mg; optionally, sweetener e.g., 0.2-2

mg; and optionally, pH adjusting agents (q.s.), and wherein a pharmaceutically acceptable carrier (e.g., purified water) is present in a predetermined amount.

15. A pharmaceutical formulation as claimed in claim 14, wherein the pharmaceutical formulation comprises:
benzyl alcohol preservative 8-12 mg; mixture of microcrystalline cellulose and carboxymethylcellulose sodium 10-14 mg; optionally, hydroxypropylmethylcellulose (HPMC) 2-3 mg; optionally, citric acid.H_2O and/or phosphate such as sodium hydrogen phosphate 1.5-2.5 mg; optionally, sucralose 0.5-1.5 mg; and, optionally, NaOH and/or HCl (q.s.) in order to adjust pH, and wherein a pharmaceutically acceptable carrier (e.g., purified water) is present between 1 ml per 10 mg of ibrutinib and between 1 ml per 210 mg ibrutinib, such as 1 ml per 70 mg ibrutinib.

16. A pharmaceutical formulation as claimed in any one of claims 1-15, wherein the ibrutinib is not in the form of a salt or solvate, i.e. it is in its free form.

17. The pharmaceutical formulation of any one of claims 1-16 for use in treating a disease.

18. Use of the pharmaceutical formulation of any one of claims 1-16 in the manufacture of a medicament for treating a B-cell proliferative disorder.

19. The use of claim 18, wherein the B-cell proliferative disorder is diffuse large B cell lymphoma, follicular lymphoma or chronic lymphocytic leukemia.

20. Use of the pharmaceutical formulation of any one of claims 1-16 in the manufacture of a medicament for treating a disease, wherein the disease is a B cell malignancy.

21. The use of claim 20, wherein the disease is a B cell malignancy selected from chronic lymphocytic leukemia (CLL)/ small lymphocytic lymphoma (SLL), mantle cell lymphoma (MCL), diffuse large B Cell lymphoma (DLBCL), and multiple myeloma.

22. Use of the pharmaceutical formulation of any one of claims 1-16 in the manufacture of a medicament for treating a disease, wherein the disease is a lymphoma or leukemia.

23. The use of claim 22, wherein the disease is diffuse large B cell lymphoma, follicular lymphoma, chronic lymphocytic lymphoma, chronic lymphocytic leukemia, B-cell prolymphocytic leukemia, lymphoplasmacytic lymphoma/Waldenström macroglobulinemia, splenic marginal zone lymphoma, plasma cell myeloma, plasmacytoma, extranodal marginal zone B cell lymphoma, nodal marginal zone B cell lymphoma, mantle cell lymphoma, mediastinal (thymic) large B cell lymphoma, intravascular large B cell lymphoma, primary effusion lymphoma, burkitt lymphoma/leukemia, or lymphomatoid granulomatosis.

24. A process for preparing the pharmaceutical formulation of any one of claims 1-16, the process comprising bringing the components into association with each other.