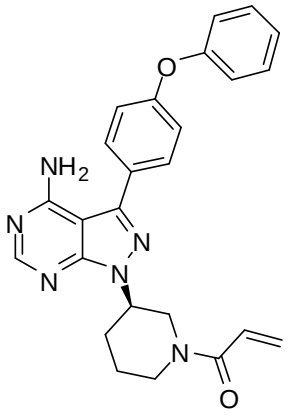
SUMMARY

There is now provided a pharmaceutical formulation (intended to form a suspension) comprising:

(i) ibrutinib, 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; and

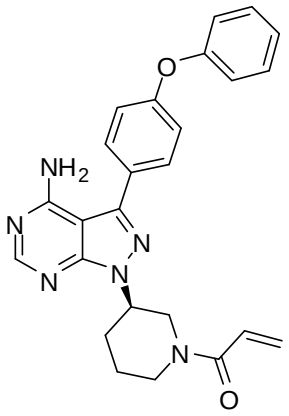
(ii) at least one preservative that is benzyl alcohol;

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

which formulation may be referred to herein as a “formulation of the invention” or “formulation of the disclosure”.

In one aspect, there is provided 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,

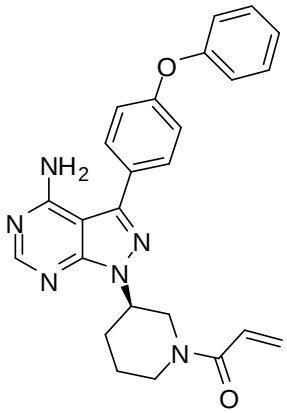


Compound 1,

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.

The formulation of the disclosure may be reconstitutable, i.e. it may not contain a pharmaceutically acceptable carrier (e.g., purified water or another suitable carrier as defined herein), or it may be a suspension product already containing the carrier (e.g., purified water or another suitable carrier as defined herein). Hence, in the latter case, there is provided a pharmaceutical formulation in the form of a suspension comprising: (i) ibrutinib, wherein ibrutinib is a compound with the structure of Compound 1,



Compound 1,

suspended in a pharmaceutically acceptable carrier; and
(ii) at least one preservative that is benzyl alcohol;
and, optionally, one or more other pharmaceutically acceptable excipients.

The disclosure thus concerns a variety of formulations that are suspensions containing ibrutinib, or a pharmaceutically acceptable salt or solvate thereof, and wherein benzyl alcohol is the main preservative present, and the formulations may further contain one or more further pharmaceutically acceptable excipients. The disclosure further concerns methods for preparing such pharmaceutical formulations. The disclosure yet further concerns the use of such formulations as a pharmaceutical, for instance in the treatment of a disease as described hereinafter. The disclosure also concerns a method of treating a disease in a patient in need of such treatment, comprising administering to the patient a therapeutically effective amount of such a pharmaceutical formulation.

In another aspect, there is provided the pharmaceutical formulation as defined herein for use in treating a disease.

In another aspect, there is provided use of the pharmaceutical formulation as defined herein in the manufacture of a medicament for treating a B-cell proliferative disorder.

In another aspect, there is provided use of the pharmaceutical formulation as defined herein in the manufacture of a medicament for treating a disease, wherein the disease is a B cell malignancy.

In another aspect, there is provided a process for preparing the pharmaceutical formulation as defined herein, the process comprising bringing the components into association with each other.

It is indicated herein that benzyl alcohol is the main preservative present in the formulations of the invention, which is also understood by the skilled person to encompass suitable equivalents of benzyl alcohol that achieve the same effect, that is have the same, or similar, efficacy in terms of preservation, has the same, or similar, stability profile and/or does not form co-crystals with the active ingredient (ibrutinib). All of the foregoing may be tested in the tests used in the experimental as described hereinafter. For instance: sufficient preservation may be tested as described in the PETs (preservation efficacy tests) described herein resulting in e.g., a greater than 4 log reduction after 28 days when the following organisms are employed: *A. brasiliensis*, *C.*

albicans, *P. aeruginosa*, *S. aureus* and/or *E.coli* (e.g., with the initial concentrations of the organism as indicated in the experimental hereinafter); stability may be tested as described in the tests in the experimental (1 month, 2 month and 6 month stability tests under certain conditions); and the formation of co-crystals may also be tested by observation under the conditions also described in the experimental described hereinafter.

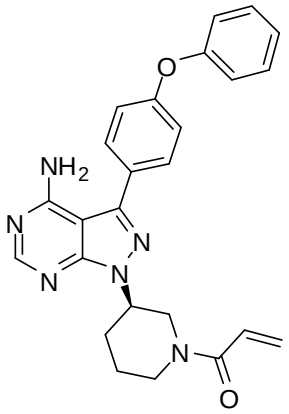
The present invention may be understood more readily by reference to the following description taken in connection with the accompanying Examples, all of which form a part of this disclosure. It is to be understood that this invention is not limited to the specific products, methods, conditions or parameters described and/or shown herein, and that the terminology used herein is for the purpose of describing particular embodiments by way of example only and is not intended to be limiting of any claimed invention. Similarly, unless otherwise stated, any description as to a possible mechanism or mode of action or reason for improvement is meant to be illustrative

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,



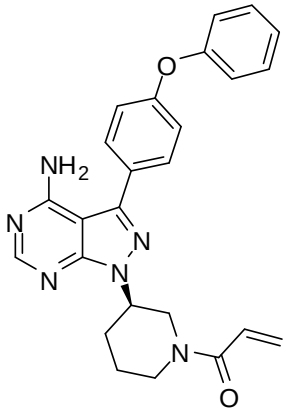
Compound 1,

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 about 0.1% and 10% w/v, or, between about 1 mg/ml and 50 mg/ml preservative.

6. A pharmaceutical formulation as claimed in claim 5, wherein the preservative is between about 0.5% and 2% w/v, or, between about 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 about 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 about 0.5% and 2% w/v, or, between about 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 (e.g., Avicel®) 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 in a predetermined amount as described herein (e.g., between 1 ml per 10 mg of ibrutinib and between 1 ml per 210 mg ibrutinib, such as about 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. The use of claim 21, wherein the disease is a lymphoma or leukemia.

23. The use of claim 21, 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.