PHARMACEUTICAL FORMULATIONS OF A BRUTON'S TYROSINE KINASE INHIBITOR

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This application claims the benefit of U.S. Provisional Application No. 62/127,717, filed March 3, 2015, and U.S. Provisional Application No. 62/193,518, filed July 16, 2015, which are incorporated herein by reference in their entirety.

FIELD OF THE INVENTION

[0002] Described herein is the Bruton's tyrosine kinase (Btk) inhibitor 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one, including pharmaceutical compositions, solvates and pharmaceutically acceptable salts thereof, as well as pharmaceutical formulations that include the Btk inhibitor and methods of using the Btk inhibitor compositions or formulations in the treatment of diseases or conditions that would benefit from inhibition of Btk activity.

BACKGROUND OF THE INVENTION

[0003] Bruton's tyrosine kinase (Btk), a member of the Tec family of non-receptor tyrosine kinases, is a key signaling enzyme expressed in all hematopoietic cells types except T lymphocytes and natural killer cells. Btk plays an essential role in the B-cell signaling pathway linking cell surface B-cell receptor (BCR) stimulation to downstream intracellular responses.

[0004] Btk is a key regulator of B-cell development, activation, signaling, and survival. In addition, Btk plays a role in a number of other hematopoietic cell signaling pathways, e.g., Toll like receptor (TLR) and cytokine receptor–mediated TNF-α production in macrophages, IgE receptor (FcepsilonRI) signaling in Mast cells, inhibition of Fas/APO-1 apoptotic signaling in B-lineage lymphoid cells, and collagen-stimulated platelet aggregation.

[0005] 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one is also known by its IUPAC name as 1-{(3*R*)-3-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]piperidin-1-yl}prop-2-en-1-one or 2-Propen-1-one, 1-[(3*R*)-3-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-piperidinyl-, and has been given the USAN name, ibrutinib. The various names given for ibrutinib are used interchangeably herein.

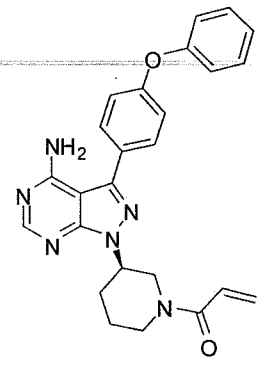
SUMMARY

[0006] Described herein is the Btk inhibitor 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one, including pharmaceutically acceptable compositions, formulations, and methods of uses thereof. Also described are pharmaceutically acceptable compositions and formulations of the Btk inhibitor, 1-((R)-3-(4-

amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one, used in the manufacture of medicaments for the treatment of diseases or conditions that are associated with Btk activity. 1-((R)-3-(4-Amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one is an irreversible Btk inhibitor. Further described are pharmaceutical compositions and formulations of the Btk inhibitor, 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one, and methods of using the Btk inhibitor in the treatment of diseases or conditions (including diseases or conditions wherein irreversible inhibition of Btk provides therapeutic benefit to a mammal having the disease or condition).

[0007] Also described herein is a process for preparing a pharmaceutical composition of 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one by a wet granulation method. Further described are pharmaceutical formulations that include a pharmaceutical composition of 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one prepared by a wet granulation method.

[0008] Described herein is a pharmaceutical composition comprising ibrutinib, wherein ibrutinib is a compound with the structure of Compound 1,



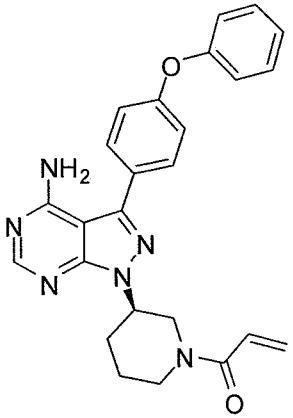
Compound 1;

and wherein the pharmaceutical composition comprises at least 50% w/w of ibrutinib.

[0009] In another embodiment is a pharmaceutical composition comprising ibrutinib, wherein the pharmaceutical composition comprises about 50% w/w to about 90% w/w of ibrutinib. In another embodiment is a pharmaceutical composition comprising ibrutinib, wherein the pharmaceutical composition comprises about 50% w/w to about 80% w/w of ibrutinib. In another embodiment is a pharmaceutical composition comprising ibrutinib, wherein the pharmaceutical composition comprises about 60% w/w to about 80% w/w of ibrutinib. In another embodiment is a pharmaceutical composition comprising ibrutinib, wherein the pharmaceutical composition comprises about 60% w/w to about 75% w/w of ibrutinib. In another embodiment is a pharmaceutical composition comprising at least 50% w/w of ibrutinib, wherein the pharmaceutical composition comprises intragranular and extragranular

ingredients. In another embodiment is a pharmaceutical composition comprising at least 50% w/w of ibrutinib, wherein the pharmaceutical composition is prepared using a wet granulation method. In another embodiment is a pharmaceutical composition comprising at least 50% w/w of ibrutinib, further comprising at least one pharmaceutically acceptable excipient.

[0009a] In one aspect is a high-load solid tablet formulation comprising ibrutinib and one or more pharmaceutically acceptable excipients, wherein ibrutinib is a compound with the structure of Compound 1,



Compound 1;

and wherein the high-load solid tablet formulation comprises at least 50% w/w of ibrutinib, and the excipients comprise

one or more diluents selected from the group consisting of lactose, sucrose, dextrose, dextrates, maltodextrin, mannitol, xylitol, sorbitol, cyclodextrins, calcium phosphate, calcium sulfate, starches, modified starches, cellulose, microcrystalline cellulose, microcellulose, and talc;

one or more disintegrating agents selected from the group consisting of natural starch, a pregelatinized starch, a sodium starch, methylcrystalline cellulose, methylcellulose, croscarmellose, croscarmellose sodium, cross-linked sodium carboxymethylcellulose, cross-linked carboxymethylcellulose, cross-linked croscarmellose, cross-linked starch, cross-linked polymer, cross-linked polyvinylpyrrolidone, sodium alginate, a clay, and a gum;

one or more binders selected from the group consisting of hydroxypropyl cellulose or polyvinylpyrrolidone;

sodium lauryl sulfate;

silica; and

magnesium stearate.

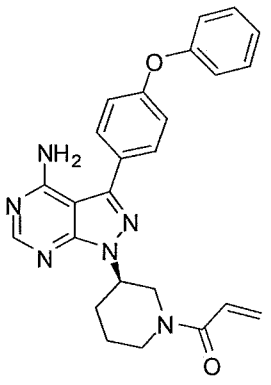
[0010] In another embodiment is a high-load solid tablet formulation comprising a pharmaceutical composition comprising at least 50% w/w of ibrutinib, about 50% w/w to about 90% w/w of ibrutinib, about 50% w/w to about 80% w/w of ibrutinib, about 60% w/w to about 80% w/w of ibrutinib, or about 60% w/w to about 75% w/w of ibrutinib, and one or more pharmaceutically acceptable excipients. In another embodiment is a high-load solid tablet formulation comprising a pharmaceutical composition comprising at least 50% w/w of ibrutinib, about 50% w/w to about 90% w/w of ibrutinib, about 50% w/w to about 80% w/w of ibrutinib, about 60% w/w to about 80% w/w of ibrutinib, or about 60% w/w to about 75% w/w of ibrutinib, and one or more pharmaceutically acceptable excipients wherein the one or more excipients are present in an amount from about 10% w/w to about 50% w/w.

[0011] In another embodiment is a high-load solid tablet formulation comprising at least 50% w/w of ibrutinib, about 50% w/w to about 90% w/w of ibrutinib, about 50% w/w to about 80% w/w of ibrutinib, about 60% w/w to about 80% w/w of ibrutinib, or about 60% w/w to about 75% w/w of ibrutinib, and one or more pharmaceutically acceptable excipients wherein the one or more excipients are selected from the group consisting of diluents, binders, disintegrating agents, lubricants, glidants, and surfactants. In some embodiments, at least one excipient is a diluent. In some embodiments, the diluent is selected from the group consisting of lactose, sucrose, dextrose, dextrates, maltodextrin, mannitol, xylitol, sorbitol, cyclodextrins, calcium phosphate, calcium sulfate, starches, modified starches, cellulose, microcrystalline cellulose, microcellulose, and talc. In some embodiments, the diluent is cellulose. In some embodiments, the diluent is the diluent is lactose; and lactose is present in an amount from about 5% w/w to about 20% w/w, about 8% w/w to about 20% w/w, or about 8% w/w to about 15% w/w. In some embodiments, the diluent is lactose; and lactose is present in an amount of about 8.5% w/w or about 14% w/w. In some embodiments, the diluent is microcrystalline cellulose. In some embodiments, the diluent is microcrystalline cellulose and the microcrystalline cellulose is present in an amount from about 1% w/w to about 20% w/w, about 1% w/w to about 10% w/w, about 1% w/w to about 5% w/w, 1% w/w to about 2% w/w, about 5% w/w to about 20% w/w, about 8% w/w to about 20% w/w, or about 8% w/w to about 15% w/w. In some embodiments, the diluent is microcrystalline cellulose and the microcrystalline cellulose is present in an amount from about 1% w/w to about 6% w/w or about 8.5% w/w or about 14% w/w. In some embodiments, the diluent comprises lactose and microcrystalline cellulose. In

lung, pancreas, kidney, bone marrow, heart, skin, intestine, or joints. In some embodiments, the fibrosis is of the liver. In some embodiments, the fibrosis is of the lung. In some embodiments, the fibrosis is of the pancreas. In some embodiments, the patient has cirrhosis, chronic pancreatitis, or cystic fibrosis.

[0039] Described herein is a process for preparing a pharmaceutical composition or tablet formulation comprising ibrutinib as described herein, wherein the process comprises a wet granulation method.

[0040] Described herein is a high-load solid tablet formulation comprising ibrutinib, wherein ibrutinib is a compound with the structure of Compound 1,



Compound 1;

and the tablet comprises about 560 mg of ibrutinib.

[0040a] In another aspect is a solid tablet formulation comprising ibrutinib, intra granular excipients and extragranular excipients; wherein the intragranular excipients comprise:

lactose in an amount from about 10% w/w to about 20% w/w;

polyvinylpyrrolidone in an amount from about 0% w/w to about 5% w/w;
croscarmellose sodium in an amount from about 1% w/w to about 10% w/w; and

sodium lauryl sulfate in an amount from about 0% w/w to about 2% w/w; and

the extragranular excipients comprise:

croscarmellose sodium in an amount from about 0% w/w to about 5% w/w;

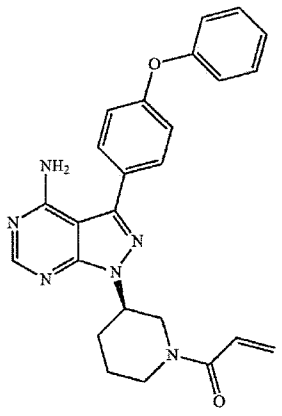
sodium lauryl sulfate in an amount from about 0% w/w to about 10% w/w;

microcrystalline cellulose in an amount from about 1% w/w to about 10% w/w;

colloidal silicon dioxide in an amount from about 0.4% wfw to about 0.8% w/w; and

magnesium stearate in an amount from about 0.4% w/w to about 0.8% w/w;

wherein ibrutinib is a compound with the structure of Compound 1,



Compound 1

and is present at about 60% w/w to about 80% w/w and in an amount of about 70 mg to about 840 mg.

[0040b] In another aspect is a solid tablet formulation comprising

about 50% w/w to about 90% w/w of ibrutinib;

about 10% w/w to about 15% w/w lactose;

about 1% w/w to about 6% w/w microcrystalline cellulose;

about 1% w/w to about 5% w/w polyvinylpyrrolidone;

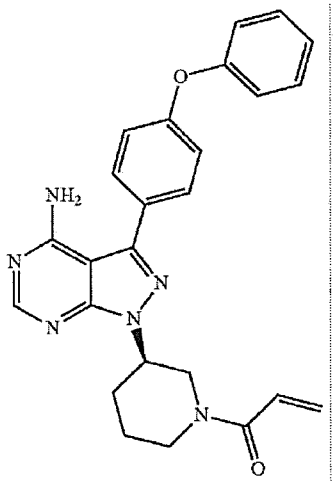
about 1% w/w to about 10% w/w croscarmellose sodium;

about 0.5% w/w to about 5% w/w sodium lauryl sulfate;

about 0.1% w/w to about 1.5% w/w silica;

about 0.01% w/w to about 2% w/w magnesium stearate;

wherein ibrutinib is a compound with the structure of Compound 1.



Compound 1

and is in an amount of about 70 mg to about 840 mg.

[0040c] In another aspect is a solid tablet formulation consisting essentially of

about 50% w/w to about 90% w/w of ibrutinib;

about 10% w/w to about 15% w/w lactose;

about 1% w/w to about 6% w/w microcrystalline cellulose;

about 1% w/w to about 5% w/w polyvinylpyrrolidone;

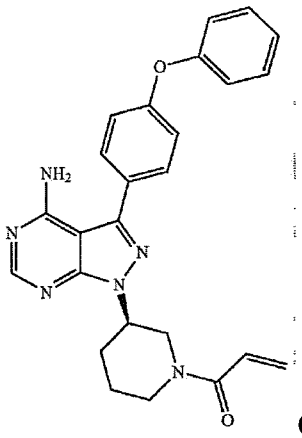
about 1% w/w to about 10% w/w croscarmellose sodium;

about 0.5% w/w to about 5% w/w sodium lauryl sulfate;

about 0.1% w/w to about 1.5% w/w silica;

about 0.01% w/w to about 2% w/w magnesium stearate;

wherein ibrutinib is a compound with the structure of Compound 1,



Compound 1;

and is in an amount of about 70 mg to about 840 mg.

[0041] In another embodiment is a high-load solid tablet formulation, wherein ibrutinib is in micronized form. In another embodiment, ibrutinib is in spray-dried form. In another embodiment, ibrutinib is not in spray-dried form. In another embodiment, the particle size is about or less than 30 micron. In one embodiment, ibrutinib is in micronized form and the particle size is about 1-30 micron. In another embodiment, the particle size is about or less than 10 micron. In another embodiment, the particle size is <1 micron. In another embodiment is a high-load solid tablet formulation, wherein the tablet is used for once a day oral dosing.

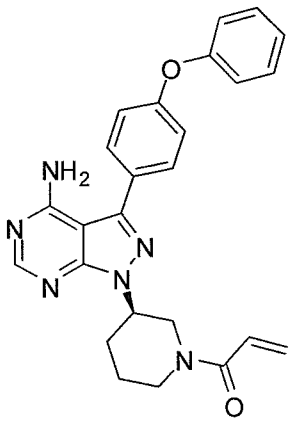
[0042] Provided herein are methods for treating a patient by administering Compound 1. In some embodiments, provided herein is a method of inhibiting the activity of tyrsoine kinase(s), such as Btk, or of treating a disease, disorder, or condition, which would benefit from inhibition of tyrosine kinase(s), such as Btk, in a mammal, which includes administering to the mammal a therapeutically effective amount of Compound 1, or pharmaceutically acceptable salt, pharmaceutically active metabolite, pharmaceutically acceptable prodrug, or pharmaceutically acceptable solvate.

[0043] Provided herein is the use of Compound 1 for inhibiting Bruton's tyrosine kinase (Btk) activity or for the treatment of a disease, disorder, or condition, which would benefit from inhibition of Bruton's tyrosine kinase (Btk) activity.

CLAIMS

WHAT IS CLAIMED IS:

1. A high-load solid tablet formulation comprising ibrutinib and one or more pharmaceutically acceptable excipients, wherein ibrutinib is a compound with the structure of Compound 1,



Compound 1;

and wherein the high-load solid tablet formulation comprises at least 50% w/w of ibrutinib, and the excipients comprise

one or more diluents selected from the group consisting of lactose, sucrose, dextrose, dextrates, maltodextrin, mannitol, xylitol, sorbitol, cyclodextrins, calcium phosphate, calcium sulfate, starches, modified starches, cellulose, microcrystalline cellulose, microcellulose, and talc;

one or more disintegrating agents selected from the group consisting of natural starch, a pregelatinized starch, a sodium starch, methylcrystalline cellulose, methylcellulose, croscarmellose, croscarmellose sodium, cross-linked sodium carboxymethylcellulose, cross-linked carboxymethylcellulose, cross-linked croscarmellose, cross-linked starch, cross-linked polymer, cross-linked polyvinylpyrrolidone, sodium alginate, a clay, and a gum;

one or more binders selected from the group consisting of hydroxypropyl cellulose or polyvinylpyrrolidone;

sodium lauryl sulfate;

silica; and

magnesium stearate.

2. The high-load solid tablet formulation of claim 1, wherein the one or more disintegrating agents selected from the group consisting of natural starch, a pregelatinized starch, a sodium starch, methylcrystalline cellulose, methylcellulose, croscarmellose, croscarmellose sodium, cross-linked sodium carboxymethylcellulose, cross-linked carboxymethylcellulose, cross-linked croscarmellose, sodium starch glycolate, crospovidone, cross-linked polyvinylpyrrolidone, sodium alginate, a clay, and a gum.

3. The high-load solid tablet formulation of claim 1, wherein the one or more diluents are lactose or microcrystalline cellulose, or a combination thereof.

4. The high-load solid tablet formulation of claim 1, wherein the excipients comprise lactose, microcrystalline cellulose, polyvinylpyrrolidone, croscarmellose sodium, sodium lauryl sulfate, colloidal silicon dioxide and magnesium stearate.

5. The high-load solid tablet formulation of claim 1, wherein the excipients comprise intragranular and extragranular excipients; and the intragranular excipients comprise lactose, microcrystalline cellulose, croscarmellose sodium, and hydroxypropyl cellulose; and the extragranular excipients comprise croscarmellose sodium, sodium lauryl sulfate, colloidal silicon dioxide, and magnesium stearate.

6. The high-load solid tablet formulation of claim 1, wherein the excipients comprise

intragranular excipients comprising:

lactose in an amount from about 5% w/w to about 20% w/w, about 8% w/w to about 15% w/w, or about 8% w/w to about 14% w/w;

microcrystalline cellulose in an amount from about 5% w/w to about 20% w/w, about 8% w/w to about 20% w/w, or about 8% w/w to about 15% w/w;

croscarmellose sodium in an amount from about 0% w/w to about 10% w/w, about 2% w/w to about 5% w/w, or about 2% w/w to about 4% w/w; and

hydroxypropyl cellulose in an amount from about 0% w/w to about 2% w/w, about 0.1% w/w to about 1.1% w/w, or about 0.1% w/w to about 1% w/w; and

extragranular excipients comprising

croscarmellose sodium in an amount from about 0% w/w to about 5% w/w, about 2% w/w to about 5% w/w, or about 2% w/w to about 4% w/w;

sodium lauryl sulfate in an amount from about 0% w/w to about 10% w/w, about 4% w/w to about 8% w/w, or about 5% w/w to about 6% w/w;

colloidal silicon dioxide in an amount from about 0.1% w/w to about 1.5% w/w, about 0.4% w/w to about 0.8% w/w, or about 0.5% w/w to about 0.6% w/w; and

magnesium stearate in an amount from about 0.1% w/w to about 1.5% w/w, about 0.4% w/w to about 0.8% w/w, or about 0.5% w/w to about 0.6% w/w.

7. The high-load solid tablet formulation of claim 1, wherein the excipients comprise intragranular and extragranular excipients; and the intragranular excipients comprise lactose, sodium lauryl sulfate, polyvinylpyrrolidone and croscarmellose sodium; and the extragranular excipients comprise croscarmellose sodium, sodium lauryl sulfate, microcrystalline cellulose, colloidal silicon dioxide, and magnesium stearate.

8. The high-load solid tablet formulation of claim 1, wherein the excipients comprise intragranular excipients comprising:

lactose in an amount from about 10% w/w to about 20% w/w or about 12% w/w to about 15% w/w;

polyvinylpyrrolidone in an amount from about 0% w/w to about 5% w/w or about 1% w/w to about 3% w/w;

croscarmellose sodium in an amount from about 1% w/w to about 10% w/w or about 3% w/w to about 7% w/w; and

sodium lauryl sulfate in an amount from about 0 % w/w to about 2% w/w or about 0.5% w/w to about 1.5% w/w; and

extragranular excipients comprising

croscarmellose sodium in an amount from about 0 % w/w to about 5% w/w or about 1% w/w to about 3% w/w;

sodium lauryl sulfate in an amount from about 0 % w/w to about 10% w/w or about 0% w/w to about 4% w/w;

microcrystalline cellulose in an amount from about 1% w/w to about 10% w/w or about 2% w/w to about 5% w/w;

colloidal silicon dioxide in an amount from about 0.4% w/w to about 0.8% w/w or about 0.5% w/w to about 0.6% w/w; and

magnesium stearate in an amount from about 0.4% w/w to about 0.8% w/w or about 0.5% w/w to about 0.6% w/w.

9. The high-load solid tablet formulation of claim 1, comprising:

a) about 69% w/w to about 71% w/w of ibrutinib,

b) about 13% w/w to about 15% w/w of lactose monohydrate,

c) about 2% w/w to about 5% w/w of microcrystalline cellulose,

d) about 1% w/w to about 3% w/w of polyvinylpyrrolidone,

e) about 6% w/w to about 8% w/w of croscarmellose sodium,

f) about 1% w/w to about 4% w/w of sodium lauryl sulfate,

g) about 0.4% w/w to about 0.6% w/w of colloidal silicon dioxide, and

h) about 0.4% w/w to about 0.6% w/w of magnesium stearate.

10. The high-load solid tablet formulation of claim 1, comprising:

a) about 70% w/w of ibrutinib,

b) about 14% w/w of lactose monohydrate,

c) about 5% w/w of microcrystalline cellulose,

d) about 2% w/w of polyvinylpyrrolidone,

e) about 7% w/w of croscarmellose sodium,

f) about 1% w/w of sodium lauryl sulfate,

g) about 0.5% w/w of colloidal silicon dioxide, and

h) about 0.5% w/w of magnesium stearate.

11. The high-load solid tablet formulation of claim 1, comprising:

a) about 70% w/w of ibrutinib,

b) about 14% w/w of lactose monohydrate,

c) about 2% w/w of microcrystalline cellulose,

d) about 2% w/w of polyvinylpyrrolidone,

e) about 7% w/w of croscarmellose sodium,

f) about 4% w/w of sodium lauryl sulfate,

g) about 0.5% w/w of colloidal silicon dioxide, and

h) about 0.5% w/w of magnesium stearate.

12. The high-load solid tablet formulation of claim 1, wherein the formulation comprises:

a) about 65% w/w to about 75% w/w of ibrutinib,

b) about 14% w/w to about 18% w/w of lactose monohydrate,

c) about 1% w/w to about 3% w/w of polyvinylpyrrolidone,

d) about 0.5% w/w to about 1.5% w/w of sodium lauryl sulfate,

e) about 5% w/w to about 15% w/w of crospovidone,

f) about 0.3% w/w to about 0.7% w/w of colloidal silicon dioxide, and

g) about 0.3% w/w to about 0.7% w/w of magnesium stearate.

13. The high-load solid tablet formulation of claim 1, wherein the formulation comprises:

a) about 59% w/w to about 61% w/w of ibrutinib,

b) about 13% w/w to about 15% w/w of lactose,

c) about 13% w/w to about 15% w/w of microcrystalline cellulose,

d) about 4% w/w to about 6% w/w of croscarmellose sodium,

e) about 5% w/w to about 7% w/w of sodium lauryl sulfate,

f) about 0.4% w/w to about 0.6% w/w of colloidal silicon dioxide, and

g) about 0.4% w/w to about 0.6% w/w of magnesium stearate.

14. The high-load solid tablet formulation of claim 6, wherein the formulation comprises:

a) about 59% w/w to about 61% w/w of ibrutinib,

b) about 13% w/w to about 14% w/w of lactose,

c) about 13% w/w to about 14% w/w of microcrystalline cellulose,

d) about 2% w/w to about 3% w/w of croscarmellose sodium (intragranular),

e) about 0.8% w/w to about 1.2% w/w of hydroxypropyl cellulose,

f) about 2% w/w to about 3% w/w of croscarmellose sodium (extragranular),

g) about 5.5% w/w to about 6.5% w/w of sodium lauryl sulfate,

h) about 0.4% w/w to about 0.6% w/w of colloidal silicon dioxide, and

i) about 0.4% w/w to about 0.6% w/w of magnesium stearate.

15. The high-load solid tablet formulation of claim 6, wherein the formulation comprises:

a) about 69% w/w to about 71% w/w of ibrutinib,

b) about 8% w/w to about 9% w/w of lactose,

c) about 8% w/w to about 9% w/w of microcrystalline cellulose,

d) about 2.5% w/w to about 3.5% w/w of croscarmellose sodium (intragranular),

e) about 2.5% w/w to about 3.5% w/w of croscarmellose sodium (extragranular),

f) about 5.5% w/w to about 6.5% w/w of sodium lauryl sulfate,

g) about 0.4% w/w to about 0.6% w/w of colloidal silicon dioxide, and

h) about 0.4% w/w to about 0.6% w/w of magnesium stearate.

16. The high-load solid tablet formulation of claim 1, wherein ibrutinib is in an amount of about 140 mg, about 420 mg, or about 560 mg.

17. The high-load solid tablet formulation of claim 1, wherein the high-load solid tablet formulation is used for one tablet once a day dosing.

18. The high-load solid tablet formulation of claim 1, wherein ibrutinib is in an amount of about 70 mg to about 840 mg.

19. The high-load solid tablet formulation of claim 3, wherein the high-load solid tablet formulation comprises about 60% w/w to about 80% w/w of ibrutinib.

20. The high-load solid tablet formulation of claim 19, wherein ibrutinib is in an amount of about 70 mg to about 840 mg.

21. The high-load solid tablet formulation of claim 19, wherein ibrutinib is in an amount of about 140 mg, about 420 mg, or about 560 mg.

22. The high-load solid tablet formulation of claim 4, wherein the high-load solid tablet formulation comprises about 60% w/w to about 80% w/w of ibrutinib.

23. The high-load solid tablet formulation of claim 22, wherein ibrutinib is in an amount of about 70 mg to about 840 mg.

24. The high-load solid tablet formulation of claim 22, wherein ibrutinib is in an amount of about 140 mg, about 420 mg, or about 560 mg.

25. A solid tablet formulation comprising ibrutinib, intra granular excipients and extragranular excipients; wherein the intragranular excipients comprise:

lactose in an amount from about 10% w/w to about 20% w/w;

polyvinylpyrrolidone in an amount from about 0% w/w to about 5% w/w;

croscarmellose sodium in an amount from about 1% w/w to about 10% w/w; and

sodium lauryl sulfate in an amount from about 0% w/w to about 2% w/w; and

the extragranular excipients comprise:

croscarmellose sodium in an amount from about 0% w/w to about 5% w/w;

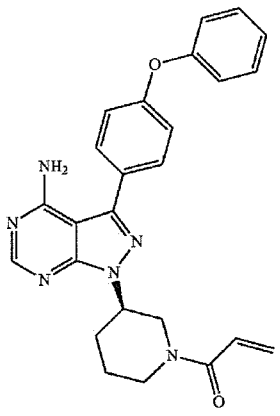
sodium lauryl sulfate in an amount from about 0% w/w to about 10% w/w;

microcrystalline cellulose in an amount from about 1% w/w to about 10% w/w;

colloidal silicon dioxide in an amount from about 0.4% wfw to about 0.8% w/w; and

magnesium stearate in an amount from about 0.4% w/w to about 0.8% w/w;

wherein ibrutinib is a compound with the structure of Compound 1,



Compound 1

and is present at about 60% w/w to about 80% w/w and in an amount of about 70 mg to about 840 mg.

26. The solid tablet formulation of claim 25, wherein the intragranular excipients comprise:

lactose in an amount from about 12% w/w to about 15% w/w;

polyvinylpyrrolidone in an amount from about 1% w/w to about 3% w/w;

croscarmellose sodium in an amount from about 3% w/w to about 7% w/w; and

sodium lauryl sulfate in an amount from about 0.5% w/w to about 1.5% w/w; and

the extragranular excipients comprise:

croscarmellose sodium in an amount from about 1% w/w to about 3% w/w;

sodium lauryl sulfate in an amount from about 0% w/w to about 4% w/w;

microcrystalline cellulose in an amount from about 2% w/w to about 5% w/w;

colloidal silicon dioxide in an amount from about 0.5% w/w to about 0.6% w/w; and

magnesium stearate in an amount from about 0.5% w/w to about 0.6% w/w.

27. A solid tablet formulation comprising

about 50% w/w to about 90% w/w of ibrutinib;

about 10% w/w to about 15% w/w lactose;

about 1% w/w to about 6% w/w microcrystalline cellulose;

about 1% w/w to about 5% w/w polyvinylpyrrolidone;

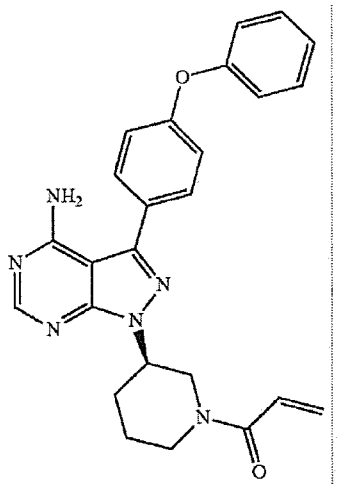
about 1% w/w to about 10% w/w croscarmellose sodium;

about 0.5% w/w to about 5% w/w sodium lauryl sulfate;

about 0.1% w/w to about 1.5% w/w silica;

about 0.01% w/w to about 2% w/w magnesium stearate;

wherein ibrutinib is a compound with the structure of Compound 1.



Compound 1

and is in an amount of about 70 mg to about 840 mg.

28. The solid tablet formulation of claim 27 comprising

a) about 69% w/w to about 71% w/w of ibrutinib,

b) about 13% w/w to about 15% w/w of lactose monohydrate,

c) about 2% w/w to about 5% w/w of microcrystalline cellulose,

d) about 1% w/w to about 3% w/w of polyvinylpyrrolidone,

e) about 6% w/w to about 8% w/w of croscarmellose sodium,

f) about 1% w/w to about 4% w/w of sodium lauryl sulfate,

g) about 0.4% w/w to about 0.6% w/w of colloidal silicon dioxide, and

h) about 0.4% w/w to about 0.6% w/w of magnesium stearate.

29. The high-load solid tablet formulation of claim 1, consisting essentially of

a) about 69% w/w to about 71% w/w of ibrutinib,

b) about 13% w/w to about 15% w/w of lactose monohydrate,

c) about 2% w/w to about 5% w/w of microcrystalline cellulose,

d) about 1% w/w to about 3% w/w of polyvinylpyrrolidone,

e) about 6% w/w to about 8% w/w of croscarmellose sodium,

f) about 1% w/w to about 4% w/w of sodium lauryl sulfate,

g) about 0.4% w/w to about 0.6% w/w of colloidal silicon dioxide, and

h) about 0.4% w/w to about 0.6% w/w of magnesium stearate.

30. The high-load solid tablet formulation of claim 1, consisting essentially of

a) about 70% w/w of ibrutinib,

b) about 14% w/w of lactose monohydrate,

c) about 5% w/w of microcrystalline cellulose,

d) about 2% w/w of polyvinylpyrrolidone,

e) about 7% w/w of croscarmellose sodium,

f) about 1% w/w of sodium lauryl sulfate,

g) about 0.5% w/w of colloidal silicon dioxide, and

h) about 0.5% w/w of magnesium stearate.

31. The high-load solid tablet formulation of claim 1, consisting essentially of

a) about 70% w/w of ibrutinib,

b) about 14% w/w of lactose monohydrate,

c) about 2% w/w of microcrystalline cellulose,

d) about 2% w/w of polyvinylpyrrolidone,

e) about 7% w/w of croscarmellose sodium,

f) about 4% w/w of sodium lauryl sulfate,

g) about 0.5% w/w of colloidal silicon dioxide, and

h) about 0.5% w/w of magnesium stearate.

32. The high-load solid tablet formulation of claim 1, wherein the formulation consists essentially of:

a) about 65% w/w to about 75% w/w of ibrutinib,

b) about 14% w/w to about 18% w/w of lactose monohydrate,

c) about 1% w/w to about 3% w/w of polyvinylpyrrolidone,

d) about 0.5% w/w to about 1.5% w/w of sodium lauryl sulfate,

e) about 5% w/w to about 15% w/w of crospovidone,

f) about 0.3% w/w to about 0.7% w/w of colloidal silicon dioxide, and

g) about 0.3% w/w to about 0.7% w/w of magnesium stearate.

33. The high-load solid tablet formulation of claim 1, wherein the formulation consists essentially of:

a) about 59% w/w to about 61% w/w of ibrutinib,

b) about 13% w/w to about 15% w/w of lactose,

c) about 13% w/w to about 15% w/w of microcrystalline cellulose,

d) about 4% w/w to about 6% w/w of croscarmellose sodium,

e) about 5% w/w to about 7% w/w of sodium lauryl sulfate,

f) about 0.4% w/w to about 0.6% w/w of colloidal silicon dioxide, and

g) about 0.4% w/w to about 0.6% w/w of magnesium stearate.

34. The high-load solid tablet formulation of claim 8, wherein the formulation consists essentially of:

a) about 59% w/w to about 61% w/w of ibrutinib,

b) about 13% w/w to about 14% w/w of lactose,

c) about 13% w/w to about 14% w/w of microcrystalline cellulose,

d) about 2% w/w to about 3% w/w of croscarmellose sodium (intragranular),

e) about 0.8% w/w to about 1.2% w/w of hydroxypropyl cellulose,

f) about 2% w/w to about 3% w/w of croscarmellose sodium (extragranular),

g) about 5.5% w/w to about 6.5% w/w of sodium lauryl sulfate,

h) about 0.4% w/w to about 0.6% w/w of colloidal silicon dioxide, and

i) about 0.4% w/w to about 0.6% w/w of magnesium stearate.

35. The high-load solid tablet formulation of claim 8, wherein the formulation consists essentially of:

a) about 69% w/w to about 71% w/w of ibrutinib,

b) about 8% w/w to about 9% w/w of lactose,

c) about 8% w/w to about 9% w/w of microcrystalline cellulose,

d) about 2.5% w/w to about 3.5% w/w of croscarmellose sodium (intragranular),

e) about 2.5% w/w to about 3.5% w/w of croscarmellose sodium (extragranular),

f) about 5.5% w/w to about 6.5% w/w of sodium lauryl sulfate,

g) about 0.4% w/w to about 0.6% w/w of colloidal silicon dioxide, and

h) about 0.4% w/w to about 0.6% w/w of magnesium stearate.

36. A solid tablet formulation consisting essentially of

about 50% w/w to about 90% w/w of ibrutinib;

about 10% w/w to about 15% w/w lactose;

about 1% w/w to about 6% w/w microcrystalline cellulose;

about 1% w/w to about 5% w/w polyvinylpyrrolidone;

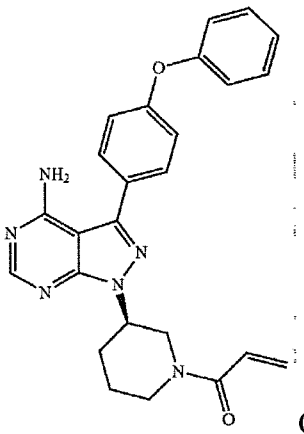
about 1% w/w to about 10% w/w croscarmellose sodium;

about 0.5% w/w to about 5% w/w sodium lauryl sulfate;

about 0.1% w/w to about 1.5% w/w silica;

about 0.01% w/w to about 2% w/w magnesium stearate;

wherein ibrutinib is a compound with the structure of Compound 1,



Compound 1;

and is in an amount of about 70 mg to about 840 mg.

37. The solid tablet formulation of claim 27 consisting essentially of

a) about 69% w/w to about 71% w/w of ibrutinib,

b) about 13% w/w to about 15% w/w of lactose monohydrate,

c) about 2% w/w to about 5% w/w of microcrystalline cellulose,

d) about 1% w/w to about 3% w/w of polyvinylpyrrolidone,

e) about 6% w/w to about 8% w/w of croscarmellose sodium,

f) about 1% w/w to about 4% w/w of sodium lauryl sulfate,

g) about 0.4% w/w to about 0.6% w/w of colloidal silicon dioxide, and

h) about 0.4% w/w to about 0.6% w/w of magnesium stearate.