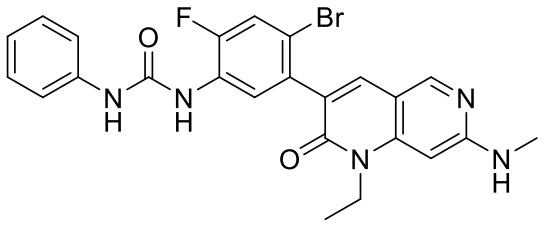
to the development of secondary mutations in KIT. Secondary resistance mutations usually arise in the catalytic domain of the kinase: 1) at the switch pocket, which typically occur in KIT exons 13 and 14 or PDGFRA exons 14 and 15 and sterically disrupt drug binding or conformationally activate KIT, and 2) in the activation loop switch encoded by KIT exons 17 and 18 and PDGFRA 18. Activation loop mutations act by shifting the kinase into an activated Type I or on-state conformation that is less amenable to drug binding by any of the approved Type II TKIs. Although uncommon in primary GIST (1%-2% of newly diagnosed cases), mutations in exons 13, 14 and 17 are often responsible for acquired imatinib resistance, with exon 17 mutations alone accounting for as many as 50% of the acquired resistance cases to imatinib, and later to sunitinib. A need exists for a TKI that can broadly inhibit clinically relevant KIT and PDGFRA mutations.

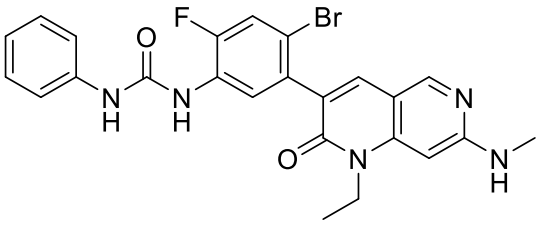
SUMMARY

[0006a] In a first aspect, the present disclosure refers to a use of a compound represented by:



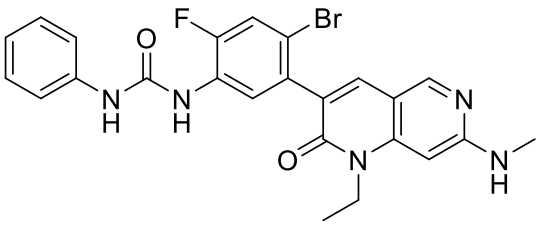
in the manufacture of a medicament for treating a patient suffering from an advanced gastrointestinal stromal tumor, wherein 150 mg of the compound is to be orally administered to the patient daily, and wherein the patient's tumor has progressed from, or the patient was intolerant to, a previous first line administration of imatinib, and wherein the patient suffers from a Grade 2 or Grade 3 adverse event and administration is interrupted for at least 7 days, and resumed at the same or a reduced level where the adverse event is lowered to Grade 1 or baseline.

[0006b] In yet another aspect, the present disclosure refers to a use of a compound represented by:



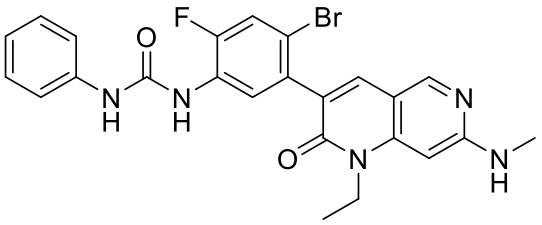
in the manufacture of a medicament for treating a patient suffering from an advanced gastrointestinal stromal tumor, wherein 150 mg of the compound is to be orally administered to the patient daily, and wherein the patient's tumor has progressed from, or the patient was intolerant to, a first line administration of imatinib, a second line administration of sunitinib, and a third line administration of regorafenib, or wherein the patient has a documented intolerance to one or more of imatinib, sunitinib and/or regorafenib, and wherein the patient suffers from a Grade 2 or Grade 3 adverse event and administration is interrupted for at least 7 days, and resumed at the same or a reduced level where the adverse event is lowered to Grade 1 or baseline.

[0006c] In a further aspect, the present disclosure refers to a use of a compound represented by:



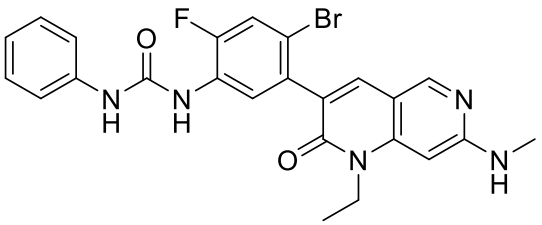
in the manufacture of a medicament for treating a patient suffering from an advanced gastrointestinal stromal tumor, wherein one or more tablets comprising 50 mg of the compound is to be orally administered to the patient daily, wherein the patient's tumor has progressed from, or the patient was intolerant to, a previous first line administration of imatinib, and wherein the patient suffers from a Grade 2 or Grade 3 adverse event and administration is interrupted for at least 7 days, and resumed at the same or a reduced level where the adverse event is lowered to Grade 1 or baseline.

[0006d] In another aspect, the present disclosure refers to a use of a compound represented by:



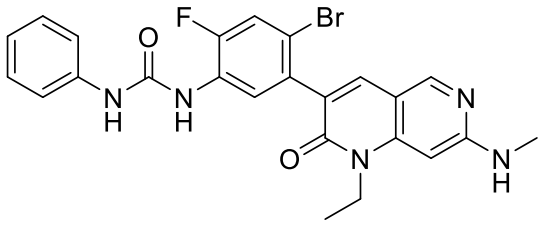
in the manufacture of a medicament for treating a patient suffering from an advanced gastrointestinal stromal tumor, wherein one or more tablets comprising 50 mg of the compound is to be orally administered to the patient, and wherein the patient's tumor has progressed from, or the patient was intolerant to, a first line administration of imatinib, a second line administration of sunitinib, and a third line administration of regorafenib or wherein the patient has a documented intolerance to one or more of imatinib, sunitinib and/or regorafenib, and wherein the patient suffers from a Grade 2 or Grade 3 adverse event and administration is interrupted for at least 7 days, and resumed at the same or a reduced level where the adverse event is lowered to Grade 1 or baseline.

[0006e] In yet another aspect, the present disclosure refers to a use of a compound represented by:



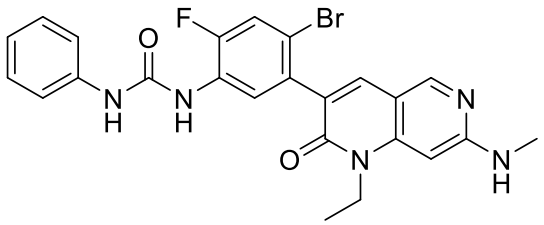
in the manufacture of a medicament for treating a patient suffering from an advanced gastrointestinal stromal tumor, wherein 150 mg of the compound is to be orally administered to the patient once daily, and wherein the patient was previously administered three or more kinase inhibitors before administration of the compound, and wherein the patient suffers from a Grade 2 or Grade 3 adverse event and administration is interrupted for at least 7 days, and resumed at the same or a reduced level where the adverse event is lowered to Grade 1 or baseline.

[0006f] In a further aspect, the present disclosure refers to a use of a compound represented by:



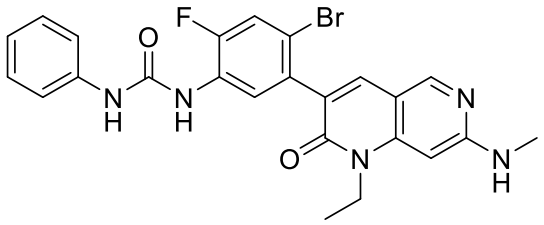
in the manufacture of a medicament for treating a patient suffering from an advanced gastrointestinal stromal tumor, wherein 150 mg of the compound is to be orally administered daily to the patient, wherein the patient's tumor has progressed from, or the patient was intolerant to, a first line administration of imatinib, a second line administration of sunitinib, and a third line administration of regorafenib, and wherein the patient suffers from a Grade 2 or Grade 3 adverse event and administration is interrupted for at least 7 days, and resumed at the same or a reduced level where the adverse event is lowered to Grade 1 or baseline.

[0006g] In another aspect, the present disclosure refers to a use of a compound represented by:



in the manufacture of a medicament for treating a patient suffering from an advanced gastrointestinal stromal tumor, wherein 150 mg of the compound is to be orally administered to the patient once or twice daily, wherein the patient's tumor has progressed from, or the patient was intolerant to, a previous first line administration of imatinib, and wherein the patient suffers from a Grade 2 or Grade 3 adverse event and administration is interrupted for at least 7 days, and resumed at the same or a reduced level where the adverse event is lowered to Grade 1 or baseline.

[0006h] In yet another aspect, the present disclosure refers to a use of a compound represented by:



in the manufacture of a medicament for treating a gastrointestinal stromal tumor in a patient in need thereof, wherein the patient is being treated concurrently with a CYP3A4 inhibitor, wherein

150 mg of the compound, or a pharmaceutically acceptable salt thereof, is to be orally administered to the patient once or twice daily, and wherein upon administration of the compound and the CYP3A4 inhibitor, an increased area under the plasma concentration curve ($AUC_{0\text{-}inf}$) of 80% or more of the compound in the patient is to be provided as compared to administration of the compound without concurrent treatment of the CYP3A4 inhibitor, and therefore the patient is at higher risk of an adverse event; and

the patient is to be monitored more frequently, as compared to a patient not being treated with a CYP3A4 inhibitor, for the adverse event

and wherein the patient suffers from a Grade 2 or Grade 3 adverse event and administration is interrupted for at least 7 days, and resumed at the same or a reduced level where the adverse event is lowered to Grade 1 or baseline.

[0007] Described herein are methods of treating a gastrointestinal stromal tumor in a patient in need thereof comprising administering to the patient a therapeutically effective amount of ripretinib or a pharmaceutically acceptable salt thereof.

[0008] For example, in one example described herein is a method of treating a patient suffering from an advanced gastrointestinal stromal tumor, comprising orally administering to the patient 100 mg to 300 mg, e.g., 150 mg, of ripretinib daily, wherein the patient's tumor has progressed from, or the patient was intolerant to, a previous first line administration of imatinib.

[0009] For example, in one example described herein is a method of treating a patient suffering from an advanced gastrointestinal stromal tumor, comprising orally administering to the patient 100 mg to 250 mg, e.g., 150 mg, of ripretinib daily, wherein the patient's tumor has progressed from, or the patient was intolerant to, a previous first line administration of imatinib.

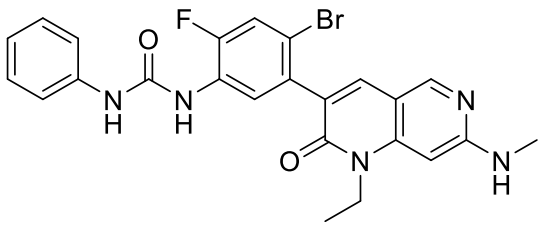
[00010] In another example, described herein is a method of treating a patient suffering from an advanced gastrointestinal stromal tumor, comprising orally administering to the patient 100 mg to 600 mg, e.g., 100 mg to 250 mg, e.g., 150 mg, of ripretinib daily, wherein the patient's tumor has progressed from, or the patient was intolerant to, a previous first line administration of imatinib.

[00011] In another example, described herein is a method of treating a patient suffering from an advanced gastrointestinal stromal tumor, comprising orally administering to the patient one or more tablets comprising ripretinib, e.g., tablets each comprising 50 mg to

CLAIMS

What is claimed is:

1. Use of a compound represented by:



in the manufacture of a medicament for treating a patient suffering from an advanced gastrointestinal stromal tumor, wherein 150 mg of the compound is to be orally administered to the patient daily, and wherein the patient's tumor has progressed from, or the patient was intolerant to, a previous first line administration of imatinib, and wherein the patient suffers from a Grade 2 or Grade 3 adverse event and administration is interrupted for at least 7 days, and resumed at the same or a reduced level where the adverse event is lowered to Grade 1 or baseline.

2. The use of claim 1, wherein:

(i) the patient was only previously treated with the first line administration of imatinib, optionally wherein the patient was not previously given a second line administration of sunitinib therapy and/or a third-line administration of regorafenib therapy; and/or

(ii) the patient has a non-nodal tumor lesion greater than or equal to 1.0 cm in the long axis or greater than or equal to double the slide thickness in the long axis, within 21 days prior to the first dose of the compound; and/or

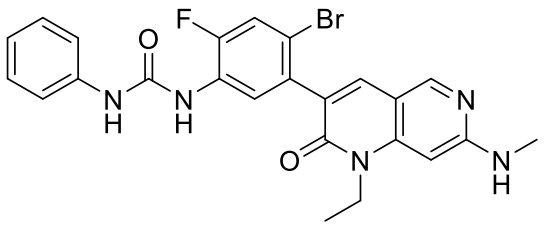
(iii) wherein the compound is to be administered in a 42-day cycle comprising daily administration of the compound without administering sunitinib, optionally wherein, after at least one 42-day cycle, the patient has a progression-free survival as measured using mRECIST v1.1 and/or the patient has a significant progression free survival as compared to a second-line daily administration of 50 mg sunitinib for four weeks followed by two weeks without daily administrations on a 42-day cycle, wherein the patient's tumor has progressed from, or the patient was intolerant to, the previous first line administration of imatinib.

3. The use of claim 1 or claim 2, wherein the tumor has:

(i) a KIT exon 9 mutation, a PDGFRA exon 18 mutation, a PDGFRA exon 12 mutation, or a PDGFRA exon 18 activation loop mutation, for example a KIT exon 9 mutation, optionally wherein the mutation is a PDGFRA D842V mutation; and/or

(ii) the tumor has an imatinib resistant mutation selected from the group consisting of a KIT exon 17 activation loop mutation, a KIT exon 18 activation loop mutation, a KIT exon 13 mutation, a KIT exon 14 mutation, a KIT exon 18 mutation, a PDGFRA exon 12 mutation, a PDGFRA exon 14 mutation, a PDGRFA exon 15 mutation, and a PDGFRA exon 18 activation loop mutation, optionally wherein the imatinib resistant mutation is a PDGFRA D842V mutation and/or the tumor has an imatinib resistant mutation selected from the group consisting of KIT exon 13 or 14 mutation, PDGFRA exon 14 or 15 mutation, a KIT 17 or 18 activation loop mutation, and a PDGFRA 18 activation loop mutation.

4. Use of a compound represented by:



in the manufacture of a medicament for treating a patient suffering from an advanced gastrointestinal stromal tumor, wherein 150 mg of the compound is to be orally administered to the patient daily, and wherein the patient's tumor has progressed from, or the patient was intolerant to, a first line administration of imatinib, a second line administration of sunitinib, and a third line administration of regorafenib, or wherein the patient has a documented intolerance to one or more of imatinib, sunitinib and/or regorafenib, and wherein the patient suffers from a Grade 2 or Grade 3 adverse event and administration is interrupted for at least 7 days, and resumed at the same or a reduced level where the adverse event is lowered to Grade 1 or baseline.

5. The use of claim 4, wherein:

(i) 150 mg of the compound is to be administered to the patient once daily; and/or

(ii) the patient has at least one measurable tumor lesion according to modified RECIST Version 1.1 within 21 days prior to the first dose of the compound; and/or

(iii) the patient has a non-nodal tumor lesion of greater than or equal to 1.0 cm in the long axis or greater than or equal to double the slide thickness in the long axis, within 21 days prior to the first dose of the compound; and/or

(iv) the tumor has, a KIT exon 9 mutation, a PDGFRA exon 18 mutation, a PDGFRA exon 12 mutation or a PDGFRA exon 18 activation loop mutation, optionally wherein the mutation is a PDGFRA D842V mutation; and/or

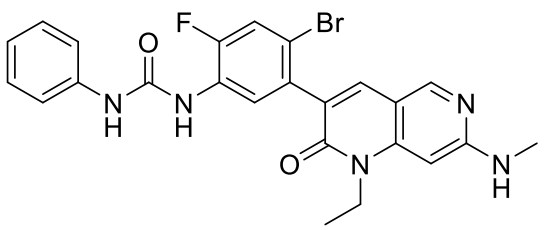
(v) the tumor has an imatinib resistant, sunitinib resistant, and/or regorafenib resistant mutation selected from the group consisting of a KIT exon 17 activation loop mutation, a KIT exon 18 activation loop mutation, a KIT exon 13 mutation, a KIT exon 14 mutation, a KIT exon 18 mutation, a PDGFRA exon 12 mutation, a PDGFRA exon 14 mutation, a PDGRFA exon 15 mutation and a PDGFRA exon 18 activation loop mutation, optionally wherein the resistant mutation is a PDGFRA D842V mutation and/or wherein the tumor has a drug resistant mutation selected from the group consisting of KIT exon 13 or 14 mutation, PDGFRA exon 14 or 15 mutation, a KIT 17 or 18 activation loop mutation, and a PDGFRA 18 activation loop mutation; and/or

(vi) the tumor has a drug resistant KIT exon 17 mutation; and/or

(vii) wherein the compound is to be administered in a 42-day cycle comprising daily administration of the compound without administering sunitinib, optionally wherein, after at least one 42-day cycle, the patient has a progression-free survival as measured using mRECIST v1.1; and/or

(viii) the patient has at least a 5- or 6-month progression-free survival as compared to placebo after at least 4 weeks of daily administration of the compound.

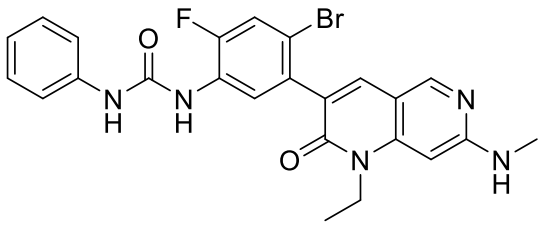
6. Use of a compound represented by:



in the manufacture of a medicament for treating a patient suffering from an advanced gastrointestinal stromal tumor, wherein one or more tablets comprising 50 mg of the compound is to be orally administered to the patient daily, wherein the patient's tumor has progressed from, or the patient was intolerant to, a previous first line administration of imatinib, and wherein the patient suffers from a Grade 2 or Grade 3 adverse event and administration is interrupted for at least 7 days, and resumed at the same or a reduced level where the adverse event is lowered to Grade 1 or baseline.

7. The use of claim 6, wherein the patient is to be administered three tablets each comprising 50 mg of the compound once daily.

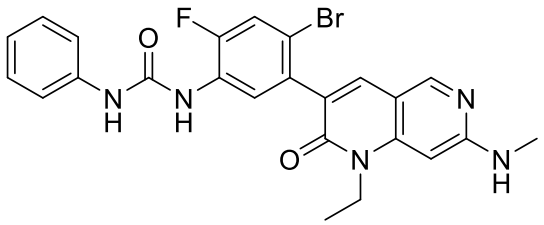
8. Use of a compound represented by:



in the manufacture of a medicament for treating a patient suffering from an advanced gastrointestinal stromal tumor, wherein one or more tablets comprising 50 mg of the compound is to be orally administered to the patient, and wherein the patient's tumor has progressed from, or the patient was intolerant to, a first line administration of imatinib, a second line administration of sunitinib, and a third line administration of regorafenib or wherein the patient has a documented intolerance to one or more of imatinib, sunitinib and/or regorafenib, and wherein the patient suffers from a Grade 2 or Grade 3 adverse event and administration is interrupted for at least 7 days, and resumed at the same or a reduced level where the adverse event is lowered to Grade 1 or baseline.

9. The use of claim 8, wherein the patient is to be administered, once daily, three tablets each comprising 50 mg of the compound.

10. Use of a compound represented by:



in the manufacture of a medicament for treating a patient suffering from an advanced gastrointestinal stromal tumor, wherein 150 mg of the compound is to be orally administered to the patient once daily, and wherein the patient was previously administered three or more kinase inhibitors before administration of the compound, and wherein the patient suffers from a Grade 2 or Grade 3 adverse event and administration is interrupted for at least 7 days, and resumed at the same or a reduced level where the adverse event is lowered to Grade 1 or baseline.

11. The use of claim 10, wherein:

(i) after at least 4 weeks of the daily compound administration, the patient has at least a 5-month progression-free survival as measured using mRECIST v1.1; and/or

(ii) 150 mg of the compound is to be orally administered to the patient once daily, wherein three tablets each tablet comprising 50 mg of the compound is to be administered to the patient; and/or

(iii) one of the three or more kinase inhibitors is imatinib; and/or

(iv) the patient was previously administered imatinib, sunitinib and regorafenib.

12. The use of any one of claims 1 to 11, wherein if the patient suffers from Grade 3 palmar-plantar erythrodysesthesia syndrome upon administration of the compound, the use further comprises a) withholding administration of the compound for at least 7 days or until the patient has less than or equal to Grade 1 palmar-plantar erythrodysesthesia syndrome, then 100 mg of the compound is to be administered to the patient daily for at least 28 days.

13. The use of any one of claims 1 to 11, wherein if the patient suffers from Grade 2 palmar-plantar erythrodysesthesia syndrome upon administration of the compound, the use

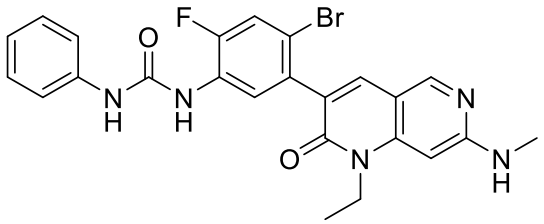
further comprises: a) withholding administration of the compound until the patient has less than or equal to Grade 1 palmar-plantar erythrodysesthesia syndrome or baseline; b) if the patient recovers from the palmar-plantar erythrodysesthesia syndrome within 7 days of withholding administration, then 150 mg of the compound is to be administered to the patient daily or c) if the patient has not recovered, then 100 mg of the compound is to be administered to the patient daily for at least 28 days.

14. The use of any one of claims 1 to 11 wherein:

(i) if the patient suffers from a Grade 3 adverse disorder selected from arthralgia or myalgia upon administration of the compound, the use further comprises: a) withholding administration of the compound until the patient has less than or equal to Grade 1 adverse disorder, then 100 mg of the compound is to be administered to the patient daily for at least 28 days; or

(ii) if the patient suffers from Grade 3 hypertension upon administration of the compound, the use further comprises withholding administration of the compound until the patient's blood pressure is controlled, and if the patient has less than or equal to Grade 1 blood pressure is, 150 mg of the compound is to be administered to the patient daily, or if the patient has more than Grade 1 blood pressure, 100 mg of the compound is to be administered to the patient daily.

15. Use of a compound represented by:



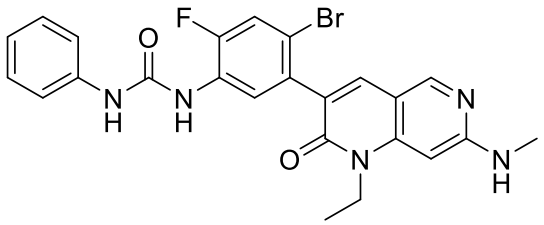
in the manufacture of a medicament for treating a patient suffering from an advanced gastrointestinal stromal tumor, wherein 150 mg of the compound is to be orally administered daily to the patient, wherein the patient's tumor has progressed from, or the patient was intolerant to, a first line administration of imatinib, a second line administration of sunitinib, and a third line administration of regorafenib, and wherein the patient suffers from a Grade 2

or Grade 3 adverse event and administration is interrupted for at least 7 days, and resumed at the same or a reduced level where the adverse event is lowered to Grade 1 or baseline.

16. The use of claim 15, wherein if the patient suffers from a Grade 3 palmar-plantar erythrodysesthesia syndrome upon administration of the compound, a) administration of the compound is to be withheld for at least 7 days or until the patient has less than or equal to Grade 1 palmar-plantar erythrodysesthesia syndrome, then 100 mg of the compound is to be administered to the patient daily for at least 28 days.

17. The use of claim 15, wherein if the patient suffers from a Grade 2 palmar-plantar erythrodysesthesia syndrome upon administration of the compound, a) administration of the compound is to be withheld until the patient has less than or equal to Grade 1 palmar-plantar erythrodysesthesia syndrome or baseline; b) if the patient recovers from the palmar-plantar erythrodysesthesia syndrome within 7 days of withholding administration, then 150 mg of the compound is to be administered to the patient daily; or c) if the patient has not recovered, then 100 mg of the compound is to be administered to the patient daily for at least 28 days.

18. Use of a compound represented by:



in the manufacture of a medicament for treating a patient suffering from an advanced gastrointestinal stromal tumor, wherein 150 mg of the compound is to be orally administered to the patient once or twice daily, wherein the patient's tumor has progressed from, or the patient was intolerant to, a previous first line administration of imatinib, and wherein the patient suffers from a Grade 2 or Grade 3 adverse event and administration is interrupted for at least 7 days, and resumed at the same or a reduced level where the adverse event is lowered to Grade 1 or baseline.

19. The use of claim 18, wherein if the patient suffers from Grade 3 palmar-plantar erythrodysesthesia syndrome upon administration of the compound, a) administration of the compound is to be withheld for at least 7 days or until the patient has less than or equal to Grade 1 palmar-plantar erythrodysesthesia syndrome, then 100 mg of the compound is to be administered to the patient daily for at least 28 days.

20. The use of any one of claims 3-7, wherein if the patient suffers from Grade 3 palmar-plantar erythrodysesthesia syndrome upon administration of the compound, a) administration of the compound is to be withheld for at least 7 days or until the patient has less than or equal to Grade 1 palmar-plantar erythrodysesthesia syndrome, then 100 mg of the compound is to be administered to the patient daily for at least 28 days.

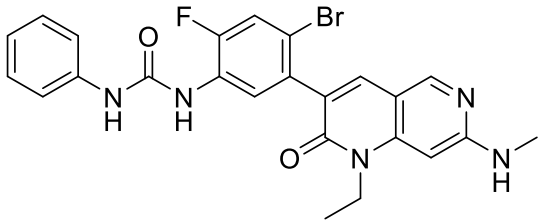
21. The use of any one of claims 3-7, wherein if the patient suffers from Grade 2 palmar-plantar erythrodysesthesia syndrome upon administration of the compound, a) administration of the compound is to be withheld until the patient has less than or equal to Grade 1 palmar-plantar erythrodysesthesia syndrome or baseline; b) if the patient recovers from the palmar-plantar erythrodysesthesia syndrome within 7 days of withholding administration, then 150 mg of the compound is to be administered to the patient daily; or c) if the patient has not recovered, then 100 mg of the compound is to be administered to the patient daily for at least 28 days.

22. The use of any one of claims 3-7, wherein if the patient suffers from a Grade 3 adverse disorder selected from arthralgia or myalgia upon administration of the compound, a) administration of the compound is to be withheld until the patient has less than or equal to Grade 1 adverse disorder, then 100 mg of the compound is to be administered to the patient daily for at least 28 days.

23. The use of any one of claims 3-7, wherein if the patient suffers from Grade 3 hypertension upon administration of the compound, administration of the compound is to be withheld until the patient's blood pressure is controlled, and if the patient has less than or equal to Grade 1 blood pressure is, 150 mg of the compound is to be administered to the

patient daily, or if the patient has more than Grade 1 blood pressure, 100 mg of the compound is to be administered to the patient daily.

24. Use of a compound represented by:



in the manufacture of a medicament for treating a gastrointestinal stromal tumor in a patient in need thereof, wherein the patient is being treated concurrently with a CYP3A4 inhibitor, wherein

150 mg of the compound, or a pharmaceutically acceptable salt thereof, is to be orally administered to the patient once or twice daily, and wherein upon administration of the compound and the CYP3A4 inhibitor, an increased area under the plasma concentration curve ($AUC_{0\text{-}inf}$) of 80% or more of the compound in the patient is to be provided as compared to administration of the compound without concurrent treatment of the CYP3A4 inhibitor, and therefore the patient is at higher risk of an adverse event; and

the patient is to be monitored more frequently, as compared to a patient not being treated with a CYP3A4 inhibitor, for the adverse event,

and wherein the patient suffers from a Grade 2 or Grade 3 adverse event and administration is interrupted for at least 7 days, and resumed at the same or a reduced level where the adverse event is lowered to Grade 1 or baseline.