

PHARMACEUTICAL COMPOSITIONS COMPRISING N-(3,5-DIMETHOXYPHENYL)-N'-(1-METHYLETHYL)-N-[3-(1-METHYL-1H-PYRAZOL-4-YL)QUINOXALIN-6-YL]ETHANE-1,2-DIAMINE

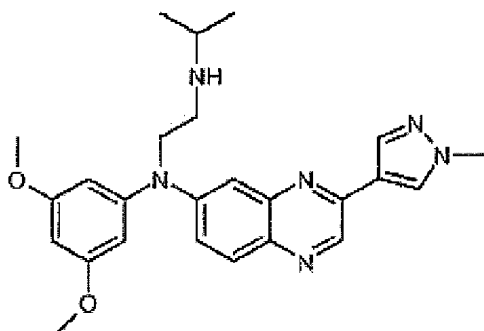
FIELD OF THE INVENTION

- 5 The invention relates to pharmaceutical compositions comprising N-(3,5-dimethoxyphenyl)-N'-(1-methylethyl)-N-[3-(1-methyl-1H-pyrazol-4-yl)quinoxalin-6-yl]ethane-1,2-diamine, or a pharmaceutically acceptable salt thereof or a solvate thereof; to processes for the preparation of said compositions and to the use of said compositions for the manufacture of a medicament for the prophylaxis of or the treatment, in particular the treatment, of
10 diseases, e.g. cancer.

BACKGROUND OF THE INVENTION

N-(3,5-dimethoxyphenyl)-N'-(1-methylethyl)-N-[3-(1-methyl-1H-pyrazol-4-yl)quinoxalin-6-yl]ethane-1,2-diamine is described in WO2011/135376, which is incorporated herein by reference.

- 15 The chemical structure of N-(3,5-dimethoxyphenyl)-N'-(1-methylethyl)-N-[3-(1-methyl-1H-pyrazol-4-yl)quinoxalin-6-yl]ethane-1,2-diamine (compound A herein) is :



SUMMARY

- 20 According to an aspect of the disclosure, there is provided a pharmaceutical composition comprising N-(3,5-dimethoxyphenyl)-N'-(1-methylethyl)-N-[3-(1-methyl-1H-pyrazol-4-yl)quinoxalin-6-yl]ethane-1,2-diamine, a pharmaceutically acceptable salt thereof or a solvate thereof, a formaldehyde scavenger and a pharmaceutically acceptable carrier.

- 25 The disclosure provides the use of a formaldehyde scavenger, in particular meglumine, to increase the stability, in particular the chemical stability of N-(3,5-dimethoxyphenyl)-N'-(1-methylethyl)-N-[3-(1-methyl-1H-pyrazol-4-yl)quinoxalin-6-yl]ethane-1,2-diamine, a pharmaceutically acceptable salt thereof or a solvate thereof, in particular N-(3,5-dimethoxyphenyl)-N'-(1-methylethyl)-N-[3-(1-methyl-1H-pyrazol-4-yl)quinoxalin-6-yl]ethane-1,2-diamine base, in a pharmaceutical

composition, in particular a solid pharmaceutical composition, in particular a capsule or a tablet.

In another aspect, there is provided use of a formaldehyde scavenger in a pharmaceutical composition to increase the chemical stability of N-(3,5-dimethoxyphenyl)-N'-(1-methylethyl)-N-[3-(1-methyl-1H-pyrazol-4-yl)quinoxalin-6-yl]ethane-1,2-diamine, a pharmaceutically acceptable salt thereof or a solvate thereof, contained in said composition.

In another aspect, there is provided use of a formaldehyde scavenger in a pharmaceutical composition to prevent, postpone, slow down or diminish the transformation of N-(3,5-dimethoxyphenyl)-N'-(1-methylethyl)-N-[3-(1-methyl-1H-pyrazol-4-yl)quinoxalin-6-yl]ethane-1,2-diamine, a pharmaceutically acceptable salt thereof or a solvate thereof, contained in the composition, into 6,8-dimethoxy-4-(1-methylethyl)-1-[3-(1-methyl-1H-pyrazol-4-yl)quinoxalin-6-yl]-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine, a pharmaceutically acceptable salt thereof or a solvate thereof.

In another aspect, there is provided a method of preventing, postponing, slowing down or diminishing the transformation of N-(3,5-dimethoxyphenyl)-N'-(1-methylethyl)-N-[3-(1-methyl-1H-pyrazol-4-yl)quinoxalin-6-yl]ethane-1,2-diamine, a pharmaceutically acceptable salt thereof or a solvate thereof, contained in a pharmaceutical composition, into 6,8-dimethoxy-4-(1-methylethyl)-1-[3-(1-methyl-1H-pyrazol-4-yl)quinoxalin-6-yl]-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine, a pharmaceutically acceptable salt thereof or a solvate thereof, comprising adding a formaldehyde scavenger to said composition.

In another aspect, there is provided use of a pharmaceutical composition as defined herein for the manufacture of a medicament for the treatment of cancer, wherein the medicament is to be administered daily for 3 weeks (3 weeks on), followed by 1 week wherein the composition is not administered (1 week off), and repeating this cycle of 3 weeks on, 1 week off.

In another aspect, there is provided use of a pharmaceutical composition as defined herein for the manufacture of a medicament for the treatment of cancer, wherein the medicament is to be administered daily for 1 week (1 week on), followed by 1 week wherein the composition is not administered (1 week off), and repeating this cycle of 1 week on, 1 week off.

In another aspect, there is provided use of a pharmaceutical composition as defined herein for the manufacture of a medicament for the treatment of cancer, wherein the medicament is to be administered daily.

In another aspect, there is provided use of a pharmaceutical composition as defined herein for the manufacture of a medicament for the treatment of cancer, wherein the medicament is to be administered once daily.

FIGURES

Fig.1 : Experimental set-up of formaldehyde stress test in solid state (N-(3,5-dimethoxyphenyl)-N'-(1-methylethyl)-N-[3-(1-methyl-1H-pyrazol-4-yl)quinoxalin-6-yl]ethane-1,2-diamine = compound A)

Fig. 2 : Degradation of N-(3,5-dimethoxyphenyl)-N'-(1-methylethyl)-N-[3-(1-methyl-1H-pyrazol-4-yl)quinoxalin-6-yl]ethane-1,2-diamine (compound A) in powder blends comprising various concentrations of meglumine in a formaldehyde stress test : ♦ represents a starting powder blend of 2% w/w of compound A, mannitol, microcrystalline cellulose, croscarmellose sodium and magnesium stearate; ■ represents a starting powder blend of 2% w/w of compound A, 1% w/w of meglumine, mannitol, microcrystalline cellulose, croscarmellose sodium and magnesium stearate; A represents a starting powder blend of 2% w/w of compound A, 9% w/w of meglumine, mannitol, microcrystalline cellulose, croscarmellose sodium and magnesium stearate. Compound B is 6,8-dimethoxy-4-(1-methylethyl)-1-[3-(1-methyl-1H-pyrazol-4-yl)quinoxalin-6-yl]-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine.

DETAILED DESCRIPTION OF THE INVENTION

It was found that N-(3,5-dimethoxyphenyl)-N'-(1-methylethyl)-N-[3-(1-methyl-1H-pyrazol-4-yl)quinoxalin-6-yl]ethane-1,2-diamine is sensitive to degradation, especially when incorporated in a solid pharmaceutical composition. In particular, N-(3,5-dimethoxyphenyl)-N'-(1-methylethyl)-N-[3-(1-methyl-1H-pyrazol-4-yl)quinoxalin-6-yl]ethane-1,2-diamine is sensitive, especially when incorporated in a solid pharmaceutical composition, to transformation into a cyclized product, 6,8-dimethoxy-4-(1-methylethyl)-1-[3-(1-methyl-1H-pyrazol-4-yl)quinoxalin-6-yl]-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine.

The chemical structure of 6,8-dimethoxy-4-(1-methylethyl)-1-[3-(1-methyl-1H-pyrazol-4-yl)quinoxalin-6-yl]-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine (compound B herein) is:

CLAIMS

1. The use of a formaldehyde scavenger in a pharmaceutical composition to increase the
5 chemical stability of N-(3,5-dimethoxyphenyl)-N'-(1-methylethyl)-N-[3-(1-methyl-1H-pyrazol-4-yl)quinoxalin-6-yl]ethane-1,2-diamine, a pharmaceutically acceptable salt thereof or a solvate thereof, contained in said composition.
2. The use of a formaldehyde scavenger in a pharmaceutical composition to prevent,
10 postpone, slow down or diminish the transformation of N-(3,5-dimethoxyphenyl)-N'-(1-methylethyl)-N-[3-(1-methyl-1H-pyrazol-4-yl)quinoxalin-6-yl]ethane-1,2-diamine, a pharmaceutically acceptable salt thereof or a solvate thereof, contained in the composition, into 6,8-dimethoxy-4-(1-methylethyl)-1-[3-(1-methyl-1H-pyrazol-4-yl)quinoxalin-6-yl]-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine, a pharmaceutically
15 acceptable salt thereof or a solvate thereof.
3. The use according to claim 1 or 2, wherein the formaldehyde scavenger is meglumine.
- 20 4. The use according to any one of claims 1 to 3, wherein the pharmaceutical composition is a tablet or a capsule.
5. The use according to any one of claims 1 to 4, wherein the pharmaceutical composition comprises N-(3,5-dimethoxyphenyl)-N'-(1-methylethyl)-N-[3-(1-methyl-1H-pyrazol-4-yl)quinoxalin-6-yl]ethane-1,2-diamine base.
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6. A method of preventing, postponing, slowing down or diminishing the transformation of N-(3,5-dimethoxyphenyl)-N'-(1-methylethyl)-N-[3-(1-methyl-1H-pyrazol-4-yl)quinoxalin-6-yl]ethane-1,2-diamine, a pharmaceutically acceptable salt thereof or a
30 solvate thereof, contained in a pharmaceutical composition, into 6,8-dimethoxy-4-(1-methylethyl)-1-[3-(1-methyl-1H-pyrazol-4-yl)quinoxalin-6-yl]-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine, a pharmaceutically acceptable salt thereof or a solvate thereof, comprising adding a formaldehyde scavenger to said composition.
- 35 7. The method according to claim 6, wherein the formaldehyde scavenger is meglumine.

8. The method according to claim 6 or 7, wherein the pharmaceutical composition is a tablet or a capsule.
9. The method according to any one of claims 6 to 8, wherein the composition
5 comprises N-(3,5-dimethoxyphenyl)-N'-(1-methylethyl)-N-[3-(1-methyl-1H-pyrazol-4-yl)quinoxalin-6-yl]ethane-1,2-diamine base.
10. A pharmaceutical composition comprising N-(3,5-dimethoxyphenyl)-N'-(1-methylethyl)-N-[3-(1-methyl-1H-pyrazol-4-yl)quinoxalin-6-yl]ethane-1,2-diamine, a
10 pharmaceutically acceptable salt thereof or a solvate thereof; a formaldehyde scavenger; and a pharmaceutically acceptable carrier.
11. A pharmaceutical composition according to claim 10 comprising from about 0.1 to about 3 % w/w of the formaldehyde scavenger.
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12. A pharmaceutical composition according to claim 10 or 11, wherein the composition is a tablet or a capsule.
13. A pharmaceutical composition according to any one of claims 10 to 12, wherein the
20 composition comprises from 0-2 % w/w of 6,8-dimethoxy-4-(1-methylethyl)-1-[3-(1-methyl-1H-pyrazol-4-yl)quinoxalin-6-yl]-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine, a pharmaceutically acceptable salt thereof or a solvate thereof.
14. A pharmaceutical composition according to claim 13, wherein the composition
25 comprise from 0-0.05 % w/w of 6,8-dimethoxy-4-(1-methylethyl)-1-[3-(1-methyl-1H-pyrazol-4-yl)quinoxalin-6-yl]-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine, a pharmaceutically acceptable salt thereof or a solvate thereof.
15. A pharmaceutical composition according to any one of claims 10 to 14 comprising
30 from 2 mg to 6 mg base equivalent of N-(3,5-dimethoxyphenyl)-N'-(1-methylethyl)-N-[3-(1-methyl-1H-pyrazol-4-yl)quinoxalin-6-yl]ethane-1,2-diamine, a pharmaceutically acceptable salt thereof or a solvate thereof.
16. A pharmaceutical composition according to any one of claims 10 to 15, wherein the
35 formaldehyde scavenger is meglumine.

17. A pharmaceutical composition according to any one of claims 10 to 16, wherein the composition comprises N-(3,5-dimethoxyphenyl)-N'-(1-methylethyl)-N-[3-(1-methyl-1H-pyrazol-4-yl)quinoxalin-6-yl]ethane-1,2-diamine base.

5 18. The use of a pharmaceutical composition according to any one of claims 10 to 17 for the manufacture of a medicament for the treatment of cancer, wherein the medicament is to be administered daily for 3 weeks (3 weeks on), followed by 1 week wherein the composition is not administered (1 week off), and repeating this cycle of 3 weeks on, 1 week off.

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19. The use of a pharmaceutical composition according to any one of claims 10 to 17 for the manufacture of a medicament for the treatment of cancer, wherein the medicament is to be administered daily for 1 week (1 week on), followed by 1 week wherein the composition is not administered (1 week off), and repeating this cycle of 1 week on, 1 week off.

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20. The use of a pharmaceutical composition according to any one of claims 10 to 17 for the manufacture of a medicament for the treatment of cancer, wherein the medicament is to be administered daily.

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21. The use of a pharmaceutical composition according to any one of claims 10 to 17 for the manufacture of a medicament for the treatment of cancer, wherein the medicament is to be administered once daily.

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22. The use of a pharmaceutical composition according to any one of claims 18 to 21, (i) for the manufacture of a medicament for the treatment of cancer, wherein the daily dose is 6 mg base equivalent;

(ii) for the manufacture of a medicament for the treatment of cancer, wherein the daily dose is 7 mg base equivalent;

5 (iii) for the manufacture of a medicament for the treatment of cancer, wherein the daily dose is 8 mg base equivalent; or

(iv) for the manufacture of a medicament for the treatment of cancer, wherein the daily dose is 9 mg base equivalent.

10 23. The use of a pharmaceutical composition according to any one of claims 18 to 22

(i) for the manufacture of a medicament for the treatment of cancer, wherein the cancer is bladder cancer;

15 (ii) for the manufacture of a medicament for the treatment of cancer wherein the cancer is urothelial cancer;

(iii) for the manufacture of a medicament for the treatment of cancer wherein the cancer is metastatic urothelial cancer;

20 (iv) for the manufacture of a medicament for the treatment of cancer wherein the cancer is surgically unresectable urothelial cancer;

25 (v) for the manufacture of a medicament for the treatment of cancer wherein the cancer is cholangiocarcinoma; or

(vi) for the manufacture of a medicament for the treatment of cancer wherein the cancer is non-muscle-invasive bladder cancer.

30 24. The use of a pharmaceutical composition according to claim 23 wherein the cancer is a cancer with FGFR genomic alterations.

25. The use of a pharmaceutical composition according to claim 24 wherein the FGFR genomic alterations are translocations, fusions and/or mutations.

35 26. The use of a pharmaceutical composition according to claim 25 wherein the alteration is a FGFR3-TACC3 translocation.

27. The use of a pharmaceutical composition according to claim 25 wherein the alteration is a mutation.
28. The use of a pharmaceutical composition according to claim 27 wherein the
5 mutation is R248C.
29. The use of a pharmaceutical composition according to claim 27 wherein the mutation is S249C.
- 10 30. The use of a pharmaceutical composition according to any one of claims 18 to 22
(i) for the manufacture of a medicament for the treatment of cancer wherein the cancer is advanced or refractory non small cell lung cancer (NSCLC), breast cancer, glioblastoma multiforme, urothelial cancer, ovarian cancer, head and neck cancer, oesophageal cancer, gastric cancer and cholangiocarcinoma;
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(ii) for the manufacture of a medicament for the treatment of cancer wherein the cancer is multiple myeloma, myeloproliferative disorders, endometrial cancer, prostate cancer, bladder cancer, lung cancer, ovarian cancer, breast cancer, gastric cancer, colorectal cancer, and oral squamous cell carcinoma; or
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(iii) for the manufacture of a medicament for the treatment of cancer wherein the cancer is endometrial, ovarian, gastric, hepatocellular, uterine, cervix and colorectal cancer.