# 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

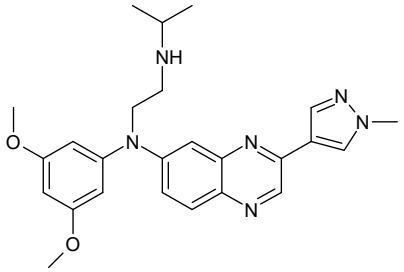
## FIELD OF THE INVENTION

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 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.

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

According to 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.

According to the disclosure there is provided 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.

According to an aspect of the disclosure there is provided a tablet consisting of the following composition:

| | |
|---|---|
| N-(3,5-dimethoxyphenyl)-N'-(1-methylethyl)-N-[3-(1-methyl-1H-pyrazol-4-yl)quinoxalin-6-yl]ethane-1,2-diamine | 3 mg |
| Meglumine | 1.5 mg |
| Mannitol | 20 % to 95 % w/w |
| Microcrystalline cellulose | 20 % to 95 % w/w |
| Croscarmellose sodium | 2.5 to 5 % w/w |
| Magnesium stearate | 0.5 to 1.5% w/w |

wherein the total weight of the tablet is 150 mg.

According to another aspect of the disclosure there is provided a tablet consisting of the following composition:

| | |
|---|---|
| N-(3,5-dimethoxyphenyl)-N'-(1-methylethyl)-N-[3-(1-methyl-1H-pyrazol-4-yl)quinoxalin-6-yl]ethane-1,2-diamine | 4 mg |
| Meglumine | 2 mg |
| Mannitol | 20 % to 95 % w/w |
| Microcrystalline cellulose | 20 % to 95 % w/w |
| Croscarmellose sodium | 2.5 to 5 % w/w |
| Magnesium stearate | 0.5 to 1.5% w/w |

wherein the total weight of the tablet is 200 mg.

According to another aspect of the disclosure there is provided a tablet consisting of the following composition:

| | |
|---|---|
| N-(3,5-dimethoxyphenyl)-N'-(1-methylethyl)-N-[3-(1-methyl-1H-pyrazol-4-yl)quinoxalin-6-yl]ethane-1,2-diamine | 5 mg |
| Meglumine | 2.5 mg |
| Mannitol | 20 % to 95 % w/w |
| Microcrystalline cellulose | 20 % to 95 % w/w |
| Croscarmellose sodium | 2.5 to 5 % w/w |
| Magnesium stearate | 0.5 to 1.5% w/w |

wherein the total weight of the tablet is 250 mg.

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

According to another aspect of the disclosure there is provided a tablet as defined herein for use in treatment of cancer, wherein the tablet is to be administered daily for 1

week (1 week on), followed by 1 week wherein the tablet is not administered (1 week off), and repeating this cycle of 1 week on, 1 week off.

According to another aspect of the disclosure there is provided a tablet as defined herein for use in the treatment of cancer, in particular wherein the tablet is to be administered daily.

According to another aspect of the disclosure there is provided a tablet as defined herein for use in therapy.

According to another aspect of the disclosure there is provided the use of a tablet as defined herein in 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 medicament is not administered (1 week off), and repeating this cycle of 3 weeks on, 1 week off.

According to another aspect of the disclosure there is provided the use of a tablet as defined herein in 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 medicament is not administered (1 week off), and repeating this cycle of 1 week on, 1 week off.

Accoring to another aspect of the disclosure there is provided the use of a tablet as defined herein in the manufacture of a medicament for the treatment of cancer, wherein the medicament is to be administered 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; ▲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. A tablet consisting of the following composition:

| | |
|---|---|
| N-(3,5-dimethoxyphenyl)-N'-(1-methylethyl)-N-[3-(1-methyl-1H-pyrazol-4-yl)quinoxalin-6-yl]ethane-1,2-diamine | 3 mg |
| Meglumine | 1.5 mg |
| Mannitol | 20 % to 95 % w/w |
| Microcrystalline cellulose | 20 % to 95 % w/w |
| Croscarmellose sodium | 2.5 to 5 % w/w |
| Magnesium stearate | 0.5 to 1.5% w/w |

wherein the total weight of the tablet is 150 mg.

2. A tablet consisting of the following composition:

| | |
|---|---|
| N-(3,5-dimethoxyphenyl)-N'-(1-methylethyl)-N-[3-(1-methyl-1H-pyrazol-4-yl)quinoxalin-6-yl]ethane-1,2-diamine | 4 mg |
| Meglumine | 2 mg |
| Mannitol | 20 % to 95 % w/w |
| Microcrystalline cellulose | 20 % to 95 % w/w |
| Croscarmellose sodium | 2.5 to 5 % w/w |
| Magnesium stearate | 0.5 to 1.5% w/w |

wherein the total weight of the tablet is 200 mg.

3. A tablet consisting of the following composition:

| | |
|---|---|
| N-(3,5-dimethoxyphenyl)-N'-(1-methylethyl)-N-[3-(1-methyl-1H-pyrazol-4-yl)quinoxalin-6-yl]ethane-1,2-diamine | 5 mg |
| Meglumine | 2.5 mg |
| Mannitol | 20 % to 95 % w/w |
| Microcrystalline cellulose | 20 % to 95 % w/w |
| Croscarmellose sodium | 2.5 to 5 % w/w |
| Magnesium stearate | 0.5 to 1.5% w/w |

wherein the total weight of the tablet is 250 mg.

4. A tablet according to any one of claims 1 to 3, wherein the tablet is further film-coated.

5. A tablet according to any one of claims 1 to 4 for use in the treatment of cancer, wherein the tablet is to be administered daily for 3 weeks (3 weeks on), followed by 1

week wherein the tablet is not administered (1 week off), and repeating this cycle of 3 weeks on, 1 week off.

6. A tablet according to any one of claims 1 to 4 for use in the treatment of cancer, wherein the tablet is to be administered daily for 1 week (1 week on), followed by 1 week wherein the tablet is not administered (1 week off), and repeating this cycle of 1 week on, 1 week off.

7. A tablet according to any one of claims 1 to 4 for use in the treatment of cancer, in particular wherein the tablet is to be administered daily.

8. A tablet for use according to claim 7 wherein the tablet is to be administered once daily.

9. A tablet for use according to any one of claims 5 to 8,
   i. wherein the daily dose is 6 mg of N-(3,5-dimethoxyphenyl)-N'-(1-methylethyl)-N-[3-(1-methyl-1H-pyrazol-4-yl)quinoxalin-6-yl]ethane-1,2-diamine;
   ii. wherein the daily dose is 7 mg of N-(3,5-dimethoxyphenyl)-N'-(1-methylethyl)-N-[3-(1-methyl-1H-pyrazol-4-yl)quinoxalin-6-yl]ethane-1,2-diamine;
   iii. wherein the daily dose is 8 mg of N-(3,5-dimethoxyphenyl)-N'-(1-methylethyl)-N-[3-(1-methyl-1H-pyrazol-4-yl)quinoxalin-6-yl]ethane-1,2-diamine; or
   iv. wherein the daily dose is 9 mg of N-(3,5-dimethoxyphenyl)-N'-(1-methylethyl)-N-[3-(1-methyl-1H-pyrazol-4-yl)quinoxalin-6-yl]ethane-1,2-diamine.

10. A tablet for use according to any one of claims 5 to 9,
   i. wherein the cancer is bladder cancer;
   ii. wherein the cancer is urothelial cancer;
   iii. wherein the cancer is metastatic urothelial cancer;
   iv. wherein the cancer is surgically unresectable urothelial cancer;
   v. wherein the cancer is cholangiocarcinoma; or
   vi. wherein the cancer is non-muscle-invasive bladder cancer.

11. A tablet for use according to claim 10 wherein the cancer is urothelial cancer.

12. A tablet for use according to claim 10 wherein the cancer is metastatic urothelial cancer.

13. A tablet for use according to claim 10 wherein the cancer is surgically unresectable urothelial cancer.

14. A tablet for use according to claim 10 wherein the cancer is non-muscle-invasive bladder cancer.

15. A tablet for use according to any one of claims 10, parts (ii) to (vi), to 14 wherein the cancer is a cancer with FGFR genomic alterations, in particular wherein the FGFR genomic alterations are translocations, fusions and/or mutations.

16. A tablet for use according to claim 15 wherein the alteration is a FGFR3-TACC3 translocation.

17. A tablet for use according to claim 15 wherein the alteration is a mutation.

18. A tablet for use according to claim 17 wherein the mutation is R248C or wherein the mutation is S249C.

19. A tablet for use according to any one of claims 5 to 9 wherein the cancer is mediated by a FGFR kinase.

20. A tablet according to any one of claims 1 to 4 for use in therapy.

21. The use of a tablet according to any one of claims 1 to 4 in 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 medicament is not administered (1 week off), and repeating this cycle of 3 weeks on, 1 week off.

22. The use of a tablet according to any one of claims 1 to 4 in 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 medicament is not administered (1 week off), and repeating this cycle of 1 week on, 1 week off.

23. The use of a tablet according to any one of claims 1 to 4 in the manufacture of a medicament for the treatment of cancer, wherein the medicament is to be administered daily.

24. The use according to claim 23, wherein the medicament is to be administered once daily.

25. The use according to any one of claims 21 to 24,
   i. wherein the daily dose is 6 mg of N-(3,5-dimethoxyphenyl)-N'-(1-methylethyl)-N-[3-(1-methyl-1H-pyrazol-4-yl)quinoxalin-6-yl]ethane-1,2-diamine;
   ii. wherein the daily dose is 7 mg of N-(3,5-dimethoxyphenyl)-N'-(1-methylethyl)-N-[3-(1-methyl-1H-pyrazol-4-yl)quinoxalin-6-yl]ethane-1,2-diamine;
   iii. wherein the daily dose is 8 mg of N-(3,5-dimethoxyphenyl)-N'-(1-methylethyl)-N-[3-(1-methyl-1H-pyrazol-4-yl)quinoxalin-6-yl]ethane-1,2-diamine; or
   iv. wherein the daily dose is 9 mg of N-(3,5-dimethoxyphenyl)-N'-(1-methylethyl)-N-[3-(1-methyl-1H-pyrazol-4-yl)quinoxalin-6-yl]ethane-1,2-diamine.

26. The use according to any one of claims 21 to 25,
   i. wherein the cancer is bladder cancer;
   ii. wherein the cancer is urothelial cancer;
   iii. wherein the cancer is metastatic urothelial cancer;
   iv. wherein the cancer is surgically unresectable urothelial cancer;
   v. wherein the cancer is cholangiocarcinoma; or
   vi. wherein the cancer is non-muscle-invasive bladder cancer.

27. The use according to claim 26, wherein the cancer is urothelial cancer.

28. The use according to claim 26, wherein the cancer is metastatic urothelial cancer.

29. The use according to claim 26, wherein the cancer is surgically unresectable urothelial cancer.

30. The use according to claim 26, wherein the cancer is non-muscle-invasive bladder cancer.

31. The use according to any one of claims 26, parts (ii) to (vi), to 30, wherein the cancer is a cancer with FGFR genomic alterations, in particular wherein the FGFR genomic alterations are translocations, fusions and/or mutations.

32. The use according to claim 31, wherein the alteration is a FGFR3-TACC3 translocation.

33. The use according to claim 31, wherein the alteration is a mutation.

34. The use according to claim 33, wherein the mutation is R248C or wherein the mutation is S249C.

35. The use according to any one of claims 21 to 25 wherein the cancer is mediated by a FGFR kinase.