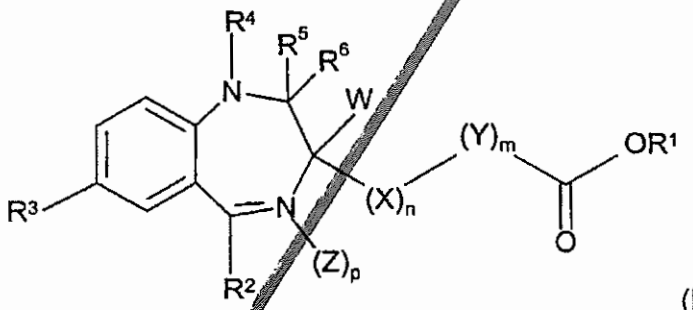
KÖNIG · SZYNKA · TILMANN · von RENESSE

PATENTANWÄLTE · PARTNERSCHAFT mbB

PCT/EP2013/060543 54 432 K
PAION UK LIMITED July 29, 2014

Amended Claims (clean copy)

1. A lyophilized or spray-dried composition comprising at least one benzodiazepine according to formula (I)



(I)

with
W is H;
X is CH_2; n is 1;
Y is CH_2; m is 1;
Z is O; p is 0 or 1;
R^1 is CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$ or $CH_2CH(CH_3)_2$;
R^2 is 2-fluorophenyl, 2-chlorophenyl or 2-pyridyl;
R^3 is Cl or Br;
R^4, R^5 and R^6 form the group-CR^8=U-V= wherein R^8 is hydrogen, C_{1-4} alkyl or C_{1-3} hydroxyalkyl, U is N or CR^9 wherein R^9 is H, C_{1-4} alkyl, C_{1-3} hydroxyalkyl or C_{1-4} alkoxy, V is N or CH and p is zero.

or a pharmaceutically acceptable salt thereof, wherein the composition comprises at least one pharmaceutically acceptable hygroscopic excipient, wherein the hygroscopic excipient is a carbohydrate selected from the group consisting of disaccharides and dextran and optionally the composition is at least in part amorphous.

2. A composition according to claim 1 , wherein p is zero and R^4, R^5 and R^6 form the group $-CR^8=U-V=$ wherein R^8 is methyl, U is CH_2, V is N;
W is H; X is CH_2, n is 1; Y is CH_2, m is 1;
R^1 is CH_3; R^2 is 2-pyridyl; R^3 is Br.

3. A composition according to claim 1 or 2, wherein the benzodiazepine is in the form of a pharmaceutically acceptable salt.

4. A composition according to any of the preceding claims, wherein in the pharmaceutically acceptable salt the benzodiazepine is formulated in cationic form and the counter ion is selected from halogenides, in particular fluoride, chloride or bromide, sulfate, organic sulfates, sulfonate, organic sulfonates, nitrate, phosphate, salicylate, tartrate, citrate, maleate, formiate, malonate, succinate, isethionate, lactobionate and sulfamate.

5. A composition according to claim 4, wherein the counter ion is selected from organic sulfates and sulfonates, in particular aromatic sulfates and sulfonates.

6. A composition according to claim 5, wherein the counter ion is benzene sulfonate (besylate).

7. A composition according to claim 5, wherein the benzodiazepine salt is remimazolam besylate.

8. A composition according to claim 5, wherein the benzodiazepine salt is a tosylate, in particular remimazolam tosylate.

9. A composition according to claim 5, wherein the bezodiazepine salt is an esylate, in particular remimazolam esylate.

10. A composition according to any of the preceding claims, wherein the carbohydrate possesses a molecular weight of less than 150 kD.

11. A composition according to claim 10, wherein the carbohydrate is a dextran molecule.

12. A composition according to claim 10, wherein the carbohydrate is selected from monosaccharides and C_{2-6}-oligosaccharides.

13. A composition according to claim 12, wherein the carbohydrate is a disaccharide, preferably selected from the group consisting of lactose, maltose, sucrose and trehalose.

14. A composition according to any of the preceding claims, wherein the composition comprises a mixture of a first hygroscopic excipient and a second hygroscopic excipient.

15. A composition according to claim 14, wherein the first excipient is a disaccharide.

16. A composition according to claim 15, wherein the disaccharide is selected form the list consisting of lactose, maltose, sucrose and trehalose.

17. A composition according to claim 14 to 16, wherein the second excipient is polymer, preferably a polysaccharide or organic polymer.

18. A composition according to claim 17, wherein the polysaccharide is dextran, preferably with a molecular weight of 80 KD or less.

19. A composition according to any of the claims 14 to 18, wherein the wt% ratio of the first excipient and the second excipient is from 20:1 to 1:10, preferably from 5:1 to 1:5 and more preferably 1:1.5 or 1:4.

20. A composition according to any of the preceding claims, wherein the composition is solid, preferably lyophilized and comprises a mixture of lactose and dextran.

21. A composition according to claim 20, wherein the wt% ratio between lactose and dextran is from 1:1.0 to 1:10, preferably from 1:1.2 to 1:5, and more preferably is 1:1.5 or 1:4.

22. A composition according to any of the preceding claims wherein the wt% ratio between the total amount of excipients and the total amount of benzodiazepines or salts, calculated for the base, in the composition is at least 1:1, preferably between 9:1 and 4.5 :1, most preferably 6:1.

23. A composition according to claim 22, wherein the excipients are carbohydrates and the benzodiazepine is remimazolam.

24. A composition according to any of the preceding claims wherein the wt% ratio between the total amount of hygroscopic excipients and the total amount of

benzodiazepines or salts thereof, calculate for the base, in the composition is from 20:1 to 1:1, preferably from 12:1 to 3:1, most preferably from 9:1 to 3:1.

25. A composition according to any of the preceding claims, wherein the composition is in the solid state and is preferably a lyophilized solid.

26. A composition according to any of the preceding claims, wherein said composition comprises a compound with a collapse temperature above -20°C (collapse temperature modifier).

27. A composition according to claim 26, wherein the collapse temperature modifier is selected from the group consisting of a sucrose-epichlorhydrin-copolymer, being preferably Ficoll®, gelatine and hydroxyethyl starch (HES), preferred is HES.

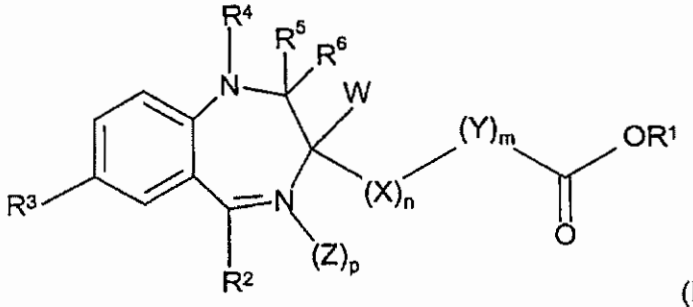
28. A composition according to any of the above claims, wherein the benzodiazepine or the salt thereof is amorphous for at least 50%, preferably for at least 75%, more preferably for at least 90% and most preferably for at least 95%.

29. A composition of any of the above claims which is a pharmaceutical formulation.

30. Pharmaceutical composition according claim 29 comprising a benzodiazepine or a salt thereof according to any of the above claims in an amount from 5 to 50% and at least one hygroscopic carbohydrate in an amount from 50% to 95%.

31. The composition according to any of the preceding claims, wherein the benzodiazepine is remimazolam, and the hygroscopic excipient is selected from the group consisting of lactose, maltose, sucrose, trehalose and dextran.

32. A stable lyophilized or stable freeze-dried composition comprising at least one benzodiazepine according to formula (I)



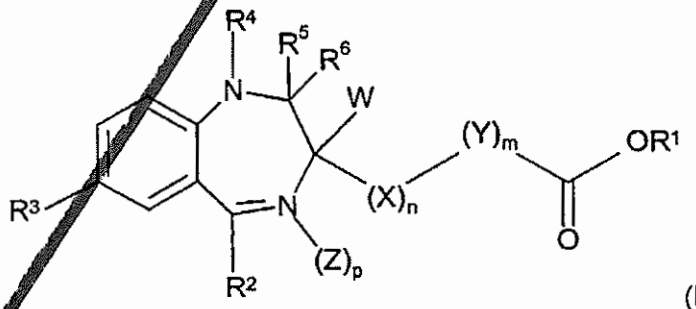
(I)

with
W is H;
X is CH_2; n is 1;
Y is CH_2; m is 1;
Z is O; p is 0 or 1;
R^1 is CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$ or $CH_2CH(CH_3)_2$;
R^2 is 2-fluorohenyl, 2-chlorophenyl or 2-pyridyl;
R^3 is Cl or Br;
R^4, R^5 and R^6 form the group-CR^8=U-V= wherein R^8 is hydrogen, C_{1-4} alkyl or C_{1-3} hydroxyalkyl, U is N or CR^9 wherein R^9 is H, C_{1-4} alkyl, C_{1-3} hydroxyalkyl or C_{1-4} alkoxy, V is N or CH and p is zero.

or a pharmaceutically acceptable salt thereof, wherein the composition

comprises at least one pharmaceutically acceptable hygroscopic excipient, wherein the hygroscopic excipient is a carbohydrate and optionally the composition is at least in part amorphous.

33. A composition comprising at least one benzodiazepine according to formula (I)



(I)

with
W is H;
X is CH_2; n is 1;
Y is CH_2; m is 1;
Z is O; p is 0 or 1;
R^1 is CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$ or $CH_2CH(CH_3)_2$;
R^2 is 2-fluorohenyl, 2-chlorophenyl or 2-pyridyl;
R^3 is Cl or Br;

R^4, R^5 and R^6 form the group-CR^8=U-V= wherein R^8 is hydrogen, C_{1-4} alkyl or C_{1-3} hydroxyalkyl, U is N or CR^9 wherein R^9 is H, C_{1-4} alkyl, C_{1-3} hydroxyalkyl or C_{1-4} alkoxy, V is N or CH and p is zero.

or a pharmaceutically acceptable salt thereof, wherein the composition

comprises at least one pharmaceutically acceptable hygroscopic excipient, wherein the hygroscopic excipient is a carbohydrate and optionally the composition is at least in part amorphous and

upon lyophilization or freeze-drying yields a stable lyophilized or stable freeze-dried composition.

34. The composition according to any of claims 32 or 33, wherein the stable composition is a composition in which less than 1% of the carboxylic ester moiety of the benzodiazepine is hydrolysed during storage for 13 weeks at storage conditions of 40°C and 75% relative humidity.

35. The composition according to any of claims 32 to 34, wherein the hygroscopic excipient is a substance which at 25°C and 1013.25 hPa reversibly binds water molecules.

36. Use of a mixture of at least one disaccharide and at least one dextran for preparing a pharmaceutical composition comprising a benzodiazepine with a carboxylic acid ester moiety as referred to in claim 1 or a pharmaceutically acceptable salt thereof, in particular remimazolam.

37. Method of preparing a pharmaceutical composition comprising the steps of

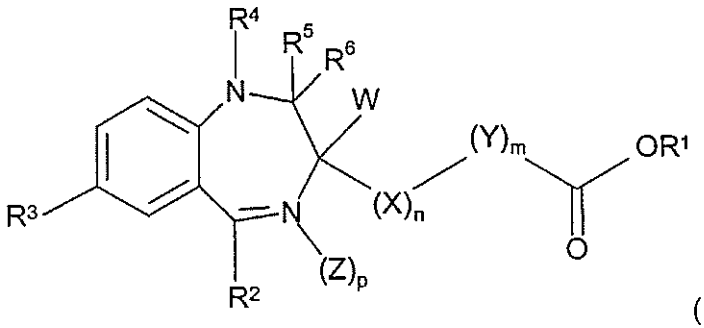
a) providing a solution comprising a benzodiazepine as referred to in claim 1;

b) adding at least one hygroscopic excipient, which is a carbohydrate selected from the group consisting of disaccharides and dextran or a mixture thereof with at least another hygroscopic excipient;

c) drying the solution from step b) by lyophilization or spray-drying.

CLAIMS

1. A lyophilized or spray-dried composition comprising at least one benzodiazepine according to formula (I)



(I)

with
W is H;
X is CH_2; n is 1;
Y is CH_2; m is 1;
Z is O; p is 0 or 1;
R^1 is CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$ or $CH_2CH(CH_3)_2$;
R^2 is 2-fluorophenyl, 2-chlorophenyl or 2-pyridyl;
R^3 is Cl or Br;
R^4, R^5 and R^6 form the group-CR^8=U-V= wherein R^8 is hydrogen, C_{1-4} alkyl or C_{1-3} hydroxyalkyl, U is N or CR^9 wherein R^9 is H, C_{1-4} alkyl, C_{1-3} hydroxyalkyl or C_{1-4} alkoxy, V is N or CH and p is zero.

or a pharmaceutically acceptable salt thereof, wherein the composition

comprises at least one pharmaceutically acceptable hygroscopic excipient, wherein the hygroscopic excipient is a carbohydrate selected from the group consisting of disaccharides and dextran and optionally the composition is at least in part amorphous.

2. A composition according to claim 1, wherein the benzodiazepine according to formula (I) is methyl 3-[(4S)-8-bromo-1-methyl-6-(pyridin-2-yl)-4H-imidazo[1,2-a][1,4]benzodiazepin-4-yl]propanoate (remimazolam).

3. A composition according to claim 2, wherein in the pharmaceutically acceptable salt of the benzodiazepine is formulated in cationic form and the counter ion is benzene sulfonate (besylate).

4. A composition according to any of claims 1 to 3, wherein the dextran possesses a molecular weight of less than 150 kD.

5. A composition according to any of claims 1 to 3, wherein the disaccharide is selected from the group consisting of lactose, maltose, sucrose and trehalose.

6. A composition according to any of claims 1 to 3, wherein the composition comprises a mixture of a first hygroscopic excipient and a second hygroscopic excipient.

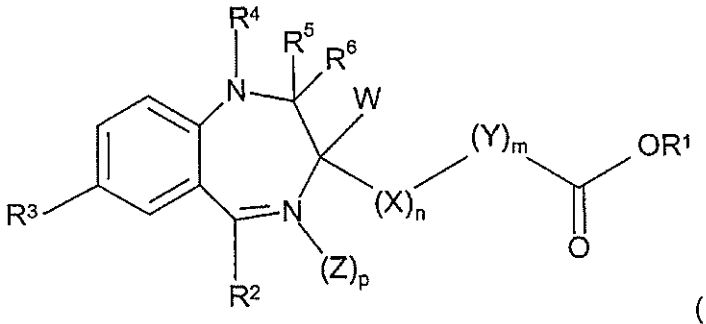
7. A composition according to claim 6, wherein the composition comprises a mixture of a disaccharide and dextran, preferably a mixture of lactose and dextran.

8. A composition according to claim 7, wherein the wt% ratio between lactose and dextran is from 1:1.0 to 1:10, preferably from 1:1.2 to 1:5, and more preferably is 1:1.5 or 1:4.

9. A composition according to any of claims 1 to 3, wherein the wt% ratio between the total amount of hygroscopic excipients and the total amount of benzodiazepines or salts thereof, calculated for the base, in the composition is from 20:1 to 1:1, preferably from 12:1 to 3:1, most preferably from 9:1 to 3:1.

10. A composition according to any of claims 1 to 3, which is a pharmaceutical formulation.

11. A stable lyophilized or stable freeze-dried composition comprising at least one benzodiazepine according to formula (I)



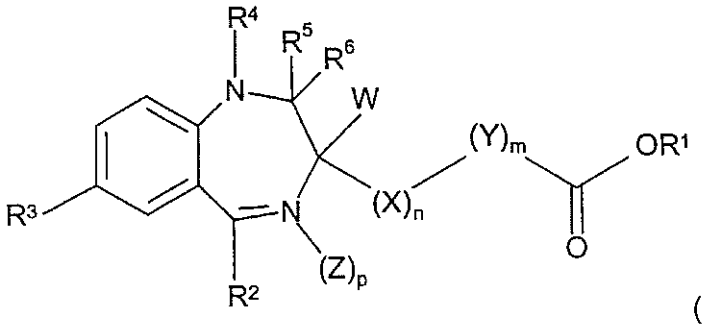
(I)

with
W is H;
X is CH_2; n is 1;
Y is CH_2; m is 1;
Z is O; p is 0 or 1;
R^1 is CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$ or $CH_2CH(CH_3)_2$;

R^2 is 2-fluorohenyl, 2-chlorophenyl or 2-pyridyl;
R^3 is Cl or Br;
R^4, R^5 and R^6 form the group-CR^8=U-V= wherein R^8 is hydrogen, C_{1-4} alkyl or C_{1-3} hydroxyalkyl, U is N or CR^9 wherein R^9 is H, C_{1-4} alkyl, C_{1-3} hydroxyalkyl or C_{1-4} alkoxy, V is N or CH and p is zero.

or a pharmaceutically acceptable salt thereof, wherein the composition
comprises at least one pharmaceutically acceptable hygroscopic excipient, wherein the hygroscopic excipient is a carbohydrate and optionally the composition is at least in part amorphous.

12. A composition comprising at least one benzodiazepine according to formula (I)



(I)

with
W is H;
X is CH_2; n is 1;
Y is CH_2; m is 1;
Z is O; p is 0 or 1;
R^1 is CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$ or $CH_2CH(CH_3)_2$;
R^2 is 2-fluorohenyl, 2-chlorophenyl or 2-pyridyl;
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R^4, R^5 and R^6 form the group-CR^8=U-V= wherein R^8 is hydrogen, C_{1-4} alkyl or C_{1-3} hydroxyalkyl, U is N or CR^9 wherein R^9 is H, C_{1-4} alkyl, C_{1-3} hydroxyalkyl or C_{1-4} alkoxy, V is N or CH and p is zero.

or a pharmaceutically acceptable salt thereof, wherein the composition
comprises at least one pharmaceutically acceptable hygroscopic excipient, wherein the hygroscopic excipient is a carbohydrate and optionally the composition is at least in part amorphous and
upon lyophilization or freeze-drying yields a stable lyophilized or stable freeze-dried composition.

13. The composition according to claim 11 or 12, wherein the stable composition is a composition in which less than 1% of the carboxylic ester moiety of the benzodiazepine is hydrolysed during storage for 13 weeks at storage conditions of 40°C and 75% relative humidity.

14. The composition according to claim 11 or 12, wherein the hygroscopic excipient is a substance which at 25°C and 1013.25 hPa reversibly binds water molecules.

15. Use of a mixture of at least one disaccharide and at least one dextran for preparing a pharmaceutical composition comprising a benzodiazepine with a carboxylic acid ester moiety as referred to in claim 1 or a pharmaceutically acceptable salt thereof, in particular remimazolam.

16. Method of preparing a pharmaceutical composition comprising the steps of
    a) providing a solution comprising a benzodiazepine as referred to in claim 1 or a pharmaceutically acceptable salt thereof, in particular remimazolam;
    b) adding at least one hygroscopic excipient, which is a carbohydrate selected from the group consisting of disaccharides and dextran or a mixture thereof with at least another hygroscopic excipient;
    c) drying the solution from step b) by lyophilization or spray-drying.