

CLAIMS

1. A composition for manufacturing a spray-dried dispersion, the composition comprising 4-chloro-5-(4-(4-fluoro-2-(trifluoromethyl)phenoxy)-5,8-dihydropyrido[3,4-d]pyrimidin-7(6H)-yl)pyridazin-3(2H)-one; a solvent; and hypromellose acetate succinate~~a polymer~~; wherein the hypromellose acetate succinate~~polymer~~ is dissolved in the solvent.
- ~~2. The composition of claim 1, wherein the 4-chloro-5-(4-(4-fluoro-2-(trifluoromethyl)phenoxy)-5,8-dihydropyrido[3,4-d]pyrimidin-7(6H)-yl)pyridazin-3(2H)-one is in an amorphous form.~~
- ~~3. The composition of claim 1 or 2, wherein the polymer is hypromellose acetate succinate.~~
- ~~4.2.~~ 2. The composition of ~~claim 3~~claim 1, wherein the ratio of 4-chloro-5-(4-(4-fluoro-2-(trifluoromethyl)phenoxy)-5,8-dihydropyrido[3,4-d]pyrimidin-7(6H)-yl)pyridazin-3(2H)-one to hypromellose acetate succinate is between ~~about 1:9 and about 2:1.~~
- ~~5.3.~~ 3. The composition of claim 1 or 2, wherein the ratio of 4-chloro-5-(4-(4-fluoro-2-(trifluoromethyl)phenoxy)-5,8-dihydropyrido[3,4-d]pyrimidin-7(6H)-yl)pyridazin-3(2H)-one to hypromellose acetate succinate is about 1:3.
- ~~6.4.~~ 4. The composition of any one of claims 1-3~~claim 4 or 5~~, wherein the hypromellose acetate succinate has an acetyl content of ~~about 5-14%~~, a succinoyl content of ~~about 4-18%~~, a methoxyl content of ~~about 20-26%~~, and a hydroxypropoxy content of ~~about 5-10%~~.
- ~~7.5.~~ 5. The composition of any one of claims 1-3~~claim 6~~, wherein the hypromellose acetate succinate has an acetyl content of ~~about 7-12%~~, a succinoyl content of ~~about 7-15%~~, a methoxyl content of ~~about 21-25%~~, and a hydroxypropoxy content of ~~about 5-9%~~.

~~8.6.~~ 6. The composition of any one of claims ~~1-75~~, wherein the solvent is acetone, methyl ethylketone, ethyl acetate, isopropyl alcohol, dioxane, acetonitrile, ethanol, water, methanol, dichloromethane, tetrahydrofuran, or a combination of any of them.

~~9.7.~~ 7. The composition of claim ~~86~~, wherein the solvent is a combination of methanol and dichloromethane.

~~10.8.~~ 8. The composition of claim ~~97~~, wherein the ratio of dichloromethane to methanol is ~~about~~ 30:70 to ~~about~~ 60:40.

~~11.9.~~ 9. The composition of claim ~~108~~, wherein the ratio of dichloromethane to methanol is about 60:40.

~~12.10.~~ 10. A method of manufacturing a spray-dried dispersion, comprising the step of spray-drying the composition of any one of claims ~~1-119~~.

~~13.11.~~ 11. The method of claim ~~1210~~, wherein the temperature of a nozzle through which the composition is spray-dried is between ~~about~~ 20°C and ~~about~~ 60 °C.

~~14.12.~~ 12. The method of claim ~~1311~~, wherein the temperature of the nozzle is between ~~about~~ 35 °C and ~~about~~ 40 °C.

~~15.13.~~ 13. The method of any one of claims ~~1210-1412~~, wherein the step of spray drying is performed at an atomization pressure of between ~~about~~ 1.0 and ~~about~~ 10.0 bars.

~~16.14.~~ 14. The method of claim ~~1513~~, wherein the step of spray drying is performed at an atomization pressure of between ~~about~~ 2.0 and ~~about~~ 4.0 bars.

~~17.15.~~ 15. A spray-dried dispersion comprising 4-chloro-5-(4-(4-fluoro-2-(trifluoromethyl)phenoxy)-5,8-dihydropyrido[3,4-d]pyrimidin-7(6H)-yl)pyridazin-3(2H)-one; a solvent; and a hypromellose acetate succinate polymer; wherein the polymer is dissolved in the

solvent.

~~18.~~16. The spray-dried dispersion of claim ~~17~~15, wherein the 4-chloro-5-(4-(4-fluoro-2-(trifluoromethyl)phenoxy)-5,8-dihydropyrido[3,4-d]pyrimidin-7(6H)-yl)pyridazin-3(2H)-one is in an amorphous form.

~~19.~~ The spray-dried dispersion of claim ~~17~~ or ~~18~~, wherein the polymer is hypromellose acetate succinate.

~~20.~~17. The spray-dried dispersion of ~~claim 19~~claim 15 or 16, wherein the ratio of 4-chloro-5-(4-(4-fluoro-2-(trifluoromethyl)phenoxy)-5,8-dihydropyrido[3,4-d]pyrimidin-7(6H)-yl)pyridazin-3(2H)-one to hypromellose acetate succinate is between ~~about 1:9~~ and ~~about 2:1~~.

~~21.~~18. The spray-dried dispersion of ~~claim 20~~any one of claims 15-17, wherein the ratio of 4-chloro-5-(4-(4-fluoro-2-(trifluoromethyl)phenoxy)-5,8-dihydropyrido[3,4-d]pyrimidin-7(6H)-yl)pyridazin-3(2H)-one to hypromellose acetate succinate is about 1:3.

~~22.~~19. The spray-dried dispersion of ~~claim 20 or 21~~any one of claims 15-18, wherein the hypromellose acetate succinate has an acetyl content of ~~about 5-14%~~, a succinoyl content of ~~about 4-18%~~, a methoxyl content of ~~about 20-26%~~, and a hydroxypropoxy content of ~~about 5-10%~~.

~~23.~~20. The spray-dried dispersion of ~~any one of claims 15-19~~claim 22, wherein the hypromellose acetate succinate has an acetyl content of ~~about 5-11%~~, a succinoyl content of ~~about 10-18%~~, a methoxyl content of ~~about 20-25%~~, and a hydroxypropoxy content of ~~about 5-9%~~.

~~24.~~ The spray-dried dispersion of ~~any one of claims 17-23~~, wherein the solvent is acetone, methyl ethylketone, ethyl acetate, isopropyl alcohol, dioxane, acetonitrile, ethanol, water, methanol, dichloromethane, tetrahydrofuran, or a combination of any of them.

~~25.~~—The spray dried dispersion of claim ~~24~~, wherein the solvent is a combination of methanol and dichloromethane.

~~26.~~—The spray dried dispersion of claim ~~25~~, wherein the ratio of dichloromethane to methanol is about 30:70 to about 60:40.

~~27.~~ The spray dried dispersion of claim ~~26~~, wherein the ratio of dichloromethane to methanol is about 60:40.

~~28.~~21. A solid dosage form comprising the spray-dried dispersion of any one of claims ~~17~~15-20~~7~~, and one or more of a filler, a disintegrant, a lubricant, a glidant, and a stabilizer.

~~29.~~22. The solid dosage form of claim ~~28~~21, wherein the filler comprises one or more of mannitol, lactose, or microcrystalline cellulose.

~~30.~~23. The solid dosage form of claim ~~29~~22, wherein the filler comprises mannitol and microcrystalline cellulose.

~~31.~~24. The solid dosage form of claim ~~30~~23, wherein the ratio of mannitol to microcrystalline cellulose is between ~~about~~ 1:3 and ~~about~~ 3:1.

~~32.~~25. The solid dosage form of claim ~~31~~24, wherein the ratio of mannitol to microcrystalline cellulose is ~~about~~ 1:1 to ~~about~~ 1:1.3.

~~33.~~26. The solid dosage form of any one of claims ~~28~~21-~~32~~25, wherein the average particle size of the microcrystalline cellulose is between ~~about~~ 5 µm and ~~about~~ 80 µm.

~~34.~~27. The solid dosage form of claim ~~33~~26, wherein the average particle size of the microcrystalline cellulose is between ~~about~~ 10 µm and ~~about~~ 50 µm.

~~35.28.~~ The solid dosage form of any one of claims ~~2821-3427~~, wherein the disintegrant is croscarmellose sodium.

~~36.29.~~ The solid dosage form of claim ~~3528~~, wherein the croscarmellose sodium is present at between ~~about~~ 3% and ~~about~~ 15% w/w.

~~37.30.~~ The solid dosage form of claim ~~3629~~, wherein the croscarmellose sodium is present at about 6% w/w.

~~38.31.~~ The solid dosage form of any one of claims ~~2821-3730~~, wherein the lubricant is stearyl fumarate sodium.

~~39.32.~~ The solid dosage form of claim ~~3831~~, wherein the stearyl fumarate sodium is present at between ~~about~~ 0.5 and ~~about~~ 5% w/w.

~~40.33.~~ The solid dosage form of claim ~~3932~~, wherein the stearyl fumarate sodium is present at about 1% w/w or about 0.95% w/w.

~~41.34.~~ The solid dosage form of any one of claims ~~2821-4033~~, wherein the glidant is colloidal silicon dioxide.

~~42.35.~~ The solid dosage form of claim ~~4134~~, wherein the silicon dioxide is present at between ~~about~~ 0.1 to ~~about~~ 5% w/w.

~~43.36.~~ The solid dosage form of claim ~~4134~~, wherein the silicon dioxide is present at ~~between~~ about 1% w/w.

~~44.37.~~ The solid dosage form of any one of claims ~~2821-4336~~, wherein the spray-dried dispersion is present at between ~~about~~ 3% to ~~about~~ 60% w/w.

~~45.38.~~ The solid dosage form of claim ~~4437~~, wherein the spray-dried dispersion is present at about 50% w/w.

~~46.39.~~ The solid dosage form of claim ~~4437~~, wherein the spray-dried dispersion is present at about 16.7% w/w.

~~47.40.~~ The solid dosage form of claim ~~4437~~, wherein the spray-dried dispersion is present at about 3.33% w/w.

~~48.41.~~ The solid dosage form of any one of claims ~~2821-4740~~, wherein the 4-chloro-5-(4-(4-fluoro-2-(trifluoromethyl)phenoxy)-5,8-dihydropyrido[3,4-d]pyrimidin-7(6H)-yl)pyridazin-3(2H)-one is present at ~~about~~ 0.75%-15% w/w.

~~49.42.~~ The solid dosage form of claim ~~2821~~, consisting essentially of:

- a. 4-chloro-5-(4-(4-fluoro-2-(trifluoromethyl)phenoxy)-5,8-dihydropyrido[3,4-d]pyrimidin-7(6H)-yl)pyridazin-3(2H)-one;
- b. hypromellose acetate succinate;
- c. mannitol;
- d. microcrystalline cellulose;
- e. croscarmellose sodium;
- f. stearyl fumarate sodium; and
- g. colloidal silicon dioxide.

~~50.43.~~ The solid dosage form of claim ~~4942~~, consisting essentially of:

- a. 0.75%-40.0% (w/w) 4-chloro-5-(4-(4-fluoro-2-(trifluoromethyl)phenoxy)-5,8-dihydropyrido[3,4-d]pyrimidin-7(6H)-yl)pyridazin-3(2H)-one;
- b. 2.0%-54.0% (w/w) hypromellose acetate succinate;
- c. 3.75%-42.3% (w/w) mannitol;
- d. 3.75%-50.0% (w/w) microcrystalline cellulose;
- e. 3.0%-15% (w/w) croscarmellose sodium;
- f. 0.5%-5.0% (w/w) stearyl fumarate sodium; and

g. 0.1%-5.0% (w/w) colloidal silicon dioxide,

wherein:

the ratio of 4-chloro-5-(4-(4-fluoro-2-(trifluoromethyl)phenoxy)-5,8-dihydropyrido[3,4-d]pyrimidin-7(6H)-yl)pyridazin-3(2H)-one to hypromellose acetate succinate is between 1:9 and 2:1;

the sum of the amounts of 4-chloro-5-(4-(4-fluoro-2-(trifluoromethyl)phenoxy)-5,8-dihydropyrido[3,4-d]pyrimidin-7(6H)-yl)pyridazin-3(2H)-one and hypromellose acetate succinate is between 3% and 60% w/w of the solid dosage form;

the ratio of mannitol to microcrystalline cellulose is between 1:3 and 3:1; and

the sum of the amounts of mannitol and microcrystalline cellulose is between 15.0 and 90% w/w of the solid dosage form.

51.44. The solid dosage form of claim ~~50~~43, consisting essentially of:

- a. 20 mg of 4-chloro-5-(4-(4-fluoro-2-(trifluoromethyl)phenoxy)-5,8-dihydropyrido[3,4-d]pyrimidin-7(6H)-yl)pyridazin-3(2H)-one;
- b. 60 mg of hypromellose acetate succinate;
- c. 33.6 mg of mannitol;
- d. 33.6 mg of microcrystalline cellulose;
- e. 9.6 mg of croscarmellose sodium;
- f. 1.6 mg stearyl fumarate sodium; and
- g. 1.6 mg colloidal silicon dioxide.

52.45. The solid dosage form of claim ~~50~~43, consisting essentially of:

- a. 100 mg of 4-chloro-5-(4-(4-fluoro-2-(trifluoromethyl)phenoxy)-5,8-dihydropyrido[3,4-d]pyrimidin-7(6H)-yl)pyridazin-3(2H)-one;
- b. 300 mg of hypromellose acetate succinate;
- c. 168 mg of mannitol;
- d. 168 mg of microcrystalline cellulose;
- e. 48 mg of croscarmellose sodium;
- f. 8 mg stearyl fumarate sodium; and

- g. 8 mg colloidal silicon dioxide.

~~53.46.~~ The solid dosage form of claim ~~5043~~, consisting essentially of:

- a. 5 mg of 4-chloro-5-(4-(4-fluoro-2-(trifluoromethyl)phenoxy)-5,8-dihydropyrido[3,4-d]pyrimidin-7(6H)-yl)pyridazin-3(2H)-one;
- b. 15 mg of hypromellose acetate succinate;
- c. 39.2 mg of mannitol;
- d. 51.2 mg of microcrystalline cellulose;
- e. 7.2 mg of croscarmellose sodium;
- f. 1.1 mg of stearyl fumarate sodium; and
- g. 1.2 mg of colloidal silicon dioxide.

~~54.47.~~ The solid dosage form of claim ~~5043~~, consisting of:

- a. 1 mg of 4-chloro-5-(4-(4-fluoro-2-(trifluoromethyl)phenoxy)-5,8-dihydropyrido[3,4-d]pyrimidin-7(6H)-yl)pyridazin-3(2H)-one;
- b. 3 mg of hypromellose acetate succinate;
- c. 47.2 mg of mannitol;
- d. 59.2 mg of microcrystalline cellulose;
- e. 7.2 mg of croscarmellose sodium;
- f. 1.1 mg of stearyl fumarate sodium; and
- g. 1.2 mg of colloidal silicon dioxide.

~~55.48.~~ The solid dosage form of any of claims ~~2821-5447~~, wherein the solid dosage form is a tablet.

~~56.49.~~ The solid dosage form of any of claims ~~2822-5447~~, wherein the solid dosage form is a capsule.

~~57.50.~~ The solid dosage form of claim ~~55-48~~ or ~~5649~~, wherein the amount of 4-chloro-5-(4-(4-fluoro-2-(trifluoromethyl)phenoxy)-5,8-dihydropyrido[3,4-d]pyrimidin-7(6H)-yl)pyridazin-

3(2H)-one in the tablet or capsule is ~~about~~ 1-200 mg.

~~58.51.~~ The solid dosage form of claim ~~5750~~, wherein the amount of 4-chloro-5-(4-(4-fluoro-2-(trifluoromethyl)phenoxy)-5,8-dihydropyrido[3,4-d]pyrimidin-7(6H)-yl)pyridazin-3(2H)-one in the tablet or capsule is about 5 mg.

~~59.52.~~ The solid dosage form of claim ~~5750~~, wherein the amount of 4-chloro-5-(4-(4-fluoro-2-(trifluoromethyl)phenoxy)-5,8-dihydropyrido[3,4-d]pyrimidin-7(6H)-yl)pyridazin-3(2H)-one in the tablet or capsule is about 20 mg.

~~60.53.~~ The solid dosage form of claim ~~5750~~, wherein the amount of 4-chloro-5-(4-(4-fluoro-2-(trifluoromethyl)phenoxy)-5,8-dihydropyrido[3,4-d]pyrimidin-7(6H)-yl)pyridazin-3(2H)-one in the tablet or capsule is about 100 mg.

~~61.54.~~ The solid dosage form of claim ~~5750~~, wherein the amount of 4-chloro-5-(4-(4-fluoro-2-(trifluoromethyl)phenoxy)-5,8-dihydropyrido[3,4-d]pyrimidin-7(6H)-yl)pyridazin-3(2H)-one in the tablet or capsule is about 1 mg.

~~62.55.~~ A method of manufacturing a solid dosage form of 4-chloro-5-(4-(4-fluoro-2-(trifluoromethyl)phenoxy)-5,8-dihydropyrido[3,4-d]pyrimidin-7(6H)-yl)pyridazin-3(2H)-one, comprising the steps of:

- a. blending a spray-dried dispersion of any one of claims ~~15-20~~~~17-27~~ with one or more of: a first filler, a first disintegrant, a first lubricant, a first glidant, and a first stabilizer to form a first solid mixture;
- b. roller compacting and milling the first solid mixture; and
- c. optionally blending the roller compacted and milled first solid mixture with one or more of a second filler, a second disintegrant, a second lubricant, a second glidant, and a second stabilizer to form a second solid mixture; and
- d. converting the first or the second solid mixture into the solid dosage form of 4-chloro-5-(4-(4-fluoro-2-(trifluoromethyl)phenoxy)-5,8-dihydropyrido[3,4-d]pyrimidin-

7(6H)-yl)pyridazin-3(2H)-one.

~~63.56.~~ The method of claim ~~6255~~, wherein:

the first and second filler are selected from mannitol, microcrystalline cellulose of a combination thereof;

the first and second disintegrant is croscarmellose sodium;

the first and second lubricant is sodium stearyl fumarate; and

the first and second glidant is silicon dioxide.

~~64.57.~~ The method of claim ~~6255~~, wherein in step c. the roller compacted and milled solid mixture is blended with a second filler, a second disintegrant and a second lubricant.

~~65.58.~~ The method of any one of claims ~~6255-6457~~, wherein the solid dosage form is a tablet formed by compressing the first solid mixture or the second solid mixture.

~~66.59.~~ The method of any one of claims ~~6255-6457~~, wherein the solid dosage form is a filled capsule formed by filling a capsule with the first solid mixture or the second solid mixture.

~~67.60.~~ Use of the spray-dried dispersion of any of claims ~~1715-2720~~ or solid dosage form of any one of claims ~~21-5428-61~~ in the preparation of a medicament for the treatment of a kidney disease or a nephropathy associated with a disease or condition.

~~68.61.~~ The use of claim ~~6760~~, wherein the kidney disease or the nephropathy associated with a disease or condition is Focal Segmental Glomerulosclerosis (FSGS), Diabetic nephropathy, Alport syndrome, hypertensive kidney disease, nephrotic syndrome, steroid-resistant nephrotic syndrome, minimal change disease, membranous nephropathy, idiopathic membranous nephropathy, membranoproliferative glomerulonephritis (MPGN), immune complex-mediated MPGN, complement-mediated MPGN, Lupus nephritis, postinfectious glomerulonephritis, thin basement membrane disease, mesangial proliferative glomerulonephritis, amyloidosis (primary), c1q nephropathy, rapidly progressive GN, anti-GBM disease, C3 glomerulonephritis, hypertensive nephrosclerosis, IgA nephropathy, IgG4 nephropathy, proteinuric kidney disease,

microalbuminuria, macroalbuminuria kidney disease, transplant-related FSGS, transplant-related nephrotic syndrome, transplant-related proteinuria, nodular glomerulonephritis, NASR disease (proliferative glomerulonephritis with monoclonal IgG deposits), polycystic kidney disease, autosomal dominant polycystic kidney disease (ADPKD), or a nephropathy associated with any one of obesity, insulin resistance, Type II diabetes, prediabetes, metabolic syndrome, dyslipidemia, pulmonary arterial hypertension, cancer, cholestatic liver disease, non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH) or Fabry's disease).

~~69-62.~~ The use of claim ~~68~~61, wherein the kidney disease or the nephropathy associated with a disease or condition is Focal Segmental Glomerulosclerosis (FSGS), Diabetic nephropathy, Alport syndrome, hypertensive kidney disease, obesity-related nephropathy, nephrotic syndrome, steroid-resistant nephrotic syndrome, minimal change disease, membranous nephropathy, membranoproliferative glomerulonephritis (MPGN), Lupus nephritis, postinfectious glomerulonephritis, thin basement membrane disease, mesangial proliferative glomerulonephritis, amyloidosis (primary), C1q nephropathy, anti-GBM disease, C3 glomerulonephritis, hypertensive nephrosclerosis, IgA nephropathy, IgG4 nephropathy, dyslipidemia-associated nephropathy, nodular glomerulonephritis, NASR disease (proliferative glomerulonephritis with monoclonal IgG deposits), polycystic kidney disease, or kidney complications due to Fabry's disease.

~~70-63.~~ The use of claim ~~69~~62, wherein the kidney disease is hypertensive nephropathy, a nephropathy associated with metabolic syndrome, a nephropathy associated with obesity, a nephropathy associated with dyslipidemia, diabetic nephropathy, nephrotic syndrome, FSGS, or minimal change disease.

~~71-64.~~ The use of claim ~~70~~63, wherein the kidney disease is diabetic nephropathy, FSGS, or minimal change disease.

~~72-65.~~ Use of the spray-dried dispersion of any one of claims ~~17~~15-27~~20~~ or the solid dosage form of any one of claims ~~28~~21-61~~54~~ in the preparation of a medicament for the treatment of pain, anxiety, or depression.