

CLAIMS

What is claimed is:

1. Use of zibotentan and dapagliflozin in the manufacture of a medicament for treating liver cirrhosis in a subject in need thereof, wherein a composition comprising a therapeutically effective amount of zibotentan and dapagliflozin is to be administered to the subject.
2. The use of claim 1, wherein the subject has features of portal hypertension.
3. The use of claim 1 or claim 2, wherein the subject has a hepatic venous pressure gradient (HVPG) greater than 5 mmHg.
4. The use of any one of claims 1 to 3, wherein the subject has an HVPG greater than 7.5 mmHg.
5. The use of any one of claims 1 to 4, wherein the subject has an HVPG greater than 10 mmHg.
6. The use of any one of claims 1 to 5, wherein the subject has at least one of oesophageal varices, splenomegaly, variceal hemorrhages, recurrent variceal hemorrhages, ascites, refractory ascites, hepatic encephalopathy, recurrent hepatic encephalopathy, lower extremity swelling, coagulopathy, pulmonary complications and portosystemic shunts.
7. The use of any one of claims 1 to 6, wherein the subject has a Child-Pugh score that equals to or is greater than 5.
8. The use of any one of claims 1 to 7, wherein the subject has a Child-Pugh score that equals to or is greater than 7.
9. The use of any one of claims 1 to 8, wherein the subject has a Child-Pugh score that equals to or is greater than 10.
10. The use of any one of claims 1 to 9, wherein the subject has a model for end-stage liver disease (MELD) score that equals to or is greater than 5.
11. The use of any one of claims 1 to 10, wherein the subject has an MELD score that equals

- to or is greater than 10.
12. The use of any one of claims 1 to 11, wherein the subject has an MELD score that equals to or is greater than 20.
 13. The use of any one of claims 1 to 12, wherein the subject has no decompensation events.
 14. The use of any one of claims 1 to 12, wherein the subject has decompensation events.
 15. The use of any one of claims 1 to 14, wherein the composition comprises about 0.1 mg to about 240 mg zibotentan.
 16. The use of any one of claims 1 to 15, wherein the composition comprises about 0.2 mg to about 50 mg zibotentan.
 17. The use of any one of claims 1 to 16, wherein the composition comprises about 0.5 mg to about 20 mg zibotentan.
 18. The use of any one of claims 1 to 17, wherein the composition comprises about 1 mg to about 10 mg zibotentan.
 19. The use of any one of claims 1 to 18, wherein the composition comprises about 1 mg zibotentan.
 20. The use of any one of claims 1 to 18, wherein the composition comprises about 2.5 mg zibotentan.
 21. The use of any one of claims 1 to 18, wherein the composition comprises about 5 mg zibotentan.
 22. The use of any one of claims 1 to 21, wherein the composition comprises about 0.1 mg to about 100 mg dapagliflozin.
 23. The use of any one of claims 1 to 22, wherein the composition comprises about 0.25 mg to about 50 mg dapagliflozin.
 24. The use of any one of claims 1 to 23, wherein the composition comprises about 1 mg to

about 10 mg dapagliflozin.

25. The use of any one of claims 1-24, wherein the composition comprises about 2.5 mg dapagliflozin.
26. The use of any one of claims 1-24, wherein the composition comprises about 5 mg dapagliflozin.
27. The use of any one of claims 1-24, wherein the composition comprises about 10 mg dapagliflozin.
28. The use of any one of claims 1 to 14, wherein the composition comprises about 1 mg zibotentan and about 2.5 mg dapagliflozin.
29. The use of any one of claims 1 to 14, wherein the composition comprises about 1 mg zibotentan and about 5 mg dapagliflozin.
30. The use of any one of claims 1 to 14, wherein the composition comprises about 2.5 mg zibotentan and about 2.5 mg dapagliflozin.
31. The use of any one of claims 1 to 14, wherein the composition comprises about 2.5 mg zibotentan and about 5 mg dapagliflozin.
32. The use of any one of claims 1 to 14, wherein the composition comprises about 2.5 mg zibotentan and about 10 mg dapagliflozin.
33. The use of any one of claims 1 to 14, wherein the composition comprises about 5 mg zibotentan and about 5 mg dapagliflozin.
34. The use of any one of claims 1 to 14, wherein the composition comprises about 5 mg zibotentan and about 10 mg dapagliflozin.
35. The use of any one of claims 1 to 34, wherein the zibotentan is in an oral dosage form.
36. The use of claim 35, wherein the oral dosage form is a capsule.
37. The use of any one of claims 1 to 36, wherein the dapagliflozin is in an oral dosage form.

38. The use of claim 37, wherein the oral dosage form is a tablet.
39. The use of any one of claims 1 to 34, wherein the composition is in an oral dosage form.
40. The use of claim 39, wherein the oral dosage form is a capsule or tablet.
41. The use of any one of claims 1 to 40, wherein the composition is to be administered to the subject once to three times daily.
42. The use of claim 41, wherein the composition is to be administered to the subject once daily.
43. The use of any one of claims 1 to 42, wherein the composition is to be administered to the subject at least once to three times daily for at least 3 weeks.
44. The use of any one of claims 1 to 42, wherein the composition is to be administered to the subject at least once to three times daily for at least 6 weeks.
45. The use of any one of claims 1 to 42, wherein the composition is to be administered to the subject at least once to three times daily for at least 12 weeks.
46. The use of any one of claims 1 to 42, wherein the composition is to be administered to the subject at least once to three times daily for at least 16 weeks.
47. The use of any one of claims 1 to 46,
wherein the subject has a hepatic venous pressure gradient (HVPG) response; and
wherein the HVPG is decreased at least 10% after administration of the composition to the subject relative to a baseline HVPG of the subject.
48. The use of claim 47, wherein the HVPG of the subject is decreased at least 20% after administration of the composition to the subject.
49. The use of claim 48, wherein the HVPG of the subject is decreased at least 25% after administration of the composition to the subject.
50. The use of claim 49, wherein the HVPG of the subject is decreased at least 40% after

administration of the composition to the subject.

51. The use of any one of claims 1 to 50,
 - wherein the subject has a hepatic venous pressure gradient (HVPG) response; and
 - wherein the HVPG is less than or equal to 12 mmHg after administration of the composition to the subject relative to a baseline HVPG of the subject.
52. The use of claim 51, wherein the HVPG of the subject is less than or equal to 10 mmHg after administration of the composition to the subject.
53. The use of claim 52, wherein the HVPG of the subject is less than or equal to 8 mmHg after administration of the composition to the subject.
54. The use of claim 53, wherein the HVPG of the subject is less than or equal to 5 mmHg after administration of the composition to the subject.
55. The use of any one of claims 1 to 54, wherein the subject has one or more of the following outcomes after administration of the composition to the subject:
 - (i) at least 5% decrease in body weight;
 - (ii) at least 5% reduction in body water volume;
 - (iii) at least 5% reduction in body fat mass;
 - (iv) systolic blood pressure is reduced to less than 130;
 - (v) diastolic blood pressure is reduced to less than 90; and
 - (vi) at least 5% reduction in accumulated additional loop-diuretic equivalents use.
56. The use of claim 55, wherein the subject has one or more of the following outcomes after administration of the composition to the subject:
 - (i) at least 10% decrease in body weight;
 - (ii) at least 10% reduction in body water volume;
 - (iii) at least 10% reduction in body fat mass;
 - (iv) systolic blood pressure is reduced to less than 120;
 - (v) diastolic blood pressure is reduced to less than 80; and
 - (vi) at least 10% reduction in accumulated additional loop-diuretic equivalents

use.

57. The use of claim 56, wherein the subject has one or more of the following outcomes after administration of the composition to the subject:

- (i) at least 15% decrease in body weight;
- (ii) at least 15% reduction in body water volume;
- (iii) at least 15% reduction in body fat mass;
- (iv) systolic blood pressure is reduced to less than 110;
- (v) diastolic blood pressure is reduced to less than 70; and
- (vi) at least 15% reduction in accumulated additional loop-diuretic equivalents

use.

58. The use of any one of claims 1 to 57, wherein the liver cirrhosis results from viral hepatitis, alcoholic liver disease, hepatic steatosis, non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), or combinations thereof.

59. The use of any one of claims 1 to 57, wherein the liver cirrhosis results from autoimmune hepatitis, primary sclerosing cholangitis, primary biliary cholangitis, haemochromatosis, Wilson's disease, biliary atresia, alpha-1-antitrypsin deficiency and cystic fibrosis related liver cirrhosis, or combinations thereof.

60. The use of any one of claims 1 to 59, wherein the subject is a human subject.

61. The use of claim 60, wherein the human subject is 18 years to 80 years of age.

62. An oral dosage form, comprising:

- a. about 0.25 mg to about 20 mg zibotentan;
- b. about 0.5 mg to about 40 mg dapagliflozin; and
- c. a pharmaceutical acceptable excipient.

63. The oral dosage form of claim 62, wherein the oral dosage form comprises about 0.5 mg to about 10 mg zibotentan, and about 1 mg to about 20 mg dapagliflozin.

64. The oral dosage form of claim 63, wherein the oral dosage form comprises about 1 mg to about 5 mg zibotentan, and about 2.5 mg to about 10 mg dapagliflozin.
65. The oral dosage form of claim 64, wherein the oral dosage form comprises about 1 mg zibotentan and about 2.5 mg dapagliflozin.
66. The oral dosage form of claim 64, wherein the oral dosage form comprises about 1 mg zibotentan and about 5 mg dapagliflozin.
67. The oral dosage form of claim 64, wherein the oral dosage form comprises about 2.5 mg zibotentan and about 2.5 mg dapagliflozin.
68. The oral dosage form of claim 64, wherein the oral dosage form comprises about 2.5 mg zibotentan and about 5 mg dapagliflozin.
69. The oral dosage form of claim 64, wherein the oral dosage form comprises about 2.5 mg zibotentan and about 10 mg dapagliflozin.
70. The oral dosage form of claim 64, wherein the oral dosage form comprises about 5 mg zibotentan and about 5 mg dapagliflozin.
71. The oral dosage form of claim 64, wherein the oral dosage form comprises about 5 mg zibotentan and about 10 mg dapagliflozin.
72. A kit comprising:
 - a. an oral dosage form comprising about 0.25 mg to about 20 mg zibotentan, and a pharmaceutically acceptable excipient; and
 - b. an oral dosage form comprising about 0.5 mg to about 40 mg dapagliflozin, and a pharmaceutically acceptable excipient.
73. A kit comprising:
 - a. an oral dosage form comprising about 2.5 mg zibotentan, and a pharmaceutically acceptable excipient; and
 - b. an oral dosage form comprising about 5 mg dapagliflozin, and a pharmaceutically acceptable excipient.

74. Use of zibotentan and dapagliflozin in the manufacture of a medicament for reducing the risk of variceal haemorrhage and/or death, or preventing and/or delaying progression of variceal haemorrhage and/or death, in a subject in need thereof, wherein a composition comprising a therapeutically effective amount of zibotentan and dapagliflozin is to be administered to the subject.
75. The use of claim 74, wherein the composition comprises about 0.25 mg to about 20 mg dapagliflozin and about 0.5 mg to about 10 mg zibotentan.
76. The use of claim 74, wherein the composition comprises about 1 mg, 2.5 mg, or 5 mg zibotentan, and about 2.5 mg, 5 mg, or 10 mg dapagliflozin.
77. Use of zibotentan and dapagliflozin in the manufacture of a medicament for reducing the risk of cirrhosis decompensation or preventing and/or delaying progression of cirrhosis decompensation, in a subject in need thereof, wherein a composition comprising a therapeutically effective amount of zibotentan and dapagliflozin is to be administered to the subject.
78. The use of claim 77, wherein the composition comprises about 0.25 mg to about 20 mg dapagliflozin and about 0.5 mg to about 10 mg zibotentan.
79. The use of claim 78, wherein the composition comprises about 1 mg, 2.5 mg, or 5 mg zibotentan, and about 2.5 mg, 5 mg, or 10 mg dapagliflozin.