CLAIMS

1. Use of levosimendan, its metabolites OR-1896 or OR-1855, or a combination thereof, in the manufacture of a medicament for treating Pulmonary Hypertension Heart Failure with preserved ejection fraction (PH-HFpEF) in a human subject afflicted with PH-HFpEF, wherein said levosimendan, its metabolites OR-1896 or OR-1855, or a combination thereof, is to be administered in an amount effective to treat the PH-HFpEF in the human subject.

2. The use of claim 1, wherein the treatment causes:

    a) a reduction in the human subject's pulmonary capillary wedge pressure at rest, preferably by 1 to 30 mmHg;

    b) a stabilization of the human subject's pulmonary capillary wedge pressure at rest at 5 to 35 mmHg or 10 to 35 mmHg;

    c) a reduction in the human subject's pulmonary capillary wedge pressure during exercise by the human subject, by 1 to 40 mmHg;

    d) stabilization of the human subject's pulmonary capillary wedge pressure during exercise by the human subject at 10 to 50 mmHg;

    e) the treating does not comprise a significant change in pulmonary capillary wedge pressure during exercise by the human subject;

    f) a reduction in the human subject's pulmonary capillary wedge pressure when the human subject's legs are elevated, wherein the reduction is 1 to 30 mmHg;

    g) stabilization of the human subject's pulmonary capillary wedge pressure when the human subject's legs are elevated, wherein the stabilization is at 10 to 50 mmHg;

    h) a reduction in the human subject's right atrial pressure at rest by 1 to 30 mmHg;

    i) stabilization of the human subject's right atrial pressure at rest at 1 to 30 mmHg or at 5 to 30 mmHg;

    j) a reduction in the human subject's right atrial pressure during exercise by the human subject by 1 to 30 mmHg;

    k) stabilization of the human subject's right atrial pressure during exercise by the human subject at 5 to 40 mmHg;

    l) a reduction in the human subject's right atrial pressure when the human subject's legs are elevated;

    m) a reduction in the human subject's mean pulmonary artery pressure at rest by 1 to 30 mmHg;

    n) stabilization of the human subject's mean pulmonary artery pressure at rest at 15 to 65 mmHg;

    o) a reduction in the human subject's mean pulmonary artery pressure during exercise by the human subject by 1 to 30 mmHg;

p) stabilization of the human subject's mean pulmonary artery pressure during exercise by the human subject at 25 to 85 mmHg or 25 to 80 mmHg;

q) a reduction in the human subject's mean pulmonary artery pressure when the human subject's legs are elevated;

r) an increase in the human subject's cardiac output at rest by 0.01 to 3 liters/min;

s) stabilization of the human subject's cardiac output at rest at 2 to 10 liters/min;

t) an increase in the human subject's cardiac output during exercise by the human subject;

u) an increase in the human subject's cardiac output during exercise by the human subject by 0.01 to 5 liters/min or by 0.01 to 4 liters/min or by at 3.0 to 15.0 liters/min;

v) does not comprise a significant increase in the human subject's heart rate or does not comprise an increase in the human subject's heart rate of more than 10 beats/min;

w) an improvement in the human subject's quality of life, wherein in (w), the improvement in the human subject's quality of life is measured by a patient reported outcome assessment tool and the improvement is a change in the human subject's patient reported outcome assessment tool score of at least 1;

x) an improvement in the human subject's six (6) minute walk distance of 5 to 150 meters;

y) an improvement in the physician's assessment of the human subject's functional class;

z) a reduction in the incidence of hospitalization for heart failure;

aa) a reduction in all-cause mortality; or

bb) an improvement in right heart failure and/or right ventricular dysfunction as evidenced by a reduction in right atrial pressure at rest and during 25 watts of exercise.

1. 5. The use of claim 1 or 2, wherein the human subject is a responder to levosimendan therapy, wherein

a) a responder to levosimendan therapy is a human subject whose pulmonary capillary wedge pressure decreases by at least 4mmHG during bicycle exercise at 25 watts following the initial infusion;
b) a responder to levosimendan therapy is a human subject whose cardiac index decreases by no more than 10% between the baseline measurements and repeated measurements following the initial infusion;
c) the human subject is a responder to levosimendan therapy if the human subject has cardiac reserve;
d) the human subject is a responder to levosimendan therapy if the human subject's stroke volume increases during exercise by the human subject;
e) the human subject is a responder to levosimendan therapy if the human subject's stroke volume increases during exercise by the human subject when determined with a catheter in the human subject's heart measuring the blood moving out of the left ventricle with every beat;
f) the human subject is a responder to levosimendan therapy if the human subject's stroke volume increases during exercise by the human subject when estimated with an electrocardiogram and/or echocardiogram;

g) the human subject is a responder to levosimendan therapy if the human subject's stroke volume increases during exercise by the human subject when determined with a dobutamine stress test;
h) the human subject is a responder to levosimendan therapy if the human subject's stroke volume increases during exercise by the human subject by at least 0.005 liters;
i) the human subject is a responder to levosimendan therapy if the human subject's stroke volume increases during exercise by the human subject by 1 to 50 mL when determined with a catheter in the human subject's heart measuring the blood moving out of the left ventricle with every beat;
j) the human subject is a responder to levosimendan therapy if the human subject's stroke volume increases during exercise by the human subject by 1 to 50 mL when estimated with an echocardiogram, right heart catheterization, or other means; or
k) the human subject is a responder to levosimendan therapy if the human subject's stroke volume increases during exercise by the human subject by 1 to 50 mL when determined with a dobutamine stress test.

4. The use of any one of claims 1-3, wherein the human subject afflicted with PH-HFpEF

a) has a left ventricular ejection fraction of at least 40%;

b) has a baseline pulmonary arterial pressure of at least 35;

c) has a baseline pulmonary capillary wedge pressure of at least 20;

d) is classified as classification IIb or classification III by the physician's assessment of New York Heart Association Classification;

e) has the ability to walk at least 50 meters in a six-minute walk test, does not have the ability to walk more than 550 meters in a six-minute walk test, or has the ability to walk at least 50 meters, but not more than 550 meters, in a six-minute walk test;

f) is not afflicted with heart failure with reduced ejection fraction;

g) is not afflicted with heart failure with preserved ejection fraction without pulmonary hypertension;

h) has a primary diagnosis of Group 2 PH-HFpEF;

i) is not afflicted with coronary artery disease;

j) has not had previous percutaneous coronary intervention;

k) has not had previous percutaneous coronary intervention, unless the human subject has had a negative stress test within the last year;

l) has not had previous cardiac surgery;

m) has not had previous cardiac surgery, unless the human subject has had a negative stress test within the last year;

n) is not afflicted with congenital heart disease;

o) is not afflicted with a clinically significant lung disease;

p) does not have a planned heart or lung surgery;

q) does not have a cardiac index greater than 4.0 L/min/m2;

r) does not concomitantly receive pulmonary vasodilator therapy;

s) has not received pulmonary vasodilator therapy within the last 14 days;

t) does not receive dialysis treatment;

u) does not have a Glomerular Filtration Rate less than 30 mL/min/1.73m2;

v) does not have liver dysfunction with Child Pugh Class B or C;

w) does not have evidence of systemic infection;

x) does not weigh more than 150 kg;

y) can manage their symptomatic systolic blood pressure to ensure it is greater than 100 mmHg;

z) does not have a heart rate greater than or equal to 100 beats per minute with the drug;

aa) does not have a heart rate greater than or equal to 100 beats per minute with the drug that is symptomatic and persistent for at least 10 minutes;

bb) does not have hemoglobin less than 80 g/L;

cc) does not have serum potassium less than 3.0 mmol/L at baseline;

dd) does not have serum potassium greater than 5.5 mmol/L at baseline;

ee) does not have serum potassium less than 3.0 mmol or greater than 5.5 mmol/L at baseline;

ff) does not have severely compromised immune function;

gg) is not pregnant, is not suspected to be pregnant, or is not breast-feeding; or

hh) is a patient with Biventricular Failure.

5. The use of any one of claims 1-4, wherein the administering is via IV administration.

6. The use of any one of claims 1-5, wherein the administering takes place intermittently, weekly, or chronically.

7. The use of any one of claims 1-6, wherein the administering is given via a 24-hour infusion or the administering is chronic adminstration given via a less than 24-hour infusion.

8. The use of any one of claims 1-7, wherein the administering is an administration of a dose of

a) levosimendan 2.5 mg/mL infusion concentrate that includes levosimendan, povidone, citric acid, and ethanol;

b) levosimendan 2.5 mg/mL infusion concentrate that includes levosimendan, povidone, citric acid, and ethanol and is supplied in 5 mL of total volume;

c) levosimendan 2.5 mg/mL infusion concentrate that includes levosimendan, povidone, citric acid, and ethanol and is supplied in 5 mL of total volume that is added to one 250 mL infusion bag of 5% Dextrose;

d) levosimendan 2.5 mg/mL infusion concentrate that includes levosimendan, povidone, citric acid, and ethanol and is supplied in 5 mL of total volume that is added to one 250 mL infusion bag of 0.9 Normal Saline;

e) levosimendan 2.5 mg/mL infusion concentrate that includes levosimendan, povidone, citric acid, and ethanol and is supplied in 5 mL of total volume that is added to one 250 mL infusion bag of 5% Dextrose or 0.9 Normal Saline where the human subject weights less than 85 kg;

f) levosimendan 2.5 mg/mL infusion concentrate that includes levosimendan, povidone, citric acid, and ethanol and is supplied in 10 mL of total volume;

g) levosimendan 2.5 mg/mL infusion concentrate that includes levosimendan, povidone, citric acid, and ethanol and is supplied in 10 mL of total volume that is added to one 500 mL infusion bag of 5% Dextrose;

h) levosimendan 2.5 mg/mL infusion concentrate that includes levosimendan, povidone, citric acid, and ethanol and is supplied in 10 mL of total volume that is added to one 500 mL infusion bag of 0.9 Normal Saline;

i) levosimendan 2.5 mg/mL infusion concentrate that includes levosimendan, povidone, citric acid, and ethanol and is supplied in 10 mL of total volume that is added to one 500 mL infusion bag of 5% Dextrose or 0.9 Normal Saline where the human subject weights at least 85 kg.

9. The use of any one of claims 1-8, wherein an administration infusion rate is reduced to 0.05 µg/kg/min when a dose is not well-tolerated by the human subject.

10. The use of any one of claims 1-9, wherein the administration is via oral dosing and the oral dosing comprises an immediate release formulation or an extended-release formulation.

11. The use of any one of claims 1-10, wherein the administration is subcutaneous administration of a subcutaneous formulation.

12. The use of claim 11, wherein the subcutaneous formulation comprises

a) 12.5 mg of levosimendan in a non-aqueous formulation that is added to 150 mL of 5% Dextrose, 0.9 Normal Saline, or other pharmaceutically acceptable diluent or carrier to create a levosimendan concentration of 0.0833 mg/mL in the subcutaneous formulation;

b) 12.5 mg of levosimendan in a non-aqueous formulation that is added to 250 mL of 5% Dextrose, 0.9 Normal Saline, or other pharmaceutically acceptable diluent or carrier to create a levosimendan concentration of 0.05 mg/mL in the subcutaneous formulation;

c) 12.5 mg of levosimendan in a non-aqueous formulation that is added to 500 mL of 5% Dextrose, 0.9 Normal Saline, or other pharmaceutically acceptable diluent or carrier to create a levosimendan concentration of 0.025 mg/mL in the subcutaneous formulation;

d) 12.5 mg of levosimendan in a non-aqueous formulation that is added to 1000 mL of 5% Dextrose, 0.9 Normal Saline, or other pharmaceutically acceptable diluent or carrier to create a levosimendan concentration of 0.0125 mg/mL in the subcutaneous formulation;

e) 12.5 mg of levosimendan in a non-aqueous formulation that is added to 1500 mL of 5% Dextrose, 0.9 Normal Saline, or other pharmaceutically acceptable diluent or carrier to create a levosimendan concentration of 0.008333 mg/mL in the subcutaneous formulation; or

f) 2.5mg of levosimendan per ml water for injection, 0.175mg sulfo-butyl-ether beta-cyclodextrin per ml water for injection, and sodium hydroxide or acetic acid in a suitable amount to adjust the pH of the formulation to a range of 7.2 to 7.8.

13. The use of any of claims 1-12 wherein the amount of levosimendan its metabolites OR-1896 or OR-1855, or a combination thereof, is to be administered in combination with a cardiovascular drug.

14. The use of claim 13, wherein the cardiovascular drug is a PDE inhibitor, a phosphodiesterase-5 (PDE5) inhibitor, an endothelin receptor antagonist (ERA), a prostanoid, a soluble guanylate cyclase stimulator, a nitrate, a nitrite, an NO donor, a calcium channel blocker (CCB), a fatty acid oxidation inhibitor, a beta-blocker (BB), an angiotensin-converting enzyme (ACE) inhibitor, a neprilysin inhibitor, a neprilysin and angiotensin receptor blocker (ANRI), an angiotensin II receptor blocker (ARB), a diuretic, an aldosterone antagonist, digoxin, ivabradine, hydralazine, seralaxin, a natriuretic peptide, an atrial natriueretic peptide (ANP), a natriuretic peptide, a K-ATP channel activator, a NEP inhibitor, or a prostacyclin.

15. The use of claim 13, wherein the cardiovascular drug is a pulmonary vasodilator drug selected from the group consisting of a phosphodiesterase-5 (PDE5) inhibitor, an endothelin receptor antagonist (ERA), or a prostacyclin and wherein the amount of levosimendan, its metabolites OR-1896 or OR-1855, or a combination thereof, administered in combination with the pulmonary vasodilator drug is administered to a human subject afflicted with pre and post capillary pulmonary hypertension and heart failure with preserved ejection fraction (Cpc-PH-HFpEF).

16. The use of claim 1, wherein the subject is to be orally administered a capsule comprising up to 0.1mg, 0.25mg, 0.5mg, 0.75mg, 1mg, 2mg, 3mg, or 4mg of levosimendan, its metabolites OR-1896 or OR-1855, or a combination thereof, and/or wherein the subject is to be orally administered between 0.1-10 mg of levosimendan, its metabolites OR-1896 or OR-1855, or a combination thereof, per day.

17. The use of claim 16, wherein the subject is to be administered a capsule once a day for a time period of 1-60 days, preferably 14 days.

18. The use of claims 16 or 17, wherein the subject increases the number of capsules taken per day after every time period if the treatment is tolerated by the subject.

19. The use of any one of claims 16-18, wherein the subject is to be orally administered between 0.1-10mg between 1-4mg of levosimendan, its metabolites OR-1896 or OR-1855, or a combination thereof per day.

20. The use of claim 1, wherein the treating comprises an improvement in the human subject's six (6) minute walk distance of at least 10 meters.