Claims

1. The use of istaroxime or a pharmaceutically acceptable salt, solvate, or hydrate thereof for the manufacture of a medicament formulated for administration by intravenous infusion for the treatment of heart failure in a human subject, wherein the administration comprises an infusion duration longer than 6 hours, whereby diastolic relaxation is improved in the human subject as compared to administration of istaroxime by intravenous infusion for an infusion duration from 3 to 6 hours, and wherein the istaroxime is to be administered at a dose between 0.2 μg/kg/min and 1.5 μg/kg/min.

2. The use according to claim 1, wherein the diastolic relaxation improvement is measured by one or more of:

(a) echocardiographic parameter E/A ratio, A wave, e', E wave deceleration time, E/e' ratio;

(b) diastolic relaxation, increased diastolic blood pressure, decreased heart rate, a decrease in dyspnea, increased stroke volume, increased cardiac index, increased cardiac output, increased pulmonary capillary wedge pressure, or increased stroke volume index; or

(c) sphygmomanometer, an electrocardiogram, cardiac catheterization, a radionuclide ventriculography scan; or

(d) any combination of (a)-(c).

3. The use according to claim 1 or 2, wherein the infusion duration is at least 24 hours.

4. The use according to claim 1 or 2, wherein the infusion duration is selected from:

at least 12 hours;

at least 36 hours; and

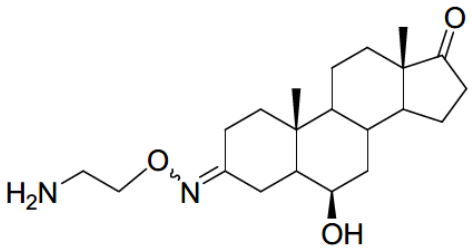
at least 48 hours.

5. The use according to any one of claims 2-4, wherein the improvement in diastolic relaxation is measured by echocardiography comprising one or more of decreased E wave,

increased E wave deceleration time, increased A wave, decreased E/A ratio, increased e', or decreased E/e' ratio.

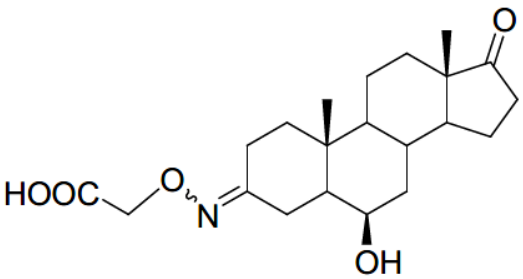
6. The use according to any one of claims 1 to 5, wherein istaroxime is to be administered at a dose between 0.25 µg/kg/min and 1.0 µg/kg/min.

7. The use according to any one of claims 1 to 6, wherein istaroxime is to be administered by infusion for a duration sufficient to produce a plasma level of an istaroxime metabolite, wherein the plasma level is greater than about 5 ng/ml for an accumulation period of at least 6 hours, and wherein the istaroxime metabolite comprises a formula (II) or a formula (III) compound



PST 2915

Formula (II)



PST 3093

Formula (III)

or a pharmaceutically acceptable salt, an ester a solvate, a hydrate, a polymorph thereof.

8. The use according to any one of claims 1 to 7, wherein the human subject suffers from heart failure with preserved ejection fraction (HFpEF) or mid-range reduction ejection fraction (HFmEF).

9. The use according to any one of claims 1 to 8 wherein the human subject is undergoing a therapeutic treatment for heart failure with one or more further therapeutically active ingredients selected from the group consisting of ACE inhibitors, AIRBs, diuretics, Ca channel blockers, beta-blockers, digitalis, NO donors, vasodilators, SERCA2a stimulators, neprilisin (NEP) inhibitors, myosin filament activators, recombinant relaxin-2 mediators, recombinant NP protein, activators of the soluble Guanylate Cyclase (sGC), and beta-arrestin ligand of Angiotensin II receptor.

10. The use according to claim 9, wherein the diuretic, is selected among furosemide, bumetanide, torasemide, metolazone, an aldosterone antagonist, in particular spironolactone and eplerenone; thiazide diuretics, in particular hydrochlorothiazide, metolazone, chlorthalidone.

11. The use according to claim 9, wherein the ACE inhibitor is selected among Lisinopril and Ramipril.

12. The use according to claim 9, wherein the Angiotensin II receptor blocker is selected among valsartan, candesartan, olmesartan, telmisartan and losartan.

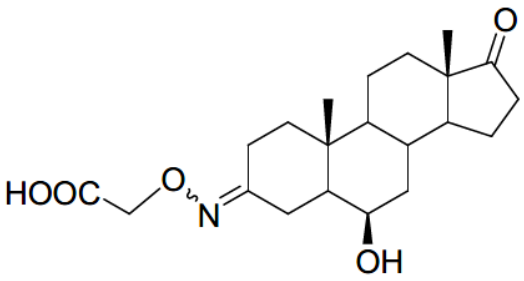
13. The use according to claim 9, wherein the Angiotensin receptor/neprilysin inhibitor is sacubitril.

14. The use according to claim 9, wherein the beta-blocker is selected among carvedilol and metoprolol.

15. The use according to claim 9, wherein the Vasodilator is selected among Hydralazine, optionally combined with isosorbide dinitrate, nitrates, in particular nitroglycerin or isosorbide nitrate, amlodipine, felodipine, non-dihydropyridines, in particular diltiazem or verapamil.

16. The use according to claim 9, wherein the agent for the treatment of heart failure is selected from Digoxin, entresto, omecantiv, serelaxin, ularitide, levosimendan.

17. A synthesized or extracted compound having a formula (III)



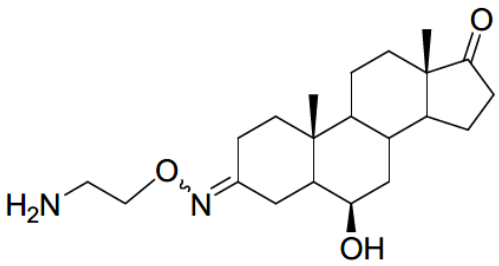
PST 3093

Formula (III)

for use in the treatment of a cardiovascular disease.

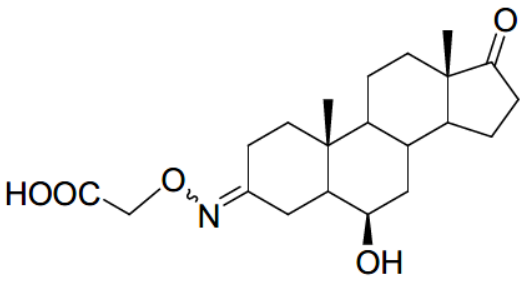
18. The compound for use according to claim 17, wherein the disease is heart failure.

19. A pharmaceutical composition comprising a compound having formula (II) or formula (III)



PST 2915

Formula (II)



PST 3093

Formula (III)

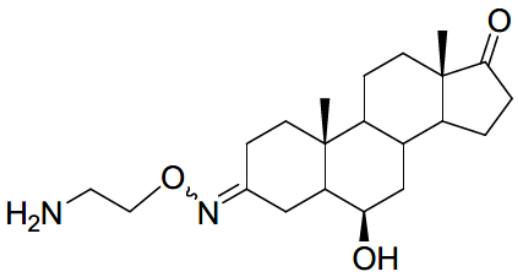
or a pharmaceutically acceptable salt, a solvate, a hydrate, a polymorph thereof in admixture with at least one pharmaceutically acceptable vehicle and/or excipient.

20. The pharmaceutical composition according to claim 19, further comprising at least one additional therapeutic ingredient.

21. The use of istaroxime or a pharmaceutically acceptable salt, solvate, or hydrate thereof for the manufacture of a medicament formulated for administration by intravenous infusion for the treatment of heart failure in a human individual, wherein the administration is for an infusion duration sufficient to produce in the individual a measured plasma concentration level of an istaroxime metabolite, wherein:

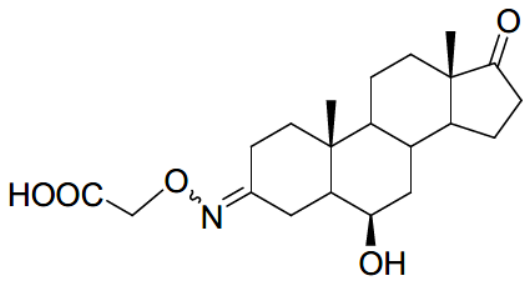
(a) the measured plasma concentration level of the istaroxime metabolite is greater than about 5 ng/ml for an accumulation period of at least 6 hours; and

(b) the istaroxime metabolite comprises formula (II) or (III):



PST 2915

Formula (II)



PST 3093

Formula (III)

or a pharmaceutically acceptable salt, an ester a solvate, a hydrate, a polymorph thereof;
whereby the diastolic relaxation is improved in the human individual as compared to administration of istaroxime prior to the accumulation period.

22. The use according to claim 21, wherein the diastolic relaxation improvement is measured by one or more of:

(a) echocardiographic parameter E/A ratio, A wave, e', E wave deceleration time, E/e' ratio;

(b) diastolic relaxation, increased diastolic blood pressure, decreased heart rate, a decrease in dyspnea, increased stroke volume, increased cardiac index, increased cardiac output, increased pulmonary capillary wedge pressure, or increased stroke volume index; or

(c) sphygmomanometer, an electrocardiogram, cardiac catheterization, a radionuclide ventriculography scan; or

(d) any combination of (a)-(c).

23. The use according to claim 21 or claim 22, wherein the improvement in diastolic relaxation is measured by echocardiography comprising one or more of decreased E wave, increased E wave deceleration time, increased A wave, decreased E/A ratio, increased e', or decreased E/e' ratio.

24. The use according to any one of claims 21-23, wherein the infusion duration is sufficient to produce in the human individual a plasma concentration level of an istaroxime metabolite greater than about 10 ng/ml for an accumulation period of at least 6 hours.

25. The use according to claim 24, wherein the infusion duration is sufficient to produce in the human individual a plasma concentration level of an istaroxime metabolite greater than about 15 ng/ml for an accumulation period of at least 6 hours.

26. The use according to claim 25, wherein the infusion duration is sufficient to produce in the human individual a plasma concentration level of an istaroxime metabolite greater than about 20 ng/ml for an accumulation period of at least 6 hours.

27. The use according to any one of claims 21-26, wherein istaroxime is to be administered at a dose comprised between 0.2 μg/kg/min and 1.5 μg/kg/min.

28. The use according to claim 27, wherein istaroxime is to be administered at a dose comprised between 0.25 μg/kg/min and 1.0 μg/kg/min.