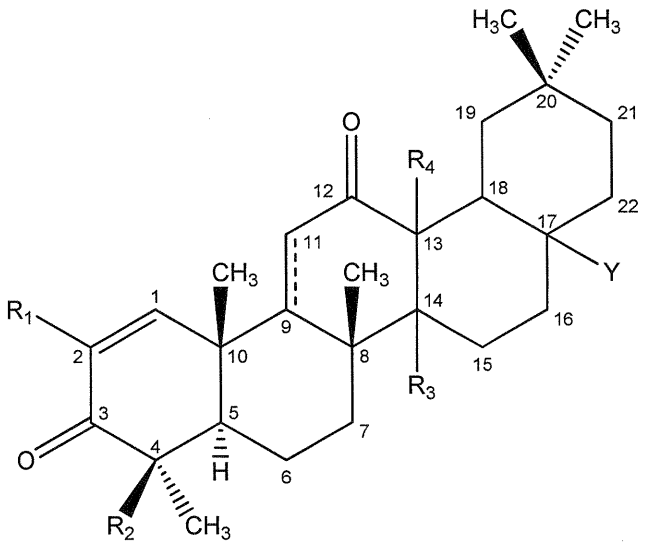
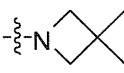
SUMMARY

In one example, disclosed herein is use of a compound of the formula:

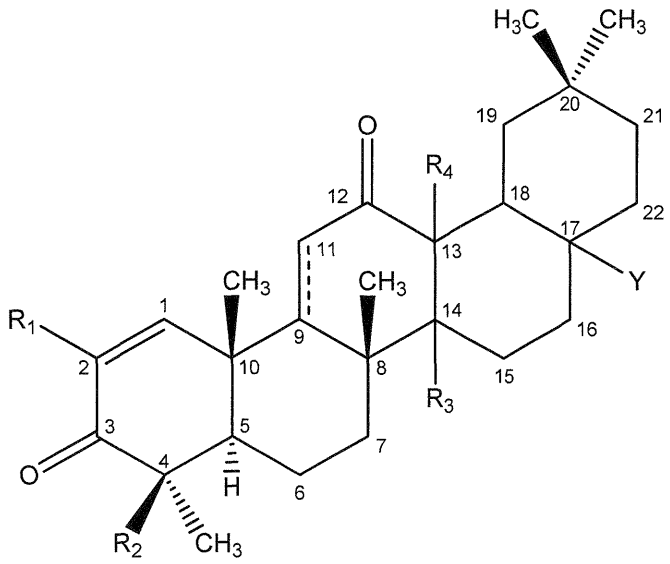


(I),

wherein R_1 is −CN, halo, $-CF_3$, or $-C(O)R_a$, wherein R_a is −OH, $alkoxy_{(C1-4)}$, $-NH_2$, $alkylamino_{(C1-4)}$, or $-NH-S(O)_2-alkyl_{(C1-4)}$; R_2 is hydrogen or methyl; R_3 and R_4 are each independently hydrogen, hydroxy, methyl or as defined below when either of these groups is taken together with group R_c; and Y is: −H, −OH, −SH, −CN, −F, $-CF_3$, $-NH_2$ or −NCO; $alkyl_{(C\leq8)}$, $alkenyl_{(C\leq8)}$, $alkynyl_{(C\leq8)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq8)}$, $heterocycloalkyl_{(C\leq12)}$, $alkoxy_{(C\leq8)}$, $aryloxy_{(C\leq12)}$, $acyloxy_{(C\leq8)}$, $alkylamino_{(C\leq8)}$, $dialkylamino_{(C\leq8)}$, $alkenylamino_{(C\leq8)}$, $arylamino_{(C\leq8)}$, $aralkylamino_{(C\leq8)}$, $alkylthio_{(C\leq8)}$, $acylthio_{(C\leq8)}$, $alkylsulfonylamino_{(C\leq8)}$, or substituted versions of any of these groups; $-alkanediyl_{(C\leq8)}-R_b$, $-alkenediyl_{(C\leq8)}-R_b$, or a substituted version of any of these groups, wherein R_b is: hydrogen, hydroxy, halo, amino or thio; $orheteroaryl_{(C\leq8)}$, $alkoxy_{(C\leq8)}$, $alkenyloxy_{(C\leq8)}$, $aryloxy_{(C\leq8)}$, $aralkoxy_{(C\leq8)}$, $heteroaryloxy_{(C\leq8)}$, $acyloxy_{(C\leq8)}$, $alkylamino_{(C\leq8)}$, $dialkylamino_{(C\leq8)}$, $alkenylamino_{(C\leq8)}$, $arylamino_{(C\leq8)}$, $aralkylamino_{(C\leq8)}$, $heteroarylamino_{(C\leq8)}$, $alkylsulfonylamino_{(C\leq8)}$, $amido_{(C\leq8)}$, $-OC(O)NH-alkyl_{(C\leq8)}$, $-OC(O)CH_2NHC(O)O-t$-butyl, $-OCH_2-alkylthio_{(C\leq8)}$, or a substituted version of any of these groups; $-(CH_2)_mC(O)R_c$, wherein m is 0–6 and R_c is: hydroxy, halo, amino, −NHOH, , or thio; or $alkyl_{(C\leq8)}$, $alkenyl_{(C\leq8)}$, $alkynyl_{(C\leq8)}$, $aryl_{(C\leq8)}$, $aralkyl_{(C\leq8)}$, $heteroaryl_{(C\leq8)}$, $heterocycloalkyl_{(C\leq8)}$, $alkoxy_{(C\leq8)}$, $alkenyloxy_{(C\leq8)}$, $aryloxy_{(C\leq8)}$, $aralkoxy_{(C\leq8)}$, $heteroaryloxy_{(C\leq8)}$, $acyloxy_{(C\leq8)}$, $alkylamino_{(C\leq8)}$, $dialkylamino_{(C\leq8)}$, $arylamino_{(C\leq8)}$, alkyl-

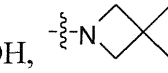
sulfonylamino$_{(C\leq 8)}$, amido$_{(C\leq 8)}$, –NH–alkoxy$_{(C\leq 8)}$, –NH–heterocycloalkyl$_{(C\leq 8)}$, –NHC(NOH)–alkyl$_{(C\leq 8)}$, –NH–amido$_{(C\leq 8)}$, or a substituted version of any of these groups; R_c and R_3, taken together, are –O– or –NR_d–, wherein R_d is hydrogen or alkyl$_{(C\leq 4)}$; or R_c and R_4, taken together, are –O– or –NR_d–, wherein R_d is hydrogen or alkyl$_{(C\leq 4)}$; or –NHC(O)R_e, wherein R_e is: hydrogen, hydroxy, amino; or alkyl$_{(C\leq 8)}$, alkenyl$_{(C\leq 8)}$, alkynyl$_{(C\leq 8)}$, aryl$_{(C\leq 8)}$, aralkyl$_{(C\leq 8)}$, heteroaryl$_{(C\leq 8)}$, heterocycloalkyl$_{(C\leq 8)}$, alkoxy$_{(C\leq 8)}$, aryloxy$_{(C\leq 8)}$, aralkoxy$_{(C\leq 8)}$, heteroaryloxy$_{(C\leq 8)}$, acyloxy$_{(C\leq 8)}$, alkylamino$_{(C\leq 8)}$, dialkylamino$_{(C\leq 8)}$, arylamino$_{(C\leq 8)}$, or a substituted version of any of these groups; or a pharmaceutically acceptable salt or tautomer thereof, in the manufacture of a medicament for treating or preventing endothelial dysfunction in a patient in need thereof, wherein the medicament is to be administered in a pharmaceutically effective amount, wherein the patient has been identified as not having at least one of the following characteristics: (a) a history of left-sided myocardial disease; (b) an elevated B-type natriuretic peptide (BNP) level; (c) an elevated albumin/creatinine ratio (ACR); and (d) chronic kidney disease (CKD).

In another example, there is disclosed use of a compound of the formula:



(I),

wherein: R_1 is –CN, halo, –CF_3, or –C(O)R_a, wherein R_a is –OH, alkoxy$_{(C1-4)}$, –NH_2, alkylamino$_{(C1-4)}$, or –NH–S(O)$_2$–alkyl$_{(C1-4)}$; R_2 is hydrogen or methyl; R_3 and R_4 are each independently hydrogen, hydroxy, methyl or as defined below when either of these groups is taken together with group R_c; and Y is: –H, –OH, –SH, –CN, –F, –CF_3, –NH_2 or –NCO; alkyl$_{(C\leq 8)}$, alkenyl$_{(C\leq 8)}$, alkynyl$_{(C\leq 8)}$, aryl$_{(C\leq 12)}$, aralkyl$_{(C\leq 12)}$, heteroaryl$_{(C\leq 8)}$, heterocycloalkyl$_{(C\leq 12)}$, alkoxy$_{(C\leq 8)}$, aryloxy$_{(C\leq 12)}$, acyloxy$_{(C\leq 8)}$, alkylamino$_{(C\leq 8)}$,

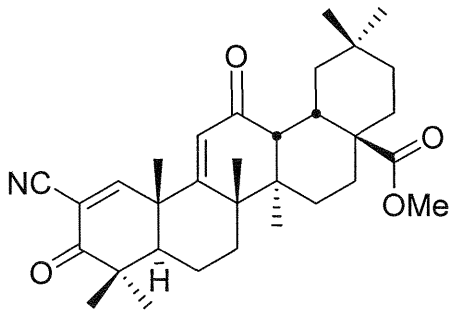
dialkylamino$_{(C\leq 8)}$, alkenylamino$_{(C\leq 8)}$, arylamino$_{(C\leq 8)}$, aralkylamino$_{(C\leq 8)}$, alkylthio$_{(C\leq 8)}$, acylthio$_{(C\leq 8)}$, alkylsulfonylamino$_{(C\leq 8)}$, or substituted versions of any of these groups; –alkanediyl$_{(C\leq 8)}$–R_b, –alkenediyl$_{(C\leq 8)}$–R_b, or a substituted version of any of these groups, wherein R_b is: hydrogen, hydroxy, halo, amino or thio; or heteroaryl$_{(C\leq 8)}$, alkoxy$_{(C\leq 8)}$, alkenyloxy$_{(C\leq 8)}$, aryloxy$_{(C\leq 8)}$, aralkoxy$_{(C\leq 8)}$, heteroaryloxy$_{(C\leq 8)}$, acyloxy$_{(C\leq 8)}$, alkylamino$_{(C\leq 8)}$, dialkylamino$_{(C\leq 8)}$, alkenylamino$_{(C\leq 8)}$, arylamino$_{(C\leq 8)}$, aralkylamino$_{(C\leq 8)}$, heteroarylamino$_{(C\leq 8)}$, alkylsulfonylamino$_{(C\leq 8)}$, amido$_{(C\leq 8)}$, –OC(O)NH–alkyl$_{(C\leq 8)}$, –OC(O)CH_2NHC(O)O–*t*-butyl, –OCH_2–alkylthio$_{(C\leq 8)}$, or a substituted version of any of these groups; –$(CH_2)_m$C(O)R_c, wherein m is 0–6 and R_c is: hydrogen, hydroxy, halo, amino, –NHOH, , or thio; or alkyl$_{(C\leq 8)}$, alkenyl$_{(C\leq 8)}$, alkynyl$_{(C\leq 8)}$, aryl$_{(C\leq 8)}$, aralkyl$_{(C\leq 8)}$, heteroaryl$_{(C\leq 8)}$, heterocycloalkyl$_{(C\leq 8)}$, alkoxy$_{(C\leq 8)}$, alkenyloxy$_{(C\leq 8)}$, aryloxy$_{(C\leq 8)}$, aralkoxy$_{(C\leq 8)}$, heteroaryloxy$_{(C\leq 8)}$, acyloxy$_{(C\leq 8)}$, alkylamino$_{(C\leq 8)}$, dialkylamino$_{(C\leq 8)}$, arylamino$_{(C\leq 8)}$, alkylsulfonylamino$_{(C\leq 8)}$, amido$_{(C\leq 8)}$, –NH–alkoxy$_{(C\leq 8)}$, –NH–heterocycloalkyl$_{(C\leq 8)}$, –NHC(NOH)–alkyl$_{(C\leq 8)}$, –NH–amido$_{(C\leq 8)}$, or a substituted version of any of these groups; R_c and R_3, taken together, are –O– or –NR_d–, wherein R_d is hydrogen or alkyl$_{(C\leq 4)}$; or R_c and R_4, taken together, are –O– or –NR_d–, wherein R_d is hydrogen or alkyl$_{(C\leq 4)}$; or –NHC(O)R_e, wherein R_e is: hydrogen, hydroxy, amino; or alkyl$_{(C\leq 8)}$, alkenyl$_{(C\leq 8)}$, alkynyl$_{(C\leq 8)}$, aryl$_{(C\leq 8)}$, aralkyl$_{(C\leq 8)}$, heteroaryl$_{(C\leq 8)}$, heterocycloalkyl$_{(C\leq 8)}$, alkoxy$_{(C\leq 8)}$, aryloxy$_{(C\leq 8)}$, aralkoxy$_{(C\leq 8)}$, heteroaryloxy$_{(C\leq 8)}$, acyloxy$_{(C\leq 8)}$, alkylamino$_{(C\leq 8)}$, dialkylamino$_{(C\leq 8)}$, arylamino$_{(C\leq 8)}$, or a substituted version of any of these groups; or a pharmaceutically acceptable salt or tautomer thereof, in the manufacture of a medicament for treating or preventing pulmonary arterial hypertension in a patient in need thereof, wherein the medicament is to be administered in a pharmaceutically effective amount.

In yet another example, there is disclosed use of a compound of the formula:

$-OCH_2-alkylthio_{(C\leq 8)}$, or a substituted version of any of these groups; $-(CH_2)_mC(O)R_c$, wherein m is 0–6 and R_c is: hydrogen, hydroxy, halo, amino, –NHOH, , or thio; or $alkyl_{(C\leq 8)}$, $alkenyl_{(C\leq 8)}$, $alkynyl_{(C\leq 8)}$, $aryl_{(C\leq 8)}$, $aralkyl_{(C\leq 8)}$, $heteroaryl_{(C\leq 8)}$, $heterocycloalkyl_{(C\leq 8)}$, $alkoxy_{(C\leq 8)}$, $alkenyloxy_{(C\leq 8)}$, $aryloxy_{(C\leq 8)}$, $aralkoxy_{(C\leq 8)}$, $heteroaryloxy_{(C\leq 8)}$, $acyloxy_{(C\leq 8)}$, $alkylamino_{(C\leq 8)}$, $dialkylamino_{(C\leq 8)}$, $arylamino_{(C\leq 8)}$, $alkylsulfonylamino_{(C\leq 8)}$, $amido_{(C\leq 8)}$, $-NH-alkoxy_{(C\leq 8)}$, $-NH-heterocycloalkyl_{(C\leq 8)}$, $-NHC(NOH)-alkyl_{(C\leq 8)}$, $-NH-amido_{(C\leq 8)}$, or a substituted version of any of these groups; R_c and R_3, taken together, are –O– or $-NR_d-$, wherein R_d is hydrogen or $alkyl_{(C\leq 4)}$; or R_c and R_4, taken together, are –O– or $-NR_d-$, wherein R_d is hydrogen or $alkyl_{(C\leq 4)}$; or $-NHC(O)R_e$, wherein R_e is: hydrogen, hydroxy, amino; or $alkyl_{(C\leq 8)}$, $alkenyl_{(C\leq 8)}$, $alkynyl_{(C\leq 8)}$, $aryl_{(C\leq 8)}$, $aralkyl_{(C\leq 8)}$, $heteroaryl_{(C\leq 8)}$, $heterocycloalkyl_{(C\leq 8)}$, $alkoxy_{(C\leq 8)}$, $aryloxy_{(C\leq 8)}$, $aralkoxy_{(C\leq 8)}$, $heteroaryloxy_{(C\leq 8)}$, $acyloxy_{(C\leq 8)}$, $alkylamino_{(C\leq 8)}$, $dialkylamino_{(C\leq 8)}$, $arylamino_{(C\leq 8)}$, or a substituted version of any of these groups; or a pharmaceutically acceptable salt or tautomer thereof, in the manufacture of a medicament for treating or preventing a cardiovascular disease in a patient in need thereof, wherein the medicament is to be administered in a pharmaceutically effective amount, wherein the patient has been identified as not having at least one of the following characteristics: (a) a history of left-sided myocardial disease; (b) an elevated B-type natriuretic peptide (BNP) level; (c) an elevated albumin/creatinine ratio (ACR); and (d) chronic kidney disease (CKD).

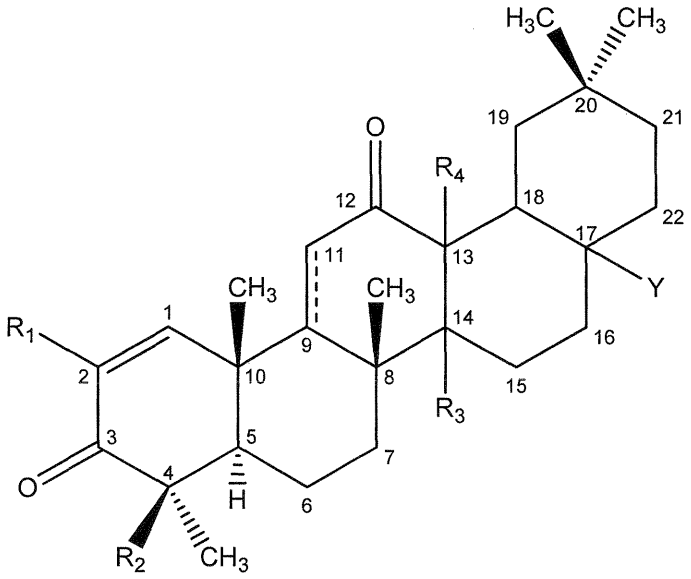
In one example, disclosed herein are methods for treating and/or preventing endothelial dysfunction in patients who are diagnosed with or at risk for cardiovascular disease (including patients diagnosed with or at risk for pulmonary arterial hypertension, other forms of pulmonary hypertension, atherosclerosis, restenosis, hyperlipidemia, hypercholesterolemia, metabolic syndrome, or obesity) and other diseases or conditions using bardoxolone methyl and analogs thereof.

In one aspect, the present invention refers to the use of a compound of the formula:



or a pharmaceutically acceptable salt or tautomer thereof, in the manufacture of a medicament for treating or preventing pulmonary hypertension in a patient in need thereof, wherein the medicament comprises a pharmaceutically effective amount of the compound, and wherein the patient does not have chronic kidney disease (CKD).

In some examples, disclosed herein are methods of treating or preventing endothelial dysfunction in a patient in need thereof, comprising administering to the patient a pharmaceutically effective amount of a compound of the formula:



(I),

wherein:

R_1 is $-CN$, halo, $-CF_3$, or $-C(O)R_a$, wherein R_a is $-OH$, $alkoxy_{(C1-4)}$, $-NH_2$, $alkylamino_{(C1-4)}$, or $-NH-S(O)_2-alkyl_{(C1-4)}$;

R_2 is hydrogen or methyl;

R_3 and R_4 are each independently hydrogen, hydroxy, methyl or as defined below when either of these groups is taken together with group R_c; and

Y is:

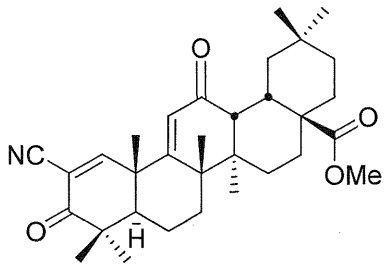
$-H$, $-OH$, $-SH$, $-CN$, $-F$, $-CF_3$, $-NH_2$ or $-NCO$;

$alkyl_{(C\leq8)}$, $alkenyl_{(C\leq8)}$, $alkynyl_{(C\leq8)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq8)}$, $heterocycloalkyl_{(C\leq12)}$, $alkoxy_{(C\leq8)}$, $aryloxy_{(C\leq12)}$, $acyloxy_{(C\leq8)}$, $alkylamino_{(C\leq8)}$, $dialkylamino_{(C\leq8)}$, $alkenylamino_{(C\leq8)}$, $arylamino_{(C\leq8)}$,

CLAIMS

What is claimed is:

1. Use of a compound of the formula:



or a pharmaceutically acceptable salt or tautomer thereof, in the manufacture of a medicament for treating or preventing pulmonary hypertension in a patient in need thereof, wherein the medicament comprises a pharmaceutically effective amount of the compound, and wherein the patient does not have chronic kidney disease (CKD).

2. The use of claim 1, wherein the patient has pulmonary arterial hypertension.

3. The use of either claim 1 or 2, wherein the patient does not have a history of left-sided myocardial disease.

4. The use according to any one of claims 1 to 3, wherein the patient does not have a BNP level greater than 200 pg/mL.

5. The use according to any one of claims 1 to 4, wherein the patient does not have an ACR greater than 300 mg/g.

6. The use according to any one of claims 1 to 5, wherein the patient's estimated glomerular filtration rate (eGFR) is greater than or equal to 45 mL/min/1.73 m^2.

7. The use according to any one of claims 1 to 6, wherein the patient's eGFR is greater than or equal to 60 mL/min/1.73 m^2.

8. The use according to any one of claims1 to 5, wherein the patient's eGFR is less than 60 mL/min/1.73 m^2.

9. The use according to any one of claims 1 to 8, wherein the patient is less than 75 years old.

10. The use of claim 9, wherein the patient is less than 70 years old.

11. The use of claim 10, wherein the patient is less than 65 years old.

12. The use of claim 11, wherein the patient is less than 60 years old.

13. The use of claim 12, wherein the patient is less than 55 years old.

14. The use according to any one of claims 1 to 13, wherein the patient has chronic obstructive pulmonary disease (COPD).

15. The use according to any one of claims 1 to 13, wherein the patient does not have COPD.

16. The use according to any one of claims 1 to 13, wherein the patient is a smoker.

17. The use according to any one of claims 1 to 13, wherein the patient is not a smoker.

18. The use according to any one of claims 1 to 17, wherein the patient does not have stage 4 CKD.

19. The use of claim 18, wherein the patient does not have stage 3 or stage 4 CKD.

20. The use of claim 19, wherein the patient does not have stage 2, stage 3 or stage 4 CKD.

21. The use according to any one of claims 1 to 20, wherein the patient has cancer.

22. The use according to any one of claims 1 to 20, wherein the patient does not have cancer.

23. The use according to any one of claims1 to 20, wherein the patient has type 2 diabetes.

24. The use according to any one of claims 1 to 20, wherein the patient does not have type 2 diabetes.

25. The use according to any one of claims 1-24, wherein the patient is a human patient.

26. The use of claim 1, wherein at least a portion of the compound is present as a crystalline form having an X-ray diffraction pattern (CuKα) comprising significant diffraction peaks at 8.8, 12.9, 13.4, 14.2 and 17.4 °2θ.

27. The use of claim 26, wherein the X-ray diffraction pattern (CuKα) is substantially as shown in FIG. 1A or FIG. 1B.

28. The use of claim 1, wherein at least a portion of the compound is present as an amorphous form having an X-ray diffraction pattern (CuKα) with a halo peak at approximately 13.5 °2θ, substantially as shown in FIG. 1C, and a transition glass temperature (T_g).

29. The use of claim 28, wherein the T_g value is in the range of 120 °C to 135 °C.

30. The use of claim 29, wherein the T_g value is in the range of 125 °C to 130 °C.

31. The use according to any one of claims 1-30, wherein the pharmaceutically effective amount is from 0.1 mg to 300 mg of the compound.

32. The use of claim 31, wherein the amount is from 0.5 mg to 200 mg of the compound.

33. The use of claim 32, wherein the amount is from 1 mg to 150 mg of the compound.

34. The use of claim 33, wherein the amount is from 1 mg to 75 mg of the compound.

35. The use of claim 34, wherein the amount is from 1 mg to 20 mg of the compound.

36. The use of claim 31, wherein the amount is from 2.5 mg to 30 mg of the compound.

37. The use of claim 36, wherein the amount is 2.5 mg of the compound.

38. The use of claim 36, wherein the amount is 5 mg of the compound.

39. The use of claim 36, wherein the amount is 10 mg of the compound.

40. The use of claim 36, wherein the amount is 20 mg of the compound.

41. The use of claim 36, wherein the amount is 30 mg of the compound.

42. The use according to any one of claims 1-30, wherein the compound is formulated as a hard or soft capsule or a tablet.

43. The use according to any one of claims 1-30, wherein the compound is formulated as a solid dispersion comprising (i) the compound and (ii) an excipient.

44. The use of claim 43, wherein the excipient is a methacrylic acid – ethyl acrylate copolymer.

45. The use of claim 44, wherein the copolymer comprises methacrylic acid and ethyl acrylate at a 1:1 ratio.

46. The use according to any of claims 1-45, further comprising a second medicament.

47. The use of claim 46, wherein the second medicament is a Rho kinase inhibitor, a tyrosine kinase inhibitor, an epoprostenol derivative, a serotonin receptor antagonist, an endothelin receptor antagonist, a phosphodiesterase (PDE) inhibitor, a calcium channel blocker, a soluble guanylate cyclase stimulator, or nitric oxide.

48. The use of claim 47, wherein the Rho kinase inhibitor is HA-1077, HA-1152P, or Y-27632.

49. The use of claim 47, wherein the tyrosine kinase inhibitor is Gleevec.

50. The use of claim 47, wherein the epoprostenol derivative is treprostinil, beraprost, or iloprost.

51. The use of claim 47, wherein the serotonin receptor antagonist is sarpogrelate.

52. The use of claim 47, wherein the endothelin receptor antagonist is bosentan, sitaxsentan, ambrisentan, TBC3711, or macitentan.

53. The use of claim 47, wherein the PDE inhibitor is amrinone, sildenafil, tadalafil, vardenafil, enoximone, udenafil, or milrinone.

54. The use of claim 47, wherein the calcium channel blocker is amlodipine, diltiazem, isradipine, nicardipine, nifedipine, nimodipine, nisoldipine, nitrendipine, and verapamil.

55. The use of claim 47, wherein the soluble guanylate cyclase stimulator is riociguat.

56. The use of claim 1, wherein the pulmonary hypertension is pulmonary arterial hypertension.

57. The use of claim 56, wherein the pulmonary arterial hypertension is associated with connective tissue disease.

58. The use of claim 56, wherein the pulmonary arterial hypertension is idiopathic.

59. The use of claim 1, wherein the pulmonary hypertension is associated with left-sided heart disease.

60. The use of claim 1, wherein the pulmonary hypertension is associated with lung disease.

61. The use of claim 1, wherein the pulmonary hypertension is chronic thromboembolic pulmonary hypertension.

62. The use of claim 1, wherein the pulmonary hypertension is pulmonary hypertension with multifactorial causes.