

Crystalline Forms of an Estrogen Receptor Modulator

FIELD OF THE INVENTION

5 [0001] Described herein is the estrogen receptor modulator (*E*)-3-(4-((*E*)-2-(2-chloro-4-fluorophenyl)-1-(1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid, pharmaceutically acceptable salts, solvates, and crystalline forms thereof.

BACKGROUND OF THE INVENTION

[0002] The estrogen receptor ("ER") is a ligand-activated transcriptional regulatory protein
10 that mediates induction of a variety of biological effects through its interaction with endogenous estrogens. Endogenous estrogens include 17 β -estradiol and estrones. ER has been found to have two isoforms, ER- α and ER- β .

[0003] Estrogens and estrogen receptors are implicated in a number of diseases or
conditions, such as breast cancer, lung cancer, ovarian cancer, colon cancer, prostate cancer,
15 endometrial cancer, uterine cancer, as well as others diseases or conditions.

SUMMARY OF THE INVENTION

[0004] Described herein is (*E*)-3-(4-((*E*)-2-(2-chloro-4-fluorophenyl)-1-(1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid, pharmaceutically acceptable salts, pharmaceutically
20 acceptable solvates (including hydrates), polymorphs, and amorphous phases thereof, and methods of uses thereof.

[0005] In one aspect, described herein is a pharmaceutically acceptable salt of (*E*)-3-(4-((*E*)-2-(2-chloro-4-fluorophenyl)-1-(1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid, wherein the
pharmaceutically acceptable salt is in crystalline form. In some embodiments, the
25 pharmaceutically acceptable salt is a potassium salt, magnesium, a L-arginine salt, choline salt, ethylenediamine salt, N-methyl glucamine salt, tromethamine salt, or hydroxyethylpyrrolidine salt, wherein the pharmaceutically acceptable salt is in crystalline form. In some embodiments, the pharmaceutically acceptable salt is a N-methyl glucamine salt, wherein the pharmaceutically acceptable salt is in crystalline form.

capsule. In some embodiments, the pharmaceutical composition is in the form of an immediate release capsule or an enteric coated capsule. In some embodiments, the pharmaceutical composition is in the form of a tablet. In some embodiments, the pharmaceutical composition is in the form of an immediate release tablet, an enteric coated tablet, or a sustained release tablet.

5 In some embodiments, the pharmaceutical composition is in the form of a moisture barrier coated tablet. In some embodiments, the pharmaceutical composition comprises about 0.5 mg to about 1000 mg of crystalline (*E*)-3-(4-((*E*)-2-(2-chloro-4-fluorophenyl)-1-(1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid, N-methyl glucamine salt. In some embodiments, the pharmaceutical composition comprises about 10 mg to about 400 mg of crystalline (*E*)-3-(4-((*E*)-2-(2-chloro-4-fluorophenyl)-1-(1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid, N-methyl
10 glucamine salt.

[0010] Also provided is an article of manufacture comprising multiple unit doses of the oral solid dosage form pharmaceutical composition described herein in a high-density polyethylene (HDPE) bottle equipped with a high-density polyethylene (HDPE) cap. In some embodiments, high-density polyethylene (HDPE) bottle further comprises an aluminum foil induction seal and
15 silica gel desiccant.

[0011] Also described herein is (*E*)-3-(4-((*E*)-2-(2-chloro-4-fluorophenyl)-1-(1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid, N-methyl glucamine salt that is in amorphous form. Also described herein is a pharmaceutical composition comprising amorphous (*E*)-3-(4-((*E*)-2-(2-chloro-4-fluorophenyl)-1-(1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid, N-methyl
20 glucamine salt, and at least one additional ingredient selected from pharmaceutically acceptable carriers, diluents and excipients. In some embodiments, the pharmaceutical composition is in a form suitable for oral administration to a mammal. In some embodiments, the pharmaceutical composition is in an oral solid dosage form.

25 [0012] ~~In one aspect, d~~Described herein is the use of a crystalline form of a pharmaceutically salt of (*E*)-3-(4-((*E*)-2-(2-chloro-4-fluorophenyl)-1-(1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid in the treatment of cancer in a mammal. ~~In another aspect, d~~Described herein is the use of crystalline (*E*)-3-(4-((*E*)-2-(2-chloro-4-fluorophenyl)-1-(1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid, N-methyl glucamine salt in the treatment of cancer in a mammal.
30 ~~In another aspect, d~~Described herein is the use of amorphous (*E*)-3-(4-((*E*)-2-(2-chloro-4-fluorophenyl)-1-(1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid, N-methyl glucamine salt in the treatment of cancer in a mammal. In some embodiments, the cancer is amenable to treatment

with an estrogen receptor modulator. In some embodiments, the cancer is breast cancer, ovarian cancer, endometrial cancer, prostate cancer, lung cancer or uterine cancer.

[0013] In certain embodiments described herein, a crystalline form of a pharmaceutically salt of (*E*)-3-(4-((*E*)-2-(2-chloro-4-fluorophenyl)-1-(1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid is used in the manufacture of medicaments for the treatment or prevention of diseases, disorders, or conditions associated with estrogen receptor activity.

[0014] Also described is a method of treating cancer in a mammal comprising administering to the mammal a crystalline pharmaceutically acceptable salt of (*E*)-3-(4-((*E*)-2-(2-chloro-4-fluorophenyl)-1-(1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid. In some embodiments, the crystalline pharmaceutically acceptable salt of (*E*)-3-(4-((*E*)-2-(2-chloro-4-fluorophenyl)-1-(1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid is (*E*)-3-(4-((*E*)-2-(2-chloro-4-fluorophenyl)-1-(1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid, N-methyl glucamine salt. In some embodiments, the cancer is breast cancer, ovarian cancer, endometrial cancer, prostate cancer, lung cancer, or uterine cancer. In some embodiments, the cancer is breast cancer. In some embodiments, the method further comprises administering at least one additional therapeutic agent to the mammal. In some embodiments, the at least one additional therapeutic agent is an anti-cancer agent.

[0015] Also described is a method of treating cancer in a mammal comprising administering to the mammal a pharmaceutical composition as described herein. In some embodiments, the cancer is breast cancer, ovarian cancer, endometrial cancer, prostate cancer, lung cancer, or uterine cancer. In some embodiments, the cancer is breast cancer.

[0016] Also provided is the use of (*E*)-3-(4-((*E*)-2-(2-chloro-4-fluorophenyl)-1-(1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid, N-methyl glucamine salt for the manufacture of a medicament for the treatment or prevention of cancer in a human. Further provided is the use of (*E*)-3-(4-((*E*)-2-(2-chloro-4-fluorophenyl)-1-(1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid, N-methyl glucamine salt for the manufacture of a medicament for the treatment or prevention of cancer in a human wherein the cancer is breast cancer, ovarian cancer, endometrial cancer, prostate cancer, lung cancer, or uterine cancer. In another aspect, described herein is the use of a pharmaceutically acceptable salt as defined herein in the manufacture of a medicament for the treatment of cancer in a mammal. In another aspect, described herein is the use of crystalline (*E*)-3-(4-((*E*)-2-(2-chloro-4-fluorophenyl)-1-(1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid, N-methyl glucamine salt as defined herein in the manufacture of a medicament for the treatment of cancer in a mammal. In another aspect, described herein is the use of a pharmaceutical

composition as defined herein in the manufacture of a medicament for the treatment of cancer in a mammal. In another aspect, described herein is the use of amorphous (*E*)-3-(4-((*E*)-2-(2-chloro-4-fluorophenyl)-1-(1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid, N-methyl glucamine salt in the manufacture of a medicament for the treatment of cancer in a mammal. In another aspect, described herein is a pharmaceutically acceptable salt as defined herein for use in the treatment of cancer in a mammal. In another aspect, described herein is a crystalline (*E*)-3-(4-((*E*)-2-(2-chloro-4-fluorophenyl)-1-(1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid, N-methyl glucamine salt as defined herein for use in the treatment of cancer in a mammal. In another aspect, described herein is a pharmaceutical composition as defined herein for use in the treatment of cancer in a mammal. In another aspect, described herein is an amorphous (*E*)-3-(4-((*E*)-2-(2-chloro-4-fluorophenyl)-1-(1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid, N-methyl glucamine salt for use in the treatment of cancer in a mammal. In some embodiments, (*E*)-3-(4-((*E*)-2-(2-chloro-4-fluorophenyl)-1-(1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid, N-methyl glucamine salt is crystalline.

[0017] Also described herein are processes for the preparation of crystalline form of a pharmaceutically acceptable salt of (*E*)-3-(4-((*E*)-2-(2-chloro-4-fluorophenyl)-1-(1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid.

38. Use of a pharmaceutically acceptable salt of any one of claims 1 to 3 in the manufacture of a medicament for the treatment of cancer in a mammal.
39. Use of crystalline (*E*)-3-(4-((*E*)-2-(2-chloro-4-fluorophenyl)-1-(1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid, N-methyl glucamine salt as described in any one of claims 4 to 26 in the manufacture of a medicament for the treatment of cancer in a mammal.
40. Use of a pharmaceutical composition according to any one of claims 27-31 or 33-37 in the manufacture of a medicament for the treatment of cancer in a mammal.
41. Use of amorphous (*E*)-3-(4-((*E*)-2-(2-chloro-4-fluorophenyl)-1-(1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid, N-methyl glucamine salt in the manufacture of a medicament for the treatment of cancer in a mammal.
42. The use of any one of claims 38 to 41, wherein the cancer is amenable to treatment with an estrogen receptor modulator.
43. The use of any one of claims 38 to 42, wherein the cancer is breast cancer, ovarian cancer, endometrial cancer, prostate cancer, lung cancer or uterine cancer.
- ~~44. A method of treating cancer in a mammal comprising administering a pharmaceutically acceptable salt as described in any one of claims 1 to 3 to the mammal in need thereof.~~
- ~~45. A method of treating cancer in a mammal comprising administering crystalline (*E*)-3-(4-((*E*)-2-(2-chloro-4-fluorophenyl)-1-(1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid, N-methyl glucamine salt as described in any one of claims 4 to 26 to the mammal in need thereof.~~
- ~~46. A method of treating cancer in a mammal comprising administering a pharmaceutical composition as described in any one of claims 27-31 or 33-37 to the mammal in need thereof.~~
- ~~47. A method of treating cancer in a mammal comprising administering amorphous (*E*)-3-(4-((*E*)-2-(2-chloro-4-fluorophenyl)-1-(1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid, N-methyl glucamine salt to the mammal in need thereof.~~
- ~~48. The method of any one of claims 44 to 47, wherein the cancer is amenable to treatment with an estrogen receptor modulator.~~
- ~~49. The method of any one of claims 44 to 48, wherein the cancer is breast cancer, ovarian cancer, endometrial cancer, prostate cancer, lung cancer or uterine cancer.~~
- ~~50.44. A pharmaceutically acceptable salt of any one of claims 1 to 3 for use in the treatment of cancer in a mammal.~~

- ~~51.45.~~ A crystalline (*E*)-3-(4-((*E*)-2-(2-chloro-4-fluorophenyl)-1-(1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid, N-methyl glucamine salt as described in any one of claims 4 to 26 for use in the treatment of cancer in a mammal.
- 5 ~~52.46.~~ A pharmaceutical composition according to any one of claims 27-31 or 33-37 for use in the treatment of cancer in a mammal.
- ~~53.47.~~ Amorphous (*E*)-3-(4-((*E*)-2-(2-chloro-4-fluorophenyl)-1-(1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid, N-methyl glucamine salt for use in the treatment of cancer in a mammal.
- 10 ~~54.48.~~ A compound for the use of any one of claims ~~50-44~~ to ~~53~~~~47~~, wherein the cancer is amenable to treatment with an estrogen receptor modulator.
- ~~55.49.~~ A compound for the use of any one of claims ~~50-44~~ to ~~53~~~~47~~, wherein the cancer is breast cancer, ovarian cancer, endometrial cancer, prostate cancer, lung cancer or uterine cancer.