CLAIMS

We claim:

1. A solid pharmaceutical composition comprising:

(a) erdafitinib free base (N-(3,5-dimethoxyphenyl)-N'-(1-methylethyl)-N-[3-(l-methyl-1*H*-pyrazol-4-yl)quinoxalin-6-yl]ethane-1,2-diamine) in a concentration of at least 45 wt% of the solid pharmaceutical composition; and

(b) at least one pharmaceutical excipient; or

a solid pharmaceutical composition comprising:

(a) a salt form of erdafitinib free base (N-(3,5-dimethoxyphenyl)-N'-(1-methylethyl)-N-[3-(l-methyl-1*H*-pyrazol-4-yl)quinoxalin-6-yl]ethane-1,2-diamine) in a concentration of at least 45 wt% of the solid pharmaceutical composition; and

(b) at least one pharmaceutical excipient.

2. A solid pharmaceutical composition according to claim 1 comprising:

(a) erdafitinib free base (N-(3,5-dimethoxyphenyl)-N'-(1-methylethyl)-N-[3-(l-methyl-1*H*-pyrazol-4-yl)quinoxalin-6-yl]ethane-1,2-diamine) in a concentration of at least 45 wt% of the solid pharmaceutical composition; and

(b) at least one pharmaceutical excipient.

3. The solid pharmaceutical composition of claim 1 or 2, wherein the at least one pharmaceutical excipient comprises a solubilizer, a binder, a diluent, a wetting agent, a disintegrant, a glidant, a lubricant, a formaldehyde scavenger, or any combination thereof.

4. A process for making a solid pharmaceutical composition comprising:

(a) preparing an intragranular solid composition comprising or consisting essentially of:

(i) erdafitinib free base (N-(3,5-dimethoxyphenyl)-N'-(1-methylethyl)-N-[3-(l-methyl-1*H*-pyrazol-4-yl)quinoxalin-6-yl]ethane-1,2-diamine); and

(ii) at least one intragranular pharmaceutical excipient;

(b) combining the intragranular solid composition with at least one extragranular pharmaceutical excipient to form a blend; and

(c) tableting the blend to form the solid pharmaceutical composition, wherein the erdafitinib free base is present in a concentration of at least 45 wt% of the solid pharmaceutical composition; or

a process for making a solid pharmaceutical composition comprising:

(a) preparing an intragranular solid composition comprising or consisting essentially of:

(i) a salt form of erdafitinib free base (N-(3,5-dimethoxyphenyl)-N'-(1-methylethyl)-N-[3-(l-methyl-1*H*-pyrazol-4-yl)quinoxalin-6-yl]ethane-1,2-diamine) or ; and

(ii) at least one intragranular pharmaceutical excipient;

(b) combining the intragranular solid composition with at least one extragranular pharmaceutical excipient to form a blend; and

(c) tableting the blend to form the solid pharmaceutical composition, wherein the salt form of erdafitinib free base is present in a concentration of at least 45 wt% of the solid pharmaceutical composition.

5. The process for making a solid pharmaceutical composition according to claim 4 comprising:

(a) preparing an intragranular solid composition comprising or consisting essentially of:

(i) erdafitinib free base (N-(3,5-dimethoxyphenyl)-N'-(1-methylethyl)-N-[3-(l-methyl-1*H*-pyrazol-4-yl)quinoxalin-6-yl]ethane-1,2-diamine) or ; and

(ii) at least one intragranular pharmaceutical excipient;

(b) combining the intragranular solid composition with at least one extragranular pharmaceutical excipient to form a blend; and

(c) tableting the blend to form the solid pharmaceutical composition, wherein the erdafitinib free base is present in a concentration of at least 45 wt% of the solid pharmaceutical composition.

6. The process for making a solid pharmaceutical composition according to claim 4 or 5, wherein the at least one intragranular pharmaceutical excipient and the at least one extragranular pharmaceutical excipient comprise or are selected from at least one common pharmaceutical excipient.

7. The solid pharmaceutical composition or the process for making a solid pharmaceutical composition according to any one of claims 1-6, wherein the erdafitinib free base or the salt form of erdafitinib free base is present in the solid pharmaceutical composition in a concentration of from 45 wt% to 55 wt%, from 47 wt% to 53 wt%, or about 50 wt% and/or wherein the at least one extragranular excipient comprises microcrystalline cellulose and vinylpyrrolidone-vinyl acetate copolymer, in particular in a weight ratio of 50:50.

8. The solid pharmaceutical composition or the process for making a solid pharmaceutical composition according to any one of claims 1-7, wherein the at least one pharmaceutical excipient, the at least one intragranular pharmaceutical excipient or the at least one extragranular pharmaceutical excipient comprises a solubilizer selected from the group consisting of hydroxypropyl-beta-cyclodextrin, hydroxypropyl-gamma-cyclodextrin, sulfobutyl ether-beta-cyclodextrin sodium salt, hydroxypropyl methylcellulose acetate succinate, hydroxypropyl methylcellulose E5 (HPMC-E5), or any combination thereof.

9. The solid pharmaceutical composition or the process for making a solid pharmaceutical composition according to claim 8, wherein the solubilizer is hydroxypropyl-beta-cyclodextrin.

10. The solid pharmaceutical composition or the process for making a solid pharmaceutical composition according to claim 9, wherein the total concentration of the solubilizer in the solid pharmaceutical composition is from 1 wt% to 20 wt%, from 5 wt% to 15 wt%, from 7 wt% to 12 wt%, or about 10 wt%.

11. The solid pharmaceutical composition or the process for making a solid pharmaceutical composition according to any one of claims 1-10, wherein the solid pharmaceutical composition is a mini-tablet.

12. The solid pharmaceutical composition or the process for making a solid pharmaceutical composition of claim 11, wherein the mini-tablet is in the form of a solid

cylinder having a cylindrical axis, a cylindrical side face, circular end faces perpendicular to the cylindrical axis, a diameter across the circular end faces, and a length along the cylindrical side face, wherein the length of the mini-tablet exceeds the diameter of the mini-tablet to provide the mini-tablet with an aspect ratio of greater than 1:1, and wherein the aspect ratio is a ratio of the length to the diameter.

13. A solid pharmaceutical composition consisting essentially of:

(a) erdafitinib free base (N-(3,5-dimethoxyphenyl)-N'-(1-methylethyl)-N-[3-(l-methyl-1*H*-pyrazol-4-yl)quinoxalin-6-yl]ethane-1,2-diamine) in a concentration of 50 wt% of the solid pharmaceutical composition;

(b) hydroxypropyl-beta-cyclodextrin in a concentration of 10 wt% of the solid pharmaceutical composition;

(c) meglumine in a concentration of 1 wt% of the solid pharmaceutical composition;

(d) microcrystalline cellulose in a concentration of 17.5 wt% of the solid pharmaceutical composition;

(e) silicified microcrystalline cellulose in a concentration of 10.75 wt% of the solid pharmaceutical composition;

(f) vinylpyrrolidone-vinyl acetate copolymer in a concentration of 7.5 wt% of the solid pharmaceutical composition;

(g) colloidal silicon dioxide in a concentration of 0.25 wt% of the solid pharmaceutical composition;

(h) hydroxypropyl methylcellulose in a concentration of 1.5 wt% of the solid pharmaceutical composition; and

(i) magnesium stearate in a concentration of 1.5 wt% of the solid pharmaceutical composition; or

a solid pharmaceutical composition comprising:

(a) erdafitinib free base (N-(3,5-dimethoxyphenyl)-N'-(1-methylethyl)-N-[3-(l-methyl-1*H*-pyrazol-4-yl)quinoxalin-6-yl]ethane-1,2-diamine) in a concentration of 50 wt% of the solid pharmaceutical composition;

(b) hydroxypropyl-beta-cyclodextrin;

(c) meglumine;

(d) microcrystalline cellulose;

(e) silicified microcrystalline cellulose;

(f) vinylpyrrolidone-vinyl acetate copolymer;

(g) colloidal silicon dioxide;

(h) hydroxypropyl methylcellulose; and

(i) magnesium stearate.

14. A solid pharmaceutical composition comprising:

(a) erdafitinib free base (N-(3,5-dimethoxyphenyl)-N'-(1-methylethyl)-N-[3-(l-methyl-1*H*-pyrazol-4-yl)quinoxalin-6-yl]ethane-1,2-diamine) in a concentration of 50 wt% of the solid pharmaceutical composition;

(b) hydroxypropyl-beta-cyclodextrin in a concentration of 10 wt% of the solid pharmaceutical composition;

(c) microcrystalline cellulose in a concentration of 17.5 wt% of the solid pharmaceutical composition;

(d) silicified microcrystalline cellulose in a concentration of 11.75 wt% of the solid pharmaceutical composition;

(e) vinylpyrrolidone-vinyl acetate copolymer in a concentration of 7.5 wt% of the solid pharmaceutical composition;

(f) colloidal silicon dioxide in a concentration of 0.25 wt% of the solid pharmaceutical composition;

(g) hydroxypropyl methylcellulose in a concentration of 1.5 wt% of the solid pharmaceutical composition; and

(h) magnesium stearate in a concentration of 1.5 wt% of the solid pharmaceutical composition; or

a solid pharmaceutical composition comprising:

(a) erdafitinib free base (N-(3,5-dimethoxyphenyl)-N'-(1-methylethyl)-N-[3-(l-methyl-1*H*-pyrazol-4-yl)quinoxalin-6-yl]ethane-1,2-diamine) in a concentration of 50 wt% of the solid pharmaceutical composition;

(b) hydroxypropyl-beta-cyclodextrin;

(c) microcrystalline cellulose;

(d) silicified microcrystalline cellulose;

(e) vinylpyrrolidone-vinyl acetate copolymer;

(f) colloidal silicon dioxide;

(g) hydroxypropyl methylcellulose; and

(h) magnesium stearate.

15. A process for making a solid pharmaceutical composition comprising:

(a) preparing an intragranular solid composition by a fluid bed granulation process, the intragranular solid composition consisting essentially of:

(i) erdafitinib free base (N-(3,5-dimethoxyphenyl)-N'-(1-methylethyl)-N-[3-(l-methyl-1*H*-pyrazol-4-yl)quinoxalin-6-yl]ethane-1,2-diamine) in a concentration of 50 wt% of the solid pharmaceutical composition;

(ii) hydroxypropyl-beta-cyclodextrin in a concentration of 10 wt% of the solid pharmaceutical composition;

(iii) meglumine in a concentration of 1 wt% of the solid pharmaceutical composition;

(iv) microcrystalline cellulose in a concentration of 10 wt% of the solid pharmaceutical composition; and

(v) hydroxypropyl methylcellulose in a concentration of 1.5 wt% of the solid pharmaceutical composition;

(b) combining the intragranular solid composition with extragranular components to form a blend, wherein the extragranular components consist essentially of:

(i) microcrystalline cellulose in a concentration of 7.5 wt% of the solid pharmaceutical composition; and

(ii) vinylpyrrolidone-vinyl acetate copolymer in a concentration of 7.5 wt% of the solid pharmaceutical composition;

(iii) silicified microcrystalline cellulose in a concentration of 10.75 wt% of the solid pharmaceutical composition;

(iv) colloidal silicon dioxide in a concentration of 0.25 wt% of the solid pharmaceutical composition; and

(iv) magnesium stearate in a concentration of 1.5 wt% of the solid pharmaceutical composition; and

(c) tableting the blend to form of a solid pharmaceutical composition in the form of mini-tablets.

16. A process for making a solid pharmaceutical composition comprising:

(a) preparing an intragranular solid composition by a fluid bed granulation process, the intragranular solid composition consisting essentially of:

(i) erdafitinib free base (N-(3,5-dimethoxyphenyl)-N'-(1-methylethyl)-N-[3-(l-methyl-1*H*-pyrazol-4-yl)quinoxalin-6-yl]ethane-1,2-diamine) in a concentration of 50 wt% of the solid pharmaceutical composition;

(ii) hydroxypropyl-beta-cyclodextrin in a concentration of 10 wt% of the solid pharmaceutical composition;

(iii) microcrystalline cellulose in a concentration of 10 wt% of the solid pharmaceutical composition; and

(iv) hydroxypropyl methylcellulose in a concentration of 1.5 wt% of the solid pharmaceutical composition;

(b) combining the intragranular solid composition with extragranular components to form a blend, wherein the extragranular components consist essentially of:

(i) microcrystalline cellulose in a concentration of 7.5 wt% of the solid pharmaceutical composition; and

(ii) vinylpyrrolidone-vinyl acetate copolymer in a concentration of 7.5 wt% of the solid pharmaceutical composition;

(iii) silicified microcrystalline cellulose in a concentration of 11.75 wt% of the solid pharmaceutical composition;

(iv) colloidal silicon dioxide in a concentration of 0.25 wt% of the solid pharmaceutical composition; and

(iv) magnesium stearate in a concentration of 1.5 wt% of the solid pharmaceutical composition; and

(c) tableting the blend to form of a solid pharmaceutical composition in the form of mini-tablets.

17. A drug delivery system, comprising:

a housing defining a closed drug reservoir lumen bounded by a first wall structure formed of a first material and a second wall structure formed of a second material, the first and second wall structures being adjacent one another at two interface edges and together forming a tube defining the closed drug reservoir lumen, wherein the first material comprises a polycarbonate-based aromatic thermoplastic polyurethane and the second material comprises an aliphatic polyether-based thermoplastic polyurethane; and

a drug formulation disposed in the closed drug reservoir lumen, the drug formulation comprising erdafitinib free base or a salt form of erdafitinib free base,

wherein (i) the second wall structure, or both the first wall structure and the second wall structure, are permeable to water, and (ii) the first wall structure is impermeable to the erdafitinib free base or a salt form of erdafitinib free base and the second wall structure is permeable to the erdafitinib, such that the erdafitinib is releasable *in vivo* by diffusion through the second material forming the second wall structure.

18. A drug delivery system, comprising:

a housing defining a closed drug reservoir lumen bounded by a first wall structure formed of a first material and a second wall structure formed of a second material, the first and second wall structures being adjacent one another at two interface edges and together forming a tube defining the closed drug reservoir lumen, wherein the first material comprises an aromatic polyester hydrocarbon-based thermoplastic polyurethane and the second material comprises an aliphatic polyether-based thermoplastic polyurethane; and

a drug formulation disposed in the closed drug reservoir lumen, the drug formulation comprising erdafitinib free base or a salt form of erdafitinib free base,

wherein (i) the second wall structure, or both the first wall structure and the second wall structure, are permeable to water, and (ii) the first wall structure is impermeable to the erdafitinib free base or a salt form of erdafitinib free base and the second wall structure is permeable to the erdafitinib, such that the erdafitinib is releasable *in vivo* by diffusion through the second wall structure.

19. The drug delivery system of claim 17 or 18, wherein the second wall structure forms a longitudinal strip extending along the length of the tube.

20. The drug delivery system of any one of claims 17-19, wherein the drug delivery system is configured to release the drug over a period of 2 days to 6 months.

21. The drug delivery system of any one of claims 17-20, wherein the two interface edges are disposed at an arc angle of from 15 degrees to 270 degrees of a circumference of the tube in a cross section normal to a longitudinal axis of the tube.

22. The drug delivery system of any one of claims 17-21, wherein the drug is erdafitinib free base.

23. The drug delivery system of claim 22, wherein the drug delivery system is configured to release the erdafitinib at an average rate of 1 mg/day to 10 mg/day.

24. The drug delivery system of claim 23, wherein the system is configured to release erdafitinib at an average rate of 2 mg/day to 4 mg/day.

25. The drug delivery system of claim 23, wherein the two interface edges are disposed at an arc angle of 150 degrees to 270 degrees of a circumference of the tube in a cross section normal to a longitudinal axis of the tube.

26. The drug delivery system of claim 23 or 24, wherein the system is configured to release the erdafitinib at an average rate of 2 mg/day.

27. The drug delivery system of claim 26, wherein the two interface edges are disposed at an arc angle of about 90 degrees of a circumference of the tube in a cross section normal to a longitudinal axis of the tube.

28. The drug delivery system of claim 23 or 24, wherein the system is configured to release the erdafitinib at an average rate of 4 mg/day.

29. The drug delivery system of claim 28, wherein the two interface edges are disposed at an arc angle of about 180 degrees of a circumference of the tube in a cross section normal to a longitudinal axis of the tube.

30. The drug delivery system of any one of claims 17-29, wherein the system comprises 500 mg of the erdafitinib.

31. The drug delivery system of any one of claims 17-30, wherein the second wall structure comprises less than 50 percent of a cross sectional area of the tube, in a cross section normal to the longitudinal axis of the tube.

32. The drug delivery system of any one of claims 17-31, wherein the system is elastically deformable between a relatively straightened deployment shape suited for insertion through the urethra of a patient and into the patient's bladder and a retention shape suited to retain the system within the bladder.

33. The drug delivery system of any one of claims 17-32, wherein the system is elastically deformable and has a bi-oval retention shape, and the tube has two opposing free ends which lie within an outer boundary of the bi-oval retention shape.

34. The drug delivery system of any one of claims 17-33, further comprising a retention frame lumen.

35. The drug delivery system of any one of claims 17-34, wherein the first material has a Shore durometer value from 70A to 80A.

36. The drug delivery system of any one of claims 17-35, wherein the drug formulation comprises the solid pharmaceutical composition of any one of claims 1, 3 and 7-14.

37. The drug delivery system of any one of claims 17-36, wherein the drug formulation is in the form of a plurality of mini-tablets serially arranged in the drug lumen.

38. The drug delivery system of claim 30, wherein the plurality of mini-tablets comprise the mini-tablets of claim 12.

39. A drug delivery system, comprising:

a housing defining a drug reservoir lumen bounded by a first wall structure formed of a first material and a second wall structure formed of a second material, wherein the first material comprises a polycarbonate-based aromatic thermoplastic polyurethane and the second material comprises an aliphatic polyether-based thermoplastic polyurethane; and

a drug formulation disposed in the drug reservoir lumen, the drug formulation comprising erdafitinib free base or a salt form of erdafitinib free base,

wherein (i) the second wall structure, or both the first wall structure and the second wall structure, are permeable to water, and (ii) the first wall structure is impermeable to the erdafitinib and the second wall structure is permeable to the erdafitinib, such that the erdafitinib is releasable *in vivo* by diffusion through the second material forming the second wall structure.

40. The drug delivery system of claim 39, wherein the drug formulation comprises erdafitinib free base.

41. The drug delivery system of claim 40, wherein the first and second wall structures are adjacent one another at two interface edges and together form a tube, and (i) the drug delivery system is configured to release the erdafitinib at an average rate of 2 mg/day and the two interface edges are disposed at an arc angle of about 90 degrees of a circumference of the tube in a cross section normal to a longitudinal axis of the tube, (ii) the drug delivery system is configured to release the erdafitinib at an average rate of 4 mg/day and the two interface edges are disposed at an arc angle of about 180 degrees of a circumference of the tube in a cross section normal to a longitudinal axis of the tube, or (iii) the drug delivery system is configured to

release the erdafitinib at an average rate of 6 mg/day and the two interface edges are disposed at an arc angle of 240 degrees.

42. A drug delivery system, comprising:

a housing defining a closed drug reservoir lumen bounded by a first wall structure formed of a first material and a second wall structure formed of a second material, the first and second wall structures being adjacent one another at two interface edges and together forming a tube defining the closed drug reservoir lumen, with the second wall structure forming a longitudinal strip extending along the length of the tube, wherein the first material comprises an aromatic polyester hydrocarbon-based thermoplastic polyurethane and the second material comprises an aliphatic polyether-based thermoplastic polyurethane; and

a drug formulation disposed in the closed drug reservoir lumen, the drug formulation comprising the solid pharmaceutical composition of any one of claims 1, 3 and 7-14,

wherein (i) the second wall structure, or both the first wall structure and the second wall structure, are permeable to water, and (ii) the first wall structure is impermeable to the erdafitinib and the second wall structure is permeable to the erdafitinib, such that the erdafitinib is releasable *in vivo* by diffusion through the second wall structure,

wherein the drug delivery system is configured to release a therapeutically effective amount of the erdafitinib at a substantially zero order release rate over at least 3 days, and

wherein (i) the drug delivery system is configured to release the erdafitinib at an average rate of 2 mg/day and the two interface edges are disposed at an arc angle of about 90 degrees of a circumference of the tube in a cross section normal to a longitudinal axis of the tube, or (ii) the drug delivery system is configured to release the erdafitinib at an average rate of 4 mg/day and the two interface edges are disposed at an arc angle of about 180 degrees of a circumference of the tube in a cross section normal to a longitudinal axis of the tube.

43. Use of erdafitinib for the treatment of bladder cancer, comprising locally delivering erdafitinib into the bladder of a patient in need thereof, wherein the erdafitinib is in the form of the solid pharmaceutical composition of any one of claims 1, 3 and 7-14.

44. An intravesical system for use in intravesical administration of erdafitinib, the intravesical system configured to be deployed into the bladder of a patient and to release the erdafitinib from the intravesical system, wherein the intravesical system comprises the solid pharmaceutical composition of any one of claims 1, 3 and 7-14.

45. Use of an intravesical system for treating bladder cancer comprising deploying the intravesical system into the bladder of a patient, the intravesical system comprising the solid pharmaceutical composition of any one of claims 1, 3 and 7-14.

46. Use of erdafitinib for treating bladder cancer in a patient comprising delivering the erdafitinib to the bladder by deploying to the bladder of the patient, the drug delivery system of any one of claims 17-42.

47. The drug delivery system of any one of claims 17-42, wherein the drug delivery device comprises 44-46 of erdafitinib minitablets.

48. The drug delivery system of any one of claims 37-42 and 47, wherein the erdafitinib minitablets comprises the solid pharmaceutical formulation of claim 13.

49. The drug delivery system of any one of claims 37-42 and 47, wherein the erdafitinib minitablets comprises the solid pharmaceutical formulation of claim 14.

50. The drug delivery system of any one of claims 17-42 and 47-49, wherein the first material comprises AC-4075A-B20 or AR-75A and the second material comprises EG-80A.

51. Use of erdafitinib for the manufacture of a medicament for the treatment of bladder cancer, comprising locally delivering erdafitinib into the bladder of a patient in need thereof, wherein the erdafitinib is in the form of the solid pharmaceutical composition of any one of claims 1-3 and 7-14.

52. Use of an intravesical system in the manufacture of a medicament for treating bladder cancer, comprising deploying the intravesical system into the bladder of a patient, the intravesical system comprising the solid pharmaceutical composition of any one of claims 1-3 and 7-14.

53. Use of erdafitinib in the manufacture of a medicament for treating bladder cancer in a patient, comprising delivering the erdafitinib to the bladder by deploying to the bladder of the patient the drug delivery system of any one of claims 17-42.