What is claimed is:

1. Use of amisulpride in the preparation of a medicament for treating bipolar depression in a subject, wherein the medicament is a solid dosage form,

the solid oral dosage form comprising

amisulpride in the form of an unequal mixture of (R)-(+)-amisulpride and (S)-(-)-amisulpride, or pharmaceutically acceptable salts thereof, wherein the enantiomeric ratio of (R)-(+)-amisulpride to (S)-(-)-amisulpride is 85:15 by weight of free base, and

an extended release agent in an amount between 10% to 50% by total solid oral dosage form weight;

wherein between 200mg to 400mg per day of amisulpride by weight of free base is to be administered to the subject, and

wherein said administration provides a subject population average maximum QT interval prolongation relative to baseline that is less than 12 milliseconds (ms).

2. The use of claim 1, wherein said administration is once per day.

3. The use of claim 1 or 2, wherein said solid oral dosage form is a tablet.

4. The use of any one of claims 1 to 3, wherein the population average maximum QT interval prolongation relative to baseline is the population average maximum QTcF interval prolongation relative to baseline over the time period of 12 hours after said administration.

5. The use of any one of claims 1 to 3, wherein the population average maximum QT interval prolongation relative to baseline is less than 11 milliseconds (ms).

6. The use of any one of claims 1 to 3, wherein the population average maximum QT interval prolongation relative to baseline is less than 10 milliseconds (ms).

7. The use of any one of claims 1 to 6, wherein said administration is 200mg per day of amisulpride by weight of free base.

8. The use of claim 7, wherein the population average maximum QT interval prolongation relative to baseline is less than 9 milliseconds (ms).

9. The use of any one of claims 1 to 8, wherein the extended release agent comprises a matrix forming agent.

10. The use of claim 9, wherein the matrix forming agent comprises one or more cellulosic ethers.

11. The use of any one of claims 1 to 10, wherein the extended release agent is in an amount between 20% to 40% by total solid oral dosage form weight.

12. The use of any one of claims 1 to 11, wherein the extended release agent comprises hydroxypropyl methylcellulose in an amount between 20% to 30% by total solid oral dosage form weight.

13. The use of any one of claims 1 to 12, wherein said administration provides 27 hours after said administration a subject population average occupancy of dopamine D2 receptors between 20% and 60%, when the occupancy of D2 receptors is measured using Positron Emission Tomography (PET) substantially as described in Table 38 and accompanying text.

14. The use of any one of claims 1 to 13, wherein said administration provides:
    a. a blood plasma population geometric mean C*max* of amisulpride that is less than 80% of the population geometric mean C*max* achieved by an immediate release composition having the same total daily amount of amisulpride as the solid oral dosage form, and
    b. a population geometric mean AUC from 0 to 24 hours after administration (AUC_{0-24}) of amisulpride that is less than 80% of the population geometric mean AUC_{0-24} achieved by an immediate release composition having the same total daily amount of amisulpride as the solid oral dosage form.

15. The use of claim 14, wherein said immediate release composition is the immediate release composition substantially as described in Table 25 and having the same total daily amount of amisulpride as the pharmaceutical composition.

16. Use of amisulpride in the preparation of medicament for treating bipolar depression in a subject, wherein the medicament is a tablet,

the tablet comprising

amisulpride in the form of an unequal mixture of (R)-(+)-amisulpride and (S)-(-)-amisulpride, or pharmaceutically acceptable salts thereof, wherein the enantiomeric ratio of (R)-(+)-amisulpride to (S)-(-)-amisulpride is 85:15 by weight of free base, and

an extended release agent in an amount between 10% to 50% by total tablet weight;

wherein between 200mg to 400mg per day of amisulpride by weight of free base is to be administered to the subject, and

wherein said administration provides a subject population average maximum QT interval prolongation relative to baseline that is less than 0.4 milliseconds (ms) per 10 mg of amisulpride.

17. The use of claim 16, wherein said administration is once per day.

18. The use of claim 16 or 17, wherein the population average maximum QT interval prolongation relative to baseline is the population average maximum QTcF interval prolongation relative to baseline over the time period of 12 hours after said administration.

19. The use of claim 16 or 17, wherein the population average maximum QT interval prolongation relative to baseline is less than 0.35 milliseconds (ms) per 10 mg of amisulpride.

20. The use of claim 16 or 17, wherein the population average maximum QT interval prolongation relative to baseline is less than 0.3 milliseconds (ms) per 10 mg of amisulpride.

21. The use of claim 16 or 17, wherein the extended release agent comprises a matrix forming agent.

22. The use of claim 21, wherein the matrix forming agent comprises one or more cellulosic ethers.

23. The use of claim 22, wherein the extended release agent comprises hydroxypropyl methylcellulose in an amount between 20% to 40% by total tablet weight.

24. The use of any one of claims 16 to 23, wherein said administration provides 27 hours after said administration a subject population average occupancy of dopamine D2 receptors between 20% and 60%, when the occupancy of D2 receptors is measured using Positron Emission Tomography (PET) substantially as described in Table 38 and accompanying text.

25. The use of any one of claims 16 to 23, wherein said administration provides a population C*max* / C*min* ratio of amisulpride that is less than 2, wherein the values of C*max* and C*min* are determined within 9 hours after administration.

26. The use of any one of claims 16 to 23, wherein said administration provides:
    a. a blood plasma population geometric mean C*max* of amisulpride that is less than 80% of the population geometric mean C*max* achieved by an immediate release composition having the same total daily amount of amisulpride as the pharmaceutical composition, and
    b. a population geometric mean AUC from 0 to 24 hours after administration (AUC_{0-24}) of amisulpride that is less than 80% of the population geometric mean AUC_{0-24} achieved by an immediate release composition having the same total daily amount of amisulpride as the pharmaceutical composition.

27. The use of claim 26, wherein said immediate release composition is the immediate release composition substantially as described in Table 25 and having the same total daily amount of amisulpride as the pharmaceutical composition

28. Use of amisulpride in the preparation of a medicament for treating bipolar depression in a subject wherein the medicament is a solid oral dosage form,
    the solid oral dosage form comprising
        amisulpride in the form of an unequal mixture of (R)-(+)-amisulpride and (S)-(-)-amisulpride, or pharmaceutically acceptable salts

thereof, wherein the enantiomeric ratio of (R)-(+)-amisulpride to (S)-(-)-amisulpride is 85:15 by weight of free base, and

an extended release agent in an amount between 10% to 50% by total solid oral dosage form weight;

wherein between 200mg to 400mg per day of amisulpride by weight of free base is to be administered to the subject, and

wherein said administration provides:

a subject population average maximum QTcF interval prolongation relative to baseline that is less than 12 milliseconds (ms) over the time period of 12 hours after said administration, and

27 hours after said administration a subject population average occupancy of dopamine D2 receptors between 20% and 60%.

29. The use of claim 28, wherein said administration is once per day.

30. The use of claim 28 or 29, wherein said solid oral dosage form is a tablet.

31. The use of any one of claims 28 to 30, wherein the occupancy of D2 receptors is measured using Positron Emission Tomography (PET) substantially as described in Table 38 and accompanying text.

32. The use of any one of claims 28 to 31, wherein the extended release agent comprises a matrix forming agent.

33. The use of claim 32, wherein the matrix forming agent comprises one or more cellulosic ethers.

34. Theuse of any one of claims 28 to 33, wherein the extended release agent comprises hydroxypropyl methylcellulose in an amount between 20% to 40% by total solid oral dosage form weight.

35. The use of any one of claims 28 to 34, wherein said administration provides a population C*max* / C*min* ratio of amisulpride that is less than 2, wherein the values of C*max* and C*min* are determined within 9 hours after administration.

36. The use of any one of claims 28 to 34, wherein said administration provides:

a. a blood plasma population geometric mean C*max* of amisulpride that is less than 80% of the population geometric mean C*max* achieved by an immediate release composition having the same total daily amount of amisulpride as the pharmaceutical composition, and
b. a population geometric mean AUC from 0 to 24 hours after administration (AUC_{0-24}) of amisulpride that is less than 80% of the population geometric mean AUC_{0-24} achieved by an immediate release composition having the same total daily amount of amisulpride as the pharmaceutical composition.

37. The use of claim 36, wherein said immediate release composition is the immediate release composition substantially as described in Table 25 and having the same total daily amount of amisulpride as the pharmaceutical composition.

38. A pharmaceutical composition in a solid oral dosage form, the solid oral dosage form comprising,

amisulpride in the form of an unequal mixture of (R)-(+)-amisulpride and (S)-(-)-amisulpride, or pharmaceutically acceptable salts thereof, wherein the amount of (R)-(+)-amisulpride is greater than the amount of (S)-(-)-amisulpride;

an extended release agent;

and

one or more pharmaceutically acceptable excipients,

wherein when administered to a subject population, said pharmaceutical composition provides a population average maximum QT interval prolongation relative to baseline over the time period of 12 hours after administration of: (a) less than 0.45 milliseconds (ms) per 10 mg of amisulpride; or (b) less than 0.40 milliseconds (ms) per 10 mg of amisulpride; or (c) less than 0.35 milliseconds (ms) per 10 mg of amisulpride; or (d) less than 0.30 milliseconds (ms) per 10 mg of amisulpride; or (e) less than 0.25 milliseconds (ms) per 10 mg of amisulpride; or (f) less than 0.20 milliseconds (ms) per 10 mg of amisulpride; or (g) less than 0.15 milliseconds (ms) per 10 mg of amisulpride; or (h) less than 0.10 milliseconds (ms) per 10 mg of amisulpride; or (i) less than 0.05 milliseconds (ms) per 10 mg of amisulpride or (j) less than 0.02 milliseconds (ms) per 10 mg of amisulpride.

39. The pharmaceutical composition of claim 38, wherein the population average maximum QT interval prolongation relative to baseline is the population average maximum QTcF interval prolongation relative to baseline.

40. The pharmaceutical composition of claim 38 or 39, wherein the combined amount of (R)-(+)-amisulpride and (S)-(-)-amisulpride, or pharmaceutically acceptable salts thereof, is: (a) 100mg; or (b) 160 mg; or (c) 200mg; or (d) 300mg; or (e) 400mg; or (f) 500mg; or (g) or 600mg by weight of free base.

41. A pharmaceutical composition in a solid oral dosage form, the solid oral dosage form comprising,

200 mg of amisulpride in the form of an unequal mixture of (R)-(+)-amisulpride and (S)-(-)-amisulpride, or pharmaceutically acceptable salts thereof, wherein the amount of (R)-(+)-amisulpride is greater than the amount of (S)-(-)-amisulpride;

an extended release agent;

and

one or more pharmaceutically acceptable excipients,

wherein when administered to a subject population provides a population average maximum QTcF interval prolongation relative to baseline over the time period of 12 hours after administration of: (a) less than 10 milliseconds (ms); or (b) less than 9 milliseconds (ms); or (c) less than 8 milliseconds (ms); or (d) less than 7 milliseconds (ms); or (e) less than 6 milliseconds (ms); or (f) less than 5 milliseconds (ms).

42. The pharmaceutical composition of claim 41, wherein the population average maximum QTcF interval prolongation relative to baseline is the population average maximum QTcF interval prolongation relative to baseline at geometric mean C*max*.

43. A pharmaceutical composition in a solid oral dosage form, the solid oral dosage form comprising,

amisulpride in the form of an unequal mixture of (R)-(+)-amisulpride and (S)-(-)-amisulpride, or pharmaceutically acceptable salts thereof, wherein the amount of (R)-(+)-amisulpride is greater than the amount of (S)-(-)-amisulpride;

an extended release agent;

and

one or more pharmaceutically acceptable excipients,

wherein when administered to a subject population, the pharmaceutical composition provides a population average maximum QT interval prolongation relative to baseline over the time period of 12 hours after administration, compared to an immediate release composition having the same total daily amount of amisulpride as the pharmaceutical composition, that is: (a) at least 75% less than that of said immediate release composition; or (b) at least 65% less than that of said immediate release composition; or (c) at least 60% less than that of said immediate release composition; or (d) at least 55% less than that of said immediate release composition; or (e) at least 50% less than that of said immediate release composition.

44. The pharmaceutical composition of claim 43, wherein the population average maximum QT interval prolongation relative to baseline is the population average maximum QTcF interval prolongation relative to baseline.

45. The pharmaceutical composition of claim 43 or 44, wherein said immediate release composition is the immediate release composition substantially as described in Table 25 and having the same total daily amount of amisulpride as the pharmaceutical composition.

46. The pharmaceutical composition of claim 43 or 44, wherein the combined amount of (R)-(+)-amisulpride and (S)-(-)-amisulpride, or pharmaceutically acceptable salts thereof, is: (a) 100mg; or (b) 160 mg; or (c) 200mg; or (d) 300mg; or (e) 400mg; or (f) 500mg; or (g) or 600mg by weight of free base.

47. A pharmaceutical composition in a solid oral dosage form, the solid oral dosage form comprising,

amisulpride in the form of an unequal mixture of (R)-(+)-amisulpride and (S)-(-)-amisulpride, or pharmaceutically acceptable salts thereof, wherein the amount of (R)-(+)-amisulpride is greater than the amount of (S)-(-)-amisulpride;

an extended release agent;

and

one or more pharmaceutically acceptable excipients,

wherein when said pharmaceutical composition is administered to a subject population provides at 27 hours after administration a population average occupancy of dopamine D2 receptors that is:

(a) at least 85% of the dopamine D2 receptors occupancy achieved by an immediate release composition having the same total daily amount of amisulpride as the pharmaceutical composition; or

(b) at least 90% of the dopamine D2 receptors occupancy achieved by an immediate release composition having the same total daily amount of amisulpride as the pharmaceutical composition; or

(c) at least 95% of the dopamine D2 receptors occupancy achieved by an immediate release composition having the same total daily amount of amisulpride as the pharmaceutical composition.

48. The pharmaceutical composition of claim 47, wherein said immediate release composition is the immediate release composition substantially as described in Table 25 and having the same total daily amount of amisulpride as the pharmaceutical composition.

49. The pharmaceutical composition of claim 47, wherein the combined amount of (R)-(+)-amisulpride and (S)-(-)-amisulpride, or pharmaceutically acceptable salts thereof, is: (a) 100mg; or (b) 160 mg; or (c) 200mg; or (d) 300mg; or (e) 400mg; or (f) 500mg; or (g) or 600mg by weight of free base.

50. A pharmaceutical composition in a solid oral dosage form, the solid oral dosage form comprising,

amisulpride in the form of an unequal mixture of (R)-(+)-amisulpride and (S)-(-)-amisulpride, or pharmaceutically acceptable salts thereof, wherein the amount of (R)-(+)-amisulpride is greater than the amount of (S)-(-)-amisulpride,

an extended release agent;

and

one or more pharmaceutically acceptable excipients,

wherein said pharmaceutical composition when administered to a subject population is effective in minimizing the difference between C*min* and C*max* of

amisulpride compared to an immediate release composition having the same total daily amount of amisulpride as the pharmaceutical composition, wherein the value of C*min* is determined within 9 hours after administration.

51. The pharmaceutical composition of claim 50, wherein the combined amount of (R)-(+)-amisulpride and (S)-(-)-amisulpride, or pharmaceutically acceptable salts thereof, is: (a) 100mg; or (b) 160 mg; or (c) 200mg; or (d) 300mg; or (e) 400mg; or (f) 500mg; or (g) or 600mg by weight of free base.

52. A pharmaceutical composition in a solid oral dosage form, the solid oral dosage form comprising,

amisulpride in the form of an unequal mixture of (R)-(+)-amisulpride and (S)-(-)-amisulpride, or pharmaceutically acceptable salts thereof, wherein the amount of (R)-(+)-amisulpride is greater than the amount of (S)-(-)-amisulpride,

an extended release agent;

and

one or more pharmaceutically acceptable excipients,

wherein when said composition is administered to a subject population provides a C*max* / C*min* ratio of amisulpride, wherein the value of C*min* is determined within 9 hours after administration, that is: (a) less than 2; or (b) less than 1.9; or (c) less than 1.8.

53. The pharmaceutical composition of claim 52, wherein the values of C*max* and C*min* are the population geometric mean values and the values are determined within 9 hours after administration.

54. The pharmaceutical composition of claim 52 or 53, wherein the solid oral dosage when administered in a total amount of amisulpride of 200 mg provides a blood plasma population geometric mean C*max* of (a) less than 350 ng/mL; (b) less than 300 ng/mL; or (c) less than 250 ng/mL.

55. The pharmaceutical composition of claim 52 or 53, wherein the solid oral dosage when administered in a total amount of amisulpride of 400 mg provides a blood

plasma population geometric mean C*max* of (a) less than 500 ng/mL; (b) less than 475 ng/mL; or (c) less than 450 ng/mL.

56. The pharmaceutical composition of claim 52 or 53, wherein the combined amount of (R)-(+)-amisulpride and (S)-(-)-amisulpride, or pharmaceutically acceptable salts thereof, is: (a) 100mg; or (b) 160 mg; or (c) 200mg; or (d) 300mg; or (e) 400mg; or (f) 500mg; or (g) or 600mg by weight of free base.

57. A pharmaceutical composition in a solid oral dosage form, the solid oral dosage form comprising,

amisulpride in the form of an unequal mixture of (R)-(+)-amisulpride and (S)-(-)-amisulpride, or pharmaceutically acceptable salts thereof, wherein the amount of (R)-(+)-amisulpride is greater than the amount of (S)-(-)-amisulpride; and

an extended release agent,

wherein the solid oral dosage form when dissolution tested using a two-stage in vitro gastrointestinal simulation dissolution test:

(a) releases less than 30% of the amisulpride after 1 hour, releases more than 20% and less than 60% of the amisulpride after 3 hours, and releases more than 30% and less than 100% of the amisulpride after 6 hours; or

(b) releases less than 30% of the amisulpride after 1 hour, releases more than 20% and less than 60% of the amisulpride after 3 hours, and releases more than 30% and less than 75% of the amisulpride after 6 hours; or

(c) releases less than 20% of the amisulpride after 1 hour, releases more than 20% and less than 50% of the amisulpride after 3 hours, and releases more than 30% and less than 75% of the amisulpride after 6 hours; or

(d) releases less than 20% of the amisulpride after 1 hour, releases more than 20% and less than 50% of the amisulpride after 3 hours, and releases more than 30% and less than 50% of the amisulpride after 6 hours; or

(e) releases no more than 30% of the amisulpride after 1 hour, releases between 30% and 75% of the amisulpride after 3 hours, and releases more than 75% of the amisulpride after 12 hours; or

(f) releases less than 30% of the amisulpride after 1 hour, releases more than 20% and less than 60% of the amisulpride after 3 hours, releases more than 30% and less

than 100% of the amisulpride after 6 hours, and releases more than 75% of the amisulpride after 10 hours; or

(g) releases less than 30% of the amisulpride after 1 hour, releases more than 20% and less than 60% of the amisulpride after 3 hours, releases more than 30% and less than 100% of the amisulpride after 6 hours, and releases more than 75% of the amisulpride after 8 hours; or

(h) releases less than 30% of the amisulpride after 1 hour, releases more than 20% and less than 60% of the amisulpride after 3 hours, releases more than 30% and less than 75% of the amisulpride after 6 hours, and releases more than 75% of the amisulpride after 10 hours; or

(i) releases less than 20% of the amisulpride after 1 hour, releases more than 20% and less than 60% of the amisulpride after 3 hours, releases more than 30% and less than 100% of the amisulpride after 6 hours, and releases more than 75% of the amisulpride after 10 hours; or

(j) releases less than 30% of the amisulpride after 1 hour, releases more than 20% and less than 60% of the amisulpride after 3 hours, releases more than 30% and less than 50% of the amisulpride after 6 hours, and releases more than 75% of the amisulpride after 10 hours.

58. The pharmaceutical composition of claim 57, wherein the two-stage gastrointestinal simulation dissolution test comprises in the first stage 500ml of an aqueous media having a pH of 2 and adding after 1 hour 400ml of an aqueous buffer media such that the second stage pH is 6.8; where the temperature in both stages of the two-stage in vitro gastrointestinal simulation dissolution test is 37°C.

59. The pharmaceutical composition of claim 57, wherein the two-stage gastrointestinal simulation dissolution test is conducted in a paddle apparatus substantially in accord with that described in one of more of: (a) United States Pharmacopeia Convention (USP) Apparatus 2 of Chapter 711 Dissolution; USP41-NF36 General Chapter <711> Dissolution, and (b) Japanese Pharmacopeia (JP) General test <6.10>.

60. A pharmaceutical composition in a solid oral dosage form, the solid oral dosage form comprising,

amisulpride in the form of an unequal mixture of (R)-(+)-amisulpride and (S)-(-)-amisulpride, or pharmaceutically acceptable salts thereof, wherein the amount of (R)-(+)-amisulpride is greater than the amount of (S)-(-)-amisulpride; and

an extended release agent,

wherein the solid oral dosage form when dissolution tested using the two-stage in vitro dissolution test described in Table 5 in the paddle apparatus described in United States Pharmacopeia Convention (USP) Apparatus 2 of Chapter 711 Dissolution; USP41-NF36 General Chapter <711> Dissolution has a dissolution profile substantially the same as: (a) the profile of Lot 3C in FIG. 1C; or (b) the profile of Lot 2C in FIG. 1C; or (c) the profile of Lot 3Z used in the study of Example 7A, Part 1 or Part 2 in FIG. 1D; or (d) the profile of Lot 3Z used in fed state study of Example 7A, Part 1 in FIG. 1D; or (e) the profile of Lot 3Z used in MAD/PET study of Example 7B in FIG. 1D; or (f) the profile of Lot 4Z in FIG. 1D; or (g) the profile of Lot 5Z in FIG. 1D; or (h) the profile of Lot 6Z in FIG. 1D; or (i) the profile of Lot 7C in FIG. 1E over the time period from 0 to 6 hours; or (j) the profile of Lot 8C in FIG. 1E over the time period from 0 to 6 hours; or (k) the profile of Lot 3Z used in the study of Example 7B, Example 7A Part 1, or (l) the profile of Lot 3Z used in the study of Example 7A Part 2 in FIG. 1D.

61. A pharmaceutical composition in a solid oral dosage form, the solid oral dosage form comprising,

amisulpride in the form of an unequal mixture of (R)-(+)-amisulpride and (S)-(-)-amisulpride, or pharmaceutically acceptable salts thereof, wherein the amount of (R)-(+)-amisulpride is greater than the amount of (S)-(-)-amisulpride; and

an extended release agent,

wherein when said pharmaceutical composition is administered to a subject population provides a plasma concentration profile substantially the same as: (a) the profile of Lot 4Z in FIG. 22B; or (b) the profile of Lot 3Z in FIG. 22C; or (c) the profile of Lot 3Z Fed State in FIG. 22D; (d) the profile of Lot 4Z in FIG. 22F; or (e) the profile of Lot 3Z in FIG. 22H; or (f) the profile of Lot 3Z Fed State in FIG. 22I; or (g) the profile of Lot 3Z in FIG. 22J; or (h) the profile of Lot 5Z in FIG. 22G; or (i) the profile of Lot 6Z in FIG. 22K.

62. A pharmaceutical composition in a solid oral dosage form, the solid oral dosage form comprising,

amisulpride in the form of an unequal mixture of (R)-(+)-amisulpride and (S)-(-)-amisulpride, or pharmaceutically acceptable salts thereof, wherein the amount of (R)-(+)-amisulpride is greater than the amount of (S)-(-)-amisulpride; and

an extended release agent,

wherein when said solid oral dosage form is administered to a subject population provides:

(i) a population geometric mean T*max* of amisulpride is between 4 hours and 6 hours after administration; and

(ii) a AUC to *Tmax* ($AUC_{0\text{-}Tmax}$) that is less than: (a) 19% of the area under the curve from administration to 48 hours ($AUC_{0\text{-}48}$); or (b) 18% of the population mean area under the curve from administration to 48 hours ($AUC_{0\text{-}48}$); or (c) 17% of the area under the curve from administration to 48 hours ($AUC_{0\text{-}48}$); or (d) 16% of the area under the curve from administration to 48 hours ($AUC_{0\text{-}48}$); or (e) 15% of the area under the curve from administration to 48 hours ($AUC_{0\text{-}48}$); or (f) 14% of the area under the curve from administration to 48 hours ($AUC_{0\text{-}48}$); or (g) 13% of the area under the curve from administration to 48 hours ($AUC_{0\text{-}48}$); or (h) 12% of the area under the curve from administration to 48 hours ($AUC_{0\text{-}48}$).

63. The pharmaceutical composition of any one of claims 40, 41, 46, 47, 51, and 56 wherein the enantiomeric ratio of (R)-(+)-amisulpride to (S)-(-)-amisulpride, or pharmaceutically acceptable salts thereof, is 85:15 by weight of free base.

64. The pharmaceutical composition of claim 63, wherein the one or more pharmaceutically acceptable excipients comprise an extended release agent.

65. The pharmaceutical composition of claim 64, wherein the extended release agent is in an amount: (a) between 10% and 50% by total solid oral dosage form weight; or (b) between 30% and 50% by total solid oral dosage form weight; or (c) between 20%

and 40% by total solid oral dosage form weight; or (d) between 20% and 30% by total solid oral dosage form weight.

66. The pharmaceutical composition of claim 65, wherein the solid oral dosage form is a tablet.

67. The pharmaceutical composition of claim 66, wherein the extended release agent comprises a matrix forming agent.

68. The pharmaceutical composition of claim 67, wherein the matrix forming agent comprises one or more cellulosic ethers.

69. The pharmaceutical composition of claim 66, wherein the extended release agent comprises hydroxypropyl methylcellulose in an amount between 20% to 40% by total solid oral dosage form weight.

70. The pharmaceutical composition of claim 63, wherein the solid oral dosage form comprises by total solid oral dosage form weight:

between 35% to 45% of said amisulpride,
between 20% to 40% of a pharmaceutically acceptable filler, and
between 20% to 35% of the extended release agent.

71. The pharmaceutical composition of claim 63, wherein when said pharmaceutical composition is administered to the subject population provides:

a. a blood plasma population geometric mean C*max* of amisulpride that is less than 80% of the population geometric mean C*max* achieved by an immediate release composition having the same total daily amount of amisulpride as the pharmaceutical composition, and
b. a population geometric mean AUC from 0 to 24 hours after administration (AUC_{0-24}) of amisulpride that is less than 80% of the population geometric mean AUC_{0-24} achieved by an immediate release composition having the same total daily amount of amisulpride as the pharmaceutical composition.

72. The pharmaceutical composition of claim 71, wherein said immediate release composition is the immediate release composition substantially as described in Table 25 and having the same total daily amount of amisulpride as the pharmaceutical composition.

73. The pharmaceutical composition of claim 63, wherein when said pharmaceutical composition is administered to the subject population provides 27 hours after said administration:

    (a) a population average occupancy of dopamine D2 receptors between 20% and 60%, or

    (b) a population average occupancy of dopamine D2 receptors between 30% and 50%;

    wherein the occupancy of D2 receptors is measured using Positron Emission Tomography (PET) substantially as described in Table 38 and accompanying text.

74. The pharmaceutical composition according of claim 73, wherein the amount of (S)-(-)-amisulpride, or pharmaceutically acceptable salts thereof, is less than 100mg by weight of free base.

75. The use of a solid oral dosage form of claim 63 in the manufacture of a medicament for treating a psychiatric disorder.

76. The use of claim 75, wherein the solid oral dosage form is to be administered once per day in a total daily amount of between 200mg to 400mg per day of said amisulpride by weight of free base.

77. The use of claim 76, wherein the psychiatric disorder is: (a) a depressive disorder; or (b) bipolar disorder; or (c) bipolar depression; or (d) major depressive disorder (MDD); or (e) major depressive disorder with mixed features (MDD-MF); or (f) treatment resistant depression (TRD); or (g) schizophrenia; or (h) negative symptoms of schizophrenia.

78. The use of claim 76, wherein the psychiatric disorder is bipolar disorder; bipolar depression; or both.

79. A use of a solid oral dosage form of claim 63 in the manufacture of a medicament for treating bipolar depression wherein the medicament is for once per day administration in a total daily amount of between 200mg to 400mg per day of said amisulpride by weight of free base.

80. A use of a therapeutically effective amount of a pharmaceutical composition of claim 63 in the preparation of a medicament for treating bipolar depression.

81. The pharmaceutical composition of any one of claims 57, 60, 61, and 62, wherein the enantiomeric ratio of (R)-(+)-amisulpride to (S)-(-)-amisulpride, or pharmaceutically acceptable salts thereof, is 85:15 by weight of free base.

82. The pharmaceutical composition of claim 81, wherein the extended release agent is in an amount: (a) between 10% and 50% by total solid oral dosage form weight; or (b) between 30% and 50% by total solid oral dosage form weight; or (c) between 20% and 40% by total solid oral dosage form weight; or (d) between 20% and 30% by total solid oral dosage form weight.

83. The pharmaceutical composition of claim 82, wherein the solid oral dosage form is a tablet.

84. The pharmaceutical composition of claim 83, wherein the extended release agent comprises a matrix forming agent.

85. The pharmaceutical composition of claim 84, wherein the matrix forming agent comprises one or more cellulosic ethers.

86. The pharmaceutical composition of any one of claims 83 to 85, wherein the extended release agent comprises hydroxypropyl methylcellulose in an amount between 20% to 40% by total solid oral dosage form weight.

87. The pharmaceutical composition of any one of claims 83 to 86, wherein the solid oral dosage form comprises one or more of (a) a filler; (b) a binder; and (c) a lubricant.

88. The pharmaceutical composition of claim 87, wherein the lubricant comprises magnesium stearate.

89. The pharmaceutical composition of claim 87 or 88, wherein the filler comprises D-mannitol and wherein the solid oral dosage form comprises between 0.5% to 2% by total tablet weight of a binder comprising polyvinyl alcohol.

90. The pharmaceutical composition of claim 81, wherein the solid oral dosage form comprises by total solid oral dosage form weight:

between 35% to 45% of said amisulpride,
between 20% to 40% of a pharmaceutically acceptable filler, and
between 20% to 35% of the extended release.

91. The pharmaceutical composition of any one of claims 38, 41, 43, 47, 50, 52, 57, 60, 61, and 62, wherein the enantiomeric ratio of (R)-(+)-amisulpride to (S)-(-)-amisulpride is from: (a) 65:35 to 88:12 by weight of free base; or (b) 75:25 to 88:12 by weight of free base; or (c) 80:20 to 88:12 by weight of free base; or (d) 85:15 to 90:10 by weight of free base.

92. The pharmaceutical composition of any one of claims 38, 43, 47, 50, 52, 57, 60, and 62, wherein the combined amount of (R)-(+)-amisulpride and (S)-(-)-amisulpride, or pharmaceutically acceptable salts thereof, is from: (a) 50 mg to 600 mg by weight of free base; or (b) 200 mg to 600 mg by weight of free base; or (c) 100 mg to 500 mg by weight of free base; or (d) 100 mg to 400 mg by weight of free base; or (e) 200 mg to 400 mg by weight of free base.

93. The pharmaceutical composition of claim 92, comprising:

170 mg of (R)-(+)-amisulpride, or a pharmaceutically acceptable salt thereof, by weight of free base; and

30 mg of (S)-(-)-amisulpride, or a pharmaceutically acceptable salt thereof, by weight of free base.

94. The pharmaceutical composition of claim 92, comprising:

85 mg of (R)-(+)-amisulpride, or a pharmaceutically acceptable salt thereof, by weight of free base; and

15 mg of (S)-(-)-amisulpride, or a pharmaceutically acceptable salt thereof, by weight of free base.

95. A pharmaceutical composition of any one of claims 47, 50, 52, 57, 60, 61, and 62, wherein when administered to a subject population provides a population average maximum QT interval prolongation relative to baseline over the time period of 12 hours after administration of:

(a) less than 0.45 milliseconds (ms) per 10 mg of amisulpride; or
(b) less than 0.40 milliseconds (ms) per 10 mg of amisulpride; or
(c) less than 0.35 milliseconds (ms) per 10 mg of amisulpride; or
(d) less than 0.30 milliseconds (ms) per 10 mg of amisulpride; or
(e) less than 0.25 milliseconds (ms) per 10 mg of amisulpride; or
(f) less than 0.20 milliseconds (ms) per 10 mg of amisulpride; or
(g) less than 0.15 milliseconds (ms) per 10 mg of amisulpride; or
(h) less than 0.10 milliseconds (ms) per 10 mg of amisulpride; or
(i) less than 0.05 milliseconds (ms) per 10 mg of amisulpride or
(j) less than 0.02 milliseconds (ms) per 10 mg of amisulpride.

96. A pharmaceutical composition of any one of claims 38, 41, 43, 47, 50, 52, 57, 60, and 61, wherein, when administered to a subject population provides, compared to an immediate release composition having the same total daily amount of amisulpride as the pharmaceutical composition, a blood plasma C*max* of amisulpride that is: (a) less than 80% of the C*max* of said immediate release composition; (b) less than 75% of the C*max* of said immediate release composition; or (c) less than 65% of the C*max* of said immediate release composition; or (d) is less than 60% of the C*max* of said immediate release composition; or (e) less than 55% of the C*max* of said immediate release composition; or (f) less than 50% of the C*max* of said immediate release composition.

97. A pharmaceutical composition of any one of claims 40, 41, 46, 47, 50, 56, 57, 60, 61, and 62, wherein, when administered to a subject population provides a suppression of the time in rapid eye movement (REM) sleep as characterized by: (a) a decrease in REM sleep by an amount greater than 10 minutes; or (b) a decrease in REM sleep by an

amount 15 minutes to 45 minutes; or (c) a decrease in REM sleep by an amount 15 minutes to 30 minutes.

98. A pharmaceutical composition of any one of claims 40, 41, 46, 47, 50, 56, 57, 60, 61, and 62, wherein, when administered to a subject population provides a suppression of the time in rapid eye movement (REM) sleep as characterized by: (a) a latency to REM sleep by an amount greater than 20 minutes; or (b) a latency to REM sleep by an amount greater than 30 minutes.

99. A pharmaceutical composition of any one of claims 40, 41, 46, 47, 50, 56, 57, 60, 61, and 62, wherein, when administered to a subject population provides a suppression of the time in rapid eye movement (REM) sleep as characterized by: (a) a decrease in total REM sleep time relative to total sleep time by an amount greater than 5 %; or (b) a decrease in total REM sleep time relative to total sleep time by an amount greater than 6.5 %.

100. The pharmaceutical composition of any one of claims 40, 41, 46, 47, 50, 56, 57, 60, and 61, wherein the pharmaceutical composition when administered to a subject population provides a population geometric mean T*max* between 4 hours and 6 hours after administration.

101. A pharmaceutical composition in the form of a tablet, the tablet comprising,

amisulpride in the form of an unequal mixture of (R)-(+)-amisulpride and (S)-(-)-amisulpride, or pharmaceutically acceptable salts thereof, wherein

the enantiomeric ratio of (R)-(+)-amisulpride to (S)-(-)-amisulpride is from 80:20 to 88:12 by weight of free base, and

the combined amount of (R)-(+)-amisulpride and (S)-(-)-amisulpride, or pharmaceutically acceptable salts thereof, is from 100 mg to 500 mg by weight of free base; and

an extended release agent in an amount between 10% and 50% by total tablet weight.

102. The pharmaceutical composition of claim 101, wherein the combined amount of (R)-(+)-amisulpride and (S)-(-)-amisulpride, or pharmaceutically acceptable salts thereof,

is 200 mg by weight of free base and the enantiomeric ratio of (R)-(+)-amisulpride to (S)-(-)-amisulpride is 85:15 by weight of free base.

103. The pharmaceutical composition of claim 102, wherein the tablet comprises:

between 35% to 45% by total tablet weight of amisulpride,

between 20% to 40% by total tablet weight of a pharmaceutically acceptable filler, and

between 20% to 30% by total tablet weight of the extended release agent.

104. The pharmaceutical composition of claim 103, wherein the extended release agent comprises hydroxypropyl methylcellulose.

105. The pharmaceutical composition of claim 104, wherein the hydroxypropyl methylcellulose has a median particle size that is 5-15 times larger than the median particle size of the amisulpride.

106. The pharmaceutical composition of claim 104 or 105, wherein the filler comprises D-mannitol and wherein the tablet comprises between 0.5% to 2% by total tablet weight of a binder comprising polyvinyl alcohol.

107. The pharmaceutical composition of any one of claims 101 to 106, wherein the tablet comprises:

a granular component admixed with an extra-granular component,

the granular component comprising

amisulpride and a binder; and

the extra-granular component comprising,

an extended release agent.

108. The pharmaceutical composition of claim 107, wherein the granular component comprises one or more of (a) a filler; and (b) a binder.

109. The pharmaceutical composition of claim 108, wherein the granules comprise: (a) between 60% to 80% by weight of amisulpride, between 10% to 30% by weight of filler, and between 1% to 5% by weight of binder; or (b) between 70% to 80% by

weight of amisulpride, between 20% to 25% by weight of filler, and between 1% to 5% by weight of binder.

110. The pharmaceutical composition of claim 108, wherein the granular component comprises:

between 73% to 78% by weight of amisulpride,

between 10% to 12% by weight of a D-mannitol,

between 10% to 12% by weight of a pregelatinized starch, and

between 1% to 3% by weight of polyvinyl alcohol;

based on the weight of the granular component.

111. The pharmaceutical composition of claim 107, wherein the extragranular component comprises one or more of (a) a filler; (b) a binder; and (c) a lubricant.

112. The pharmaceutical composition of claim 107, wherein the tablet (granules plus extragranular component) comprises: (a) between 20% to 70% by total tablet weight of granules of extended release agent; or (b) between 10% to 50% by total tablet weight of extended release agent.

113. The pharmaceutical composition of claim 107, wherein the tablet (granules plus extragranular component) comprises: (a) a combined amount of filler in both granular and extragranular between 6% to 60% by total tablet weight; or (b) a combined amount of filler in both granular and extragranular between 10% to 50% by total tablet weight.

114. The pharmaceutical composition of claim 107, wherein the tablet (granules plus extragranular component) comprises between 1% to 2% by total tablet weight of a lubricant.

115. The pharmaceutical composition of claim 114, wherein the lubricant is magnesium stearate.

116. The pharmaceutical composition of claim 107, wherein the tablet (granules plus extragranular component) comprises:

(a) between 34% to 39% by total tablet weight of a D-mannitol, and
15% by total tablet weight of hydroxypropyl methylcellulose; or
(b) between 24% to 29% by total tablet weight of a D-mannitol, and
25% by total tablet weight of hydroxypropyl methylcellulose; or
(c) between 4% to 9% by total tablet weight of a D-mannitol, and
45% by total tablet weight of hydroxypropyl methylcellulose.