

Claims:

1. A crystalline form of 5-Chloro-N2-(2-isopropoxy-5-methyl-4-piperidin-4-yl-phenyl)-N4-[2-(propane-2-sulfonyl)-phenyl]-pyrimidine-2, 4-diamine exhibiting one or more X-ray powder diffraction peaks having maxima at diffraction angles selected from 7.2°, 8.1°, 10.8°, 12.0°, 12.4°, 13.4°, 14.4°, 14.8°, 15.7°, 16.9°, 17.7°, 18.5°, 19.0°, 19.5°, 20.0°, 20.3°, 21.1°, 21.6°, 22.4°, 22.6°, 23.0°, 24.1°, 24.5°, 25.5°, 26.0°, 26.2°, 27.0°, 27.3°, 28.3°, 29.0°, 29.1°, 30.6°, 31.3°, 32.8°, 33.5°, 34.2° and 36.4° (2 θ degrees).
2. The crystalline form of claim 1, having a melting point of 174° C, as determined by differential scanning calorimetry.
3. The crystalline form of claim 1, having a decomposition point greater than 250° C and a weight loss on drying of 0.1% at 200° C, as determined by thermogravimmetric analysis.
4. The crystalline form of claim 1, having characteristic infrared absorption bands at 3440.4, 3318.9, 2973.7, 2931.3, 2921.7, 1596.8, 1562.1, 1498.4, 1442.5, 1409.7, 1382.7, 1311.4, 1284.4, 1270.9, 1251.6, 1224.6, 1139.7, 1126.2, 1139.7, 1126.2, 1105.0, 1081.9, 1049.1, 1020.2, 1012.5, 952.7, 937.3, 894.8, 877.5, 860.1, 848.5, 817.7, 798.4, 781.0, 763.7, 756.0, 732.8, 686.6, 665.3, 644.1, 586.3 and 543.8 (in units of wavenumbers, cm⁻¹).
5. The crystalline form of claim 1, having less than 1.0 % by weight total impurities.
6. The crystalline form of claim 1, having less than 0.5% by weight total impurities.
7. The crystalline form of claim 1, having less than 0.1% by weight total impurities.
8. A crystalline form of 5-Chloro-N2-(2-isopropoxy-5-methyl-4-piperidin-4-yl-phenyl)-N4-[2-(propane-2-sulfonyl)-phenyl]-pyrimidine-2, 4-diamine exhibiting one or more X-ray powder diffraction peaks having maxima at diffraction angles selected from 5.1°, 5.5°, 5.6°, 9.5°, 9.6°, 10.1°, 11.0°, 11.8°, 12.1°, 12.6°, 13.7°, 14.5°, 14.9°, 15.2°, 16.1°, 16.6°, 16.7°, 17.0°, 17.1°, 17.5°, 17.7°, 18.0°, 18.8°, 19.0°, 19.3°, 19.5°, 20.5°, 20.9°, 21.5°, 21.9°, 22.1°, 22.3°, 22.5°, 22.7°, 22.9°, 23.1°, 23.3°, 23.5°, 23.7°, 23.9°, 24.1°, 24.3°, 24.5°, 24.7°, 24.9°, 25.1°, 25.3°, 25.5°, 25.7°, 25.9°, 26.1°, 26.3°, 26.5°, 26.7°, 26.9°, 27.1°, 27.3°, 27.5°, 27.7°, 27.9°, 28.1°, 28.3°, 28.5°, 28.7°, 28.9°, 29.1°, 29.3°, 29.5°, 29.7°, 29.9°, 30.1°, 30.3°, 30.5°, 30.7°, 30.9°, 31.1°, 31.3°, 31.5°, 31.7°, 31.9°, 32.1°, 32.3°, 32.5°, 32.7°, 32.9°, 33.1°, 33.3°, 33.5°, 33.7°, 33.9°, 34.1°, 34.3°, 34.5°, 34.7°, 34.9°, 35.1°, 35.3°, 35.5°, 35.7°, 35.9°, 36.1°, 36.3°, 36.5°, 36.7°, 36.9°, 37.1°, 37.3°, 37.5°, 37.7°, 37.9°, 38.1°, 38.3°, 38.5°, 38.7°, 38.9°, 39.1°, 39.3°, 39.5°, 39.7°, 39.9°, 40.1°, 40.3°, 40.5°, 40.7°, 40.9°, 41.1°, 41.3°, 41.5°, 41.7°, 41.9°, 42.1°, 42.3°, 42.5°, 42.7°, 42.9°, 43.1°, 43.3°, 43.5°, 43.7°, 43.9°, 44.1°, 44.3°, 44.5°, 44.7°, 44.9°, 45.1°, 45.3°, 45.5°, 45.7°, 45.9°, 46.1°, 46.3°, 46.5°, 46.7°, 46.9°, 47.1°, 47.3°, 47.5°, 47.7°, 47.9°, 48.1°, 48.3°, 48.5°, 48.7°, 48.9°, 49.1°, 49.3°, 49.5°, 49.7°, 49.9°, 50.1°, 50.3°, 50.5°, 50.7°, 50.9°, 51.1°, 51.3°, 51.5°, 51.7°, 51.9°, 52.1°, 52.3°, 52.5°, 52.7°, 52.9°, 53.1°, 53.3°, 53.5°, 53.7°, 53.9°, 54.1°, 54.3°, 54.5°, 54.7°, 54.9°, 55.1°, 55.3°, 55.5°, 55.7°, 55.9°, 56.1°, 56.3°, 56.5°, 56.7°, 56.9°, 57.1°, 57.3°, 57.5°, 57.7°, 57.9°, 58.1°, 58.3°, 58.5°, 58.7°, 58.9°, 59.1°, 59.3°, 59.5°, 59.7°, 59.9°, 60.1°, 60.3°, 60.5°, 60.7°, 60.9°, 61.1°, 61.3°, 61.5°, 61.7°, 61.9°, 62.1°, 62.3°, 62.5°, 62.7°, 62.9°, 63.1°, 63.3°, 63.5°, 63.7°, 63.9°, 64.1°, 64.3°, 64.5°, 64.7°, 64.9°, 65.1°, 65.3°, 65.5°, 65.7°, 65.9°, 66.1°, 66.3°, 66.5°, 66.7°, 66.9°, 67.1°, 67.3°, 67.5°, 67.7°, 67.9°, 68.1°, 68.3°, 68.5°, 68.7°, 68.9°, 69.1°, 69.3°, 69.5°, 69.7°, 69.9°, 70.1°, 70.3°, 70.5°, 70.7°, 70.9°, 71.1°, 71.3°, 71.5°, 71.7°, 71.9°, 72.1°, 72.3°, 72.5°, 72.7°, 72.9°, 73.1°, 73.3°, 73.5°, 73.7°, 73.9°, 74.1°, 74.3°, 74.5°, 74.7°, 74.9°, 75.1°, 75.3°, 75.5°, 75.7°, 75.9°, 76.1°, 76.3°, 76.5°, 76.7°, 76.9°, 77.1°, 77.3°, 77.5°, 77.7°, 77.9°, 78.1°, 78.3°, 78.5°, 78.7°, 78.9°, 79.1°, 79.3°, 79.5°, 79.7°, 79.9°, 80.1°, 80.3°, 80.5°, 80.7°, 80.9°, 81.1°, 81.3°, 81.5°, 81.7°, 81.9°, 82.1°, 82.3°, 82.5°, 82.7°, 82.9°, 83.1°, 83.3°, 83.5°, 83.7°, 83.9°, 84.1°, 84.3°, 84.5°, 84.7°, 84.9°, 85.1°, 85.3°, 85.5°, 85.7°, 85.9°, 86.1°, 86.3°, 86.5°, 86.7°, 86.9°, 87.1°, 87.3°, 87.5°, 87.7°, 87.9°, 88.1°, 88.3°, 88.5°, 88.7°, 88.9°, 89.1°, 89.3°, 89.5°, 89.7°, 89.9°, 90.1°, 90.3°, 90.5°, 90.7°, 90.9°, 91.1°, 91.3°, 91.5°, 91.7°, 91.9°, 92.1°, 92.3°, 92.5°, 92.7°, 92.9°, 93.1°, 93.3°, 93.5°, 93.7°, 93.9°, 94.1°, 94.3°, 94.5°, 94.7°, 94.9°, 95.1°, 95.3°, 95.5°, 95.7°, 95.9°, 96.1°, 96.3°, 96.5°, 96.7°, 96.9°, 97.1°, 97.3°, 97.5°, 97.7°, 97.9°, 98.1°, 98.3°, 98.5°, 98.7°, 98.9°, 99.1°, 99.3°, 99.5°, 99.7°, 99.9°, 100.1°, 100.3°, 100.5°, 100.7°, 100.9°, 101.1°, 101.3°, 101.5°, 101.7°, 101.9°, 102.1°, 102.3°, 102.5°, 102.7°, 102.9°, 103.1°, 103.3°, 103.5°, 103.7°, 103.9°, 104.1°, 104.3°, 104.5°, 104.7°, 104.9°, 105.1°, 105.3°, 105.5°, 105.7°, 105.9°, 106.1°, 106.3°, 106.5°, 106.7°, 106.9°, 107.1°, 107.3°, 107.5°, 107.7°, 107.9°, 108.1°, 108.3°, 108.5°, 108.7°, 108.9°, 109.1°, 109.3°, 109.5°, 109.7°, 109.9°, 110.1°, 110.3°, 110.5°, 110.7°, 110.9°, 111.1°, 111.3°, 111.5°, 111.7°, 111.9°, 112.1°, 112.3°, 112.5°, 112.7°, 112.9°, 113.1°, 113.3°, 113.5°, 113.7°, 113.9°, 114.1°, 114.3°, 114.5°, 114.7°, 114.9°, 115.1°, 115.3°, 115.5°, 115.7°, 115.9°, 116.1°, 116.3°, 116.5°, 116.7°, 116.9°, 117.1°, 117.3°, 117.5°, 117.7°, 117.9°,

22.4°, 22.8°, 23.2°, 23.7°, 23.9°, 24.3°, 24.5°, 24.8°, 25.1°, 25.4°, 25.9°, 26.4°, 26.8°, 27.8°, 28.1°, 28.6°, 29.1°, 29.6°, 29.8°, 30.6°, 31.6°, 32.7°, 33.5°, 34.2°, 35.4°, 35.6° and 36.8° (2 θ degrees).

9. The crystalline form of claim 8, having a melting point of 162° C, as determined by differential scanning calorimetry.
10. The crystalline form of claim 8, having a decomposition point greater than 250° C and a weight loss on drying of 0.05% at 200° C, as determined by thermogravimetric analysis.
11. The crystalline form of claim 8, having characteristic infrared absorption bands at 3418.7, 3309.5, 3202.3, 2976.2, 2936.3, 2806.9, 2731.8, 1683.9, 1652.8, 1598.4, 1568.9, 1507.0, 1483.5, 1447.1, 1411.0, 1314.9, 1288.1, 1261.1, 1220.8, 1195.7, 1170.8, 1140.1, 1124.6, 1083.2, 1053.3, 1010.1, 947.1, 874.5, 776.0, 758.7, 734.5, 706.5, 678.5, 652.1, 586.3, 544.7, 519.1, 472.6, and 456.8 (in units of wavenumbers, cm⁻¹).
12. The crystalline form of claim 8, having less than 1.0% by weight total impurities.
13. The crystalline form of claim 8, having less than 0.5% by weight total impurities.
14. The crystalline form of claim 8, having less than 0.1% by weight total impurities.
15. A pharmaceutical composition comprising a crystalline form of claim 1, and a pharmaceutically acceptable carrier.
16. A pharmaceutical composition comprising a crystalline form of claim 8, and a pharmaceutically acceptable carrier.
17. A method for the preparation of a crystalline form of 5-Chloro-N2-(2-isopropoxy-5-methyl-4-piperidin-4-yl-phenyl)-N4-[2-(propane-2-sulfonyl)-phenyl]-pyrimidine-2, 4-diamine which comprises the step of: reacting 5-Chloro-N2-(2-isopropoxy-5-methyl-4-piperidin-4-yl-phenyl)-N4-[2-(propane-2-sulfonyl)-phenyl]-pyrimidine-2, 4-diamine dihydrochloride in a solvent with at least two equivalents of aqueous sodium hydroxide.
18. The method of claim 17, wherein the solvent is acetone:water (3:1) by volume.

19. The method of claim 18, further comprising heating the reactants at a temperature ranging from 30-70° C.
20. The method of claim 18, further comprising heating the reactants at a temperature of 55° C.
21. A method for converting crystalline form B of 5-Chloro-N2-(2-isopropoxy-5-methyl-4-piperidin-4-yl-phenyl)-N4-[2-(propane-2-sulfonyl)-phenyl]-pyrimidine-2, 4-diamine to crystalline form A of 5-Chloro-N2-(2-isopropoxy-5-methyl-4-piperidin-4-yl-phenyl)-N4-[2-(propane-2-sulfonyl)-phenyl]-pyrimidine-2, 4-diamine by adding a small amount of crystalline form A to a suspension of form B of 5-Chloro-N2-(2-isopropoxy-5-methyl-4-piperidin-4-yl-phenyl)-N4-[2-(propane-2-sulfonyl)-phenyl]-pyrimidine-2, 4-diamine in a solvent.
22. The method of claim 21, wherein the amount of form A added is 1.0 % by weight or less.
23. The method of claim 22, the solvent is acetone:water (1:1) by volume at a temperature ranging from 20-40° C.
24. A method for converting crystalline form B of 5-Chloro-N2-(2-isopropoxy-5-methyl-4-piperidin-4-yl-phenyl)-N4-[2-(propane-2-sulfonyl)-phenyl]-pyrimidine-2, 4-diamine to crystalline form A of 5-Chloro-N2-(2-isopropoxy-5-methyl-4-piperidin-4-yl-phenyl)-N4-[2-(propane-2-sulfonyl)-phenyl]-pyrimidine-2, 4-diamine by heating a suspension of form B of 5-Chloro-N2-(2-isopropoxy-5-methyl-4-piperidin-4-yl-phenyl)-N4-[2-(propane-2-sulfonyl)-phenyl]-pyrimidine-2, 4-diamine in a solvent.
25. The method of claim 24, the solvent is acetone:water 1:1 to 5:1 by volume at temperature ranging from 30° to 70° C.
26. The method of claim 24, the solvent is acetone:water 1:1 by volume at temperature of 50° C.
27. Use of a substantially pure crystalline form of 5-Chloro-N2-(2-isopropoxy-5-methyl-4-piperidin-4-yl-phenyl)-N4-[2-(propane-2-sulfonyl)-phenyl]-pyrimidine-2, 4-diamine

according to claim 1 for the preparation of a medicament for the treatment of disorders mediated by anaplastic lymphoma kinase.

28. A method for the treatment of disorders mediated by anaplastic lymphoma kinase,
5 comprising administering to a patient in need of such treatment an effective amount of a substantially pure crystalline form of 5-Chloro-N2-(2-isopropoxy-5-methyl-4-piperidin-4-yl-phenyl)-N4-[2-(propane-2-sulfonyl)-phenyl]-pyrimidine-2, 4-diamine according to claim 1.

29. The method of claim 28 wherein the disorder is a cancer selected from anaplastic large cell
10 lymphoma; non-Hodgkin's lymphoma; an inflammatory myofibroblastic tumor; a neuroblastoma; sarcoma; lung; bronchus; prostate; breast (including sporadic breast cancers and sufferers of Cowden disease); pancreas; gastrointestinal cancer; colon; rectum; colon carcinoma; colorectal adenoma; thyroid; liver; intrahepatic bile duct; hepatocellular; adrenal gland; stomach; gastric; glioma; glioblastoma; endometrial; melanoma; kidney;
15 renal pelvis; urinary bladder; uterine corpus; uterine cervix; vagina; ovary; multiple myeloma; esophagus; a leukaemia; acute myelogenous leukemia; chronic myelogenous leukemia; lymphocytic leukemia; myeloid leukemia; brain; a carcinoma of the brain; oral cavity and pharynx; larynx; small intestine; and melanoma.

Claims:

1. A method for converting crystalline form B of 5-Chloro-N2-(2-isopropoxy-5-methyl-4-piperidin-4-yl-phenyl)-N4-[2-(propane-2-sulfonyl)-phenyl]-pyrimidine-2, 4-diamine to crystalline form A of 5-Chloro-N2-(2-isopropoxy-5-methyl-4-piperidin-4-yl-phenyl)-N4-
5 [2-(propane-2-sulfonyl)-phenyl]-pyrimidine-2, 4-diamine by heating a suspension of form B of 5-Chloro-N2-(2-isopropoxy-5-methyl-4-piperidin-4-yl-phenyl)-N4-[2-(propane-2-sulfonyl)-phenyl]-pyrimidine-2, 4-diamine in a solvent, the solvent is acetone:water 1:1 by volume at temperature of 50° C.