

Claims

1. Form 2 crystalline polymorph consisting of N-[1-6-(ethynyl-3-oxo-hexahydro-furo[3,2-b]pyrrole-4-carbonyl)-3-methyl-butyl]-4-[5-fluoro-2-(4-methyl-piperazin-1-yl)thiazol-4-yl]-benzamide monohydrochloride and N-[1-6-(ethynyl-3-oxo-hexahydro-furo[3,2-b]pyrrole-4-carbonyl)-3-methyl-butyl]-4-[5-fluoro-2-(4-methyl-piperazin-1-yl)thiazol-4-yl]-benzamide hydrate monohydrochloride.
2. A pharmaceutical composition comprising Form 2 crystalline polymorph according to claim 1 and one or more pharmaceutically acceptable diluents or carriers.
3. A pharmaceutical combination comprising Form 2 crystalline polymorph according to claim 1 together with a further pharmaceutically active agent.
4. Form 2 crystalline polymorph according to claim 1 for use in the treatment of a disorder selected from the list consisting of:
 - osteoporosis;
 - gingival diseases such as gingivitis and periodontitis;
 - Paget's disease;
 - hypercalcaemia of malignancy;
 - metastatic bone disease, for example bone cancer including neoplasia;
 - diseases characterised by excessive cartilage or matrix degradation, such as osteoarthritis and rheumatoid arthritis; and
 - pain.
5. Form 2 crystalline polymorph for use according to claim 4, characterised in that the disorder is osteoarthritis.
6. Form 2 crystalline polymorph for use according to claim 4 or 5, characterised in that the Form 2 crystalline polymorph according to claim 1 is administered in combination with one or more further pharmaceutically active agents.
7. Form 2 crystalline polymorph for use according to claim 6, wherein the one or more further pharmaceutically active agent is selected from an organic bisphosphonate; an estrogen receptor modulator; an androgen receptor modulator; an inhibitor of osteoclast proton ATPase; an inhibitor of HMG-CoA reductase; an integrin receptor antagonist; Vitamin D or an analogue thereof, an osteoblast anabolic agent, such as PTH; a selective cyclooxygenase-2 inhibitor (COX-2 inhibitor); an inhibitor of interleukin-1- beta; a LOX/COX inhibitor, a RANKL inhibitor; an anti-sclerostin antibody and pharmaceutically acceptable salts and mixtures thereof.

8. A method for the preparation of Form 2 crystalline polymorph according to claim 1 comprising reacting N-[1-6-(ethynyl-3-oxo-hexahydro-furo[3,2-b]pyrrole-4-carbonyl)-3-methyl-butyl]-4-[5-fluoro-2-(4-methyl-piperazin-1-yl)thiazol-4-yl]-benzamide free base with hydrochloric acid in the presence of a solvent selected from acetone, IPA, IPAc EtOAc, THF and MEK and crystallising the Form 2 crystalline polymorph from the said solvent.
9. A method according to claim 8, wherein the solvent is acetone.
10. A method according to claim 8 or claim 9 wherein the crystallising is performed under conditions of slow cooling or temperature cycling.
11. A method according to any one of claims 8 to 10 wherein the crystallising is performed in the presence of a seed amount of Form 2 crystalline polymorph according to claim 1.
12. A method according to any one of claims 8 to 11 wherein the crystallising is promoted by use of an antisolvent such as TBME.
13. A method for the preparation of Form 2 crystalline polymorph according to claim 1 comprising:
 - (i) reacting N-[1-6-(ethynyl-3-oxo-hexahydro-furo[3,2-b]pyrrole-4-carbonyl)-3-methylbutyl]-4-[5-fluoro-2-(4-methyl-piperazin-1-yl)thiazol-4-yl]-benzamide free base with hydrochloric acid in the presence of acetone and TBME;
 - (ii) seeding the solution with Form 2 crystalline polymorph; and
 - (iii) inducing crystallization by the addition of acetone and TBME.
14. Material consisting of N-[1-6-(ethynyl-3-oxo-hexahydro-furo[3,2-b]pyrrole-4-carbonyl)-3-methyl-butyl]-4-[5-fluoro-2-(4-methyl-piperazin-1-yl)thiazol-4-yl]-benzamide monohydrochloride and N-[1-6-(ethynyl-3-oxo-hexahydrofuro[3,2-b]pyrrole-4-carbonyl)-3-methyl-butyl]-4-[5-fluoro-2-(4-methyl-piperazin-1-yl)thiazol-4-yl]-benzamide hydrate monohydrochloride in the form of its Form 2 crystalline polymorph according to claim 1 having an XRPD pattern substantially as shown in Figure 1.
15. Material consisting of N-[1-6-(ethynyl-3-oxo-hexahydro-furo[3,2-b]pyrrole-4-carbonyl)-3-methyl-butyl]-4-[5-fluoro-2-(4-methyl-piperazin-1-yl)thiazol-4-yl]-benzamide monohydrochloride and N-[1-6-(ethynyl-3-oxo-hexahydrofuro[3,2-b]pyrrole-4-carbonyl)-3-methyl-butyl]-4-[5-fluoro-2-(4-methyl-piperazin-1-yl)thiazol-4-yl]-benzamide hydrate monohydrochloride in the form of its Form 2 crystalline polymorph according to claim 1 having an XRPD pattern containing three, four, five, six, seven, eight, nine, ten, eleven or all twelve peaks selected from 6.8, 12.4, 14.9, 16.7, 17.0, 17.8, 24.1, 24.6, 24.8, 27.2, 28.2, 32.1 (± 0.2 degrees, 2-theta values).

16. Material according to claim 15 having an XRPD pattern containing three, four, five, six, seven or all eight peaks selected from 6.8, 12.4, 14.9, 16.7, 17.8, 24.1, 24.6 and 24.8 (± 0.2 degrees, 2-theta values).
17. Material according to claim 16 having an XRPD pattern containing three, four, five or all six peaks selected from 6.8, 14.9, 17.8, 24.1, 24.6 and 24.8 (± 0.2 degrees, 2-theta values).