Claims

1. A phosphate salt of 4-(R)-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-5-yl)-3-fluoro-benzonitrile in a crystalline form.

2. The phosphate salt of 4-(R)-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-5-yl)-3-fluoro-benzonitrile in crystalline form according to claim 1, with a molar ratio of 4-(R)-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-5-yl)-3-fluoro-benzonitrile to phosphate of about 1 : 1.

3. The phosphate salt in crystalline form according to claim 2 having a melting point at least 50 °C higher than that of the free base.

4. The phosphate salt in crystalline form according to claim 3 having a melting point, using thermogravimetry/differential thermal analysis (TG/DTA), between 209 and 212 °C.

5. Crystalline Form A of the phosphate salt according to claim 1 or any one of its dependent claims having a melting temperature of 210±0.5°C determined by TG/DTA.

6. Crystalline Form A of the phosphate salt according to claim 2 or any one of its dependent claims with an XRPD showing at least one or all of the following peaks, given as angle of refraction 2-theta (θ) values, where each peak may vary by ± 0.5, in particular ± 0.2 degrees: 12.9, 16.3 and 20.4 degrees.

7. Crystalline Form A of the phosphate salt according to claim 1 or any one of its dependent claims with an XRPD showing at least 4, 5, 6, 7, 8, 9 or all of the following peaks, given as angle of refraction 2-theta (θ) values, where each peak may vary by ± 0.5, in particular ± 0.2 degrees: 6.0, 12.9, 15.5, 16.0, 16.3, 19.7, 20.4, 22.1, 24.3 and 29.2 degrees.

8. Crystalline Form A of the phosphate salt according to claim 1 or any one of its dependent claims with an XRPD showing at least 7, 9, 11, 13, 15, 17 or all of the following peaks, where each peak may vary by ± 0.5, in particular ± 0.2 degrees: 6.0,

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10.0, 12.1, 12.9, 14.0, 14.5, 15.5, 16.0, 16.3, 17.5, 18.2, 18.4, 19.7, 20.4, 22.1, 24.3, 29.2.

9. Crystalline Form A of the phosphate salt according to claim 1 or any one of its dependent claims, wherein the two largest peaks in the XRPD diagram have a relative intensity of 1 to 0.5 to 0.7, especially of 1 to 0,55 to 0.65, more especially of 0.57 to 0.61, e.g. of 1 to 0.59 (obtainable by integration of each of the peaks in the XRPD diagrams), in particular the larger peak being at a 2-theta (θ) value of 6.0 ± 0.5, in particular ± 0.2 degrees and the smaller peak at a 2-theta (θ) value of 19.7 ± 0.5, in particular ± 0.2 degrees, respectively.

10.Crystalline Form A of the phosphate salt according to claim 1 or any one of its dependent claims showing an XRPD as shown in Fig. 1-A.

11. A nitrate salt of 4-(R)-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-5-yl-3-fluoro-benzonitrile.

12. A process for making a nitrate or phosphate salt in crystalline form of 4-(R)-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-5-yl-3-fluoro-benzonitrile, the process comprising:

(a) providing a solution of 4-(R)-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-5-yl-3-fluoro-benzonitrile in either a protic or an aprotic polar solvent;

(b) adding nitric acid or especially phosphoric acid; and

(c) isolating the formed crystalline form of a nitrate salt or especially a phosphate salt of 4-(R)-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-5-yl-3-fluoro-benzonitrile; .

13. A salt or salt form according to any one of claims 1 to 11 for use in the manufacture of a medicament for the treatment of Cushing's syndrome.

14. A salt or salt form according to any one of claims 1 to 11 or a pharmaceutical composition comprising said salt of salt form for use in the treatment of Cushing's disease.

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15. A method of treatment comprising administering said a salt or salt form according to any one of claims 1 to 11 to a mammal in need thereof in a therapeutically effective amount for treating Cushing's disease.

16. A pharmaceutical composition comprising a phosphate salt of 4-(R)-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-5-yl)-3-fluoro-benzonitrile in crystalline form according to any one of claims 1 to 10 and one or more pharmaceutically acceptable excipients.

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Claims

1. A phosphate salt of 4-(R)-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-5-yl)-3-fluoro-benzonitrile in a crystalline form A with an XRPD showing at least one or all of the following peaks, given as angle of refraction 2-theta (θ) values, where each peak may vary by ± 0.5 degrees: 12.9, 16.3 and 20.4 degrees; where the XRPD can be determined by using the following parameters and device:

XRPD-method	
Instrument	D8; Bruker (Karlsruhe, Germany)
Irradiation	CuKα (40 kV, 40 mA)
Scan time	4 minutes (2 minutes per frame)
Scan range	3° - 40° (2 theta value)

2. The phosphate salt of 4-(R)-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-5-yl)-3-fluoro-benzonitrile in crystalline form according to claim 1, with a molar ratio of 4-(R)-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-5-yl)-3-fluoro-benzonitrile to phosphate of about 1 : 1.

3. The phosphate salt in crystalline form A according to claim 2 having a melting point at least 50 °C higher than that of the free base.

4. The phosphate salt in crystalline form A according to claim 3 having a melting point, using thermogravimetry/differential thermal analysis (TG/DTA), between 209 and 212 °C.

5. Crystalline Form A of the phosphate salt according to claim 1 or any one of its dependent claims having a melting temperature of 210±0.5°C determined by TG/DTA.

6. Crystalline Form A of the phosphate salt according to claim 1 or any one of its dependent claims with an XRPD showing at least one or all of the following peaks, given

as angle of refraction 2-theta (θ) values, where each peak may vary by ± 0.2 degrees: 12.9, 16.3 and 20.4 degrees.

7. Crystalline Form A of the phosphate salt according to claim 1 or any one of claims 2 to 5 with an XRPD showing at least 4, 5, 6, 7, 8, 9 or all of the following peaks, given as angle of refraction 2-theta (θ) values, where each peak may vary by ± 0.5, in particular ± 0.2 degrees: 6.0, 12.9, 15.5, 16.0, 16.3, 19.7, 20.4, 22.1, 24.3 and 29.2 degrees.

8. Crystalline Form A of the phosphate salt according to claim 1 or any one of claims 2 to 5 with an XRPD showing at least 7, 9, 11, 13, 15, 17 or all of the following peaks, where each peak may vary by ± 0.5, in particular ± 0.2 degrees: 6.0, 10.0, 12.1, 12.9, 14.0, 14.5, 15.5, 16.0, 16.3, 17.5, 18.2, 18.4, 19.7, 20.4, 22.1, 24.3, 29.2.

9. Crystalline Form A of the phosphate salt according to claim 1 or any one of its dependent claims 2 to 5, 7 or 8, wherein the two largest peaks in the XRPD diagram have a relative intensity of 1 to 0.5 to 0.7, especially of 1 to 0,55 to 0.65, more especially of 0.57 to 0.61, e.g. of 1 to 0.59 (obtainable by integration of each of the peaks in the XRPD diagrams), in particular the larger peak being at a 2-theta (θ) value of 6.0 ± 0.5, in particular ± 0.2 degrees and the smaller peak at a 2-theta (θ) value of 19.7 ± 0.5, in particular ± 0.2 degrees, respectively.

10.Crystalline Form A of the phosphate salt according to claim 1 or any one of its dependent claims showing an XRPD as shown in Fig. 1-A.

11. A nitrate salt of 4-(R)-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-5-yl-3-fluoro-benzonitrile.

12. A process for making a nitrate or phosphate salt in crystalline form A as defined in claim 1 of 4-(R)-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-5-yl-3-fluoro-benzonitrile, the process comprising:

(a) providing a solution of 4-(R)-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-5-yl-3-fluoro-benzonitrile in either a protic or an aprotic polar solvent;

(b) adding nitric acid or especially phosphoric acid; and

(c) isolating the formed crystalline form of a nitrate salt or especially a phosphate salt of 4-(R)-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-5-yl-3-fluoro-benzonitrile; .

13. A salt or salt form according to any one of claims 1 to 11 for use in the manufacture of a medicament for the treatment of Cushing's syndrome.

14. A salt or salt form according to any one of claims 1 to 11 or a pharmaceutical composition comprising said salt of salt form for use in the treatment of Cushing's disease.

15. A pharmaceutical composition comprising a phosphate salt of 4-(R)-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-5-yl)-3-fluoro-benzonitrile in crystalline form according to any one of claims 1 to 10 and one or more pharmaceutically acceptable excipients.