(12) **Oversettelse av europeisk patentskrift**

(11) **NO/EP 2964622 B1**

NORGE

(19) NO

(51) Int Cl.

C07D 307/85 (2006.01)
A61K 31/343 (2006.01)
A61P 29/00 (2006.01)
A61P 35/00 (2006.01)

Patentstyret

(21)	Oversettelse publisert	2017.09.25
(80)	Dato for Den Europeiske Patentmyndighets publisering av det meddelte patentet	2017.04.19
(86)	Europeisk søknadsnr	14711833.5
(86)	Europeisk innleveringsdag	2014.03.03
(87)	Den europeiske søknadens Publiseringsdato	2016.01.13
(30)	Prioritet	2013.03.04, FR, 1351898 2013.03.04, US, 201361772191 P
(84)	Utpekte stater	AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL PT RO RS SE SI SK SM TR
	Utpekte samarbeidende stater	BA ME
(73)	Innehaver	Pharmacyclics LLC, 995 East Arques Avenue, Sunnyvale, CA 94085, US-USA
(72)	Oppfinner	PIMONT-GARRO, Anne, 39 avenue des Etats-Unis, F-78000 Versailles, FR-Frankrike LETELLIER, Philippe, 25 rue du Faubourg Saint Jean, F-45000 Orléans, FR-Frankrike
(74)	Fullmektig	Nordic Patent Service A/S, Bredgade 30, DK-1260 KØBENHAVN K, Danmark

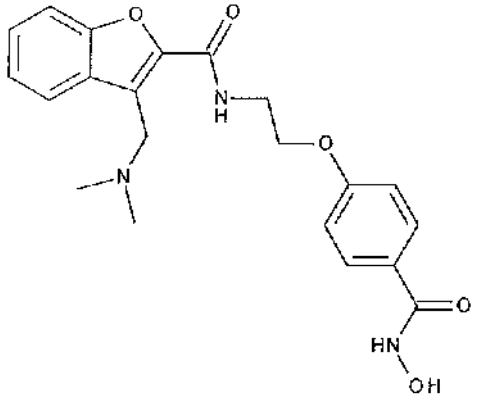
(54) Benevnelse **NOVEL ABEXINOSTAT SALT, ASSOCIATED CRYSTALLINE FORM, PREPARATION METHOD THEREOF AND THE PHARMACEUTICAL COMPOSITIONS CONTAINING SAME**

(56) Anførte publikasjoner
WO-A1-2010/123507
WO-A2-2004/092115

Vedlagt foreligger en oversettelse av patentkravene til norsk. I hht patentloven § 66i gjelder patentvernet i Norge bare så langt som det er samsvar mellom oversettelsen og teksten på behandlingsspråket. I saker om gyldighet av patentet skal kun teksten på behandlingsspråket legges til grunn for avgjørelsen. Patentdokument utgitt av EPO er tilgjengelig via Espacenet (http://worldwide.espacenet.com), eller via søkemotoren på vår hjemmeside her: https://search.patentstyret.no/

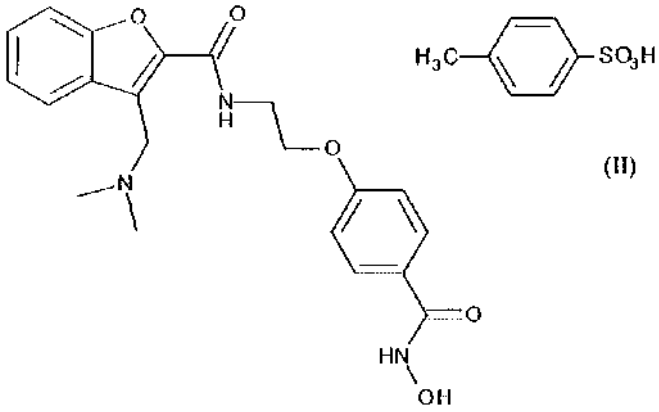
The present invention concerns *N*-hydroxy-4-{2-[3-(*N*,*N*- dimethylaminomethyl) benzofuran-2-ylcarbonylamino] ethoxy} benzamide tosylate or any of its solvates.

Alternatively, the subject of the invention concerns an abexinostat tosylate salt with the formula (I):



(I)

More especially, the application covers the formula two (II) salt:



(II)

The present invention also concerns the crystalline form I of *N*-hydroxy- 4-{2-[3-(*N*,*N*-dimethylaminomethyl) benzofuran-2-ylcarbonylamino] ethoxy} benzamide tosylate, its preparation process, and the pharmaceutical compositions it contains.

N-hydroxy-4-{2-[3-(*N*,*N*-dimethylaminmethyl) benzofuran-2-ylcarbonylamino] ethoxyl benzamide, also known as abexinostat, is a histone-deacetylase (HDAC) inhibitor, described in patent application WO2004/092115. It inhibits cell growth, causes apoptosis in tumor cells cultivated *in vitro,* and inhibits tumor growth *in vivo* in models of xenografts (Buggy *et al Mol. Cancer Ther* **2006** 5(5) 1309). Due to its pharmacological profile, abexinostat is designed to be used in cancer treatment.

From the industrial point of view, it is vital to be able to synthesize the component with excellent purity, especially in a perfectly reproducible form, presenting with interesting characteristics of dissolution, filtration, drying, ease of formulation, and stability, enabling it to be stored for long periods without special temperature, light, and humidity conditions or those relating to the oxygen level.

Patent application WO2004/092115 describes two different access routes for obtaining abexinostat. In both cases, 3-methyl-benzofuran-2-carboxylic acid was used as the starting product, but the functionality of this central nucleus through position 3 dimethylaminomethyl grouping was performed at different stages of the synthesis process, in this case before or after coupling of the benzofuran-2-carboxylic acid derivative with 4-(2-aminoethoxy) methyl benzoate. The method for obtaining abexinostat hydrochloride is specifically described in application WO2004/092115. The use of this salt on an industrial scale is nevertheless problematic due to its hygroscopic properties.

The present invention describes a process for obtaining abexinostat tosylate (4-abexinostat methylbenzenesulfonate) in a well-defined crystalline form that is perfectly reproducible, and presents with very good stability that is compatible with the industrial constraints of preparation (especially drying) and the preservation of its pharmaceutical compositions.

Crystalline form I of abexinostat tosylate is characterized by diffraction in diagram X on a powder presenting with the following diffraction rays (Bragg angle of 2 theta, expressed in degrees ±0.2°): 6.50; 9.94; 11.35; 12.33; 14.08; 18.95; 21.08; 27.05. More particularly still, crystalline form I of abexinostat tosylate is characterized by the following diffraction rays: 6.50; 9.94; 11.35; 12.33; 14.08; 18.95; 19.61; 19,96; 21.08; 22.82; 23.61; 27.05.

More specifically, crystalline form I of abexinostat tosylate is characterized by diffraction diagram X on the powder as shown below, measured using a PANalytical X'Pert Pro MPD diffractometer with an X'Celerator detector, and expressed in terms of ray position (Bragg angle of 2 theta, expressed in degrees ±0.2°) and inter-reticular distance d (expressed in Å):

Ray no.	2-theta angle (degrees)	Inter-reticulate Distance (Å)
1	6.50	13.581
2	9.94	8.894
3	11.35	7.789
4	12.33	7.173
5	14.08	6.285
6	18.95	4.683
7	19.61	4.526
8	19.96	4.449
9	21.08	4.215
10	22.82	3.897
11	23.61	3.768
12	27.05	3.296

Furthermore, the crystalline form I of abexinostat tosylate was characterized by Raman spectroscopy. Significant peaks were observed at the following positions: 940 cm^{-1}, 1088 cm^{-1}, 1132 cm^{-1}, 1242 cm^{-1}, 1360 cm^{-1}, 1608 cm^{-1}.

Alternatively, crystalline form I of abexinostat tosylate can be characterized by the X diffraction diagram on powder, consisting of the 12 significant rays presented previously as well as by a Raman spectrum showing a significant peak in position 1608 cm^{-1}.

Finally, crystalline form I of abexinostat tosylate was also characterized by NMR spectroscopy in the solid state. Significant peaks were observed at 121.2 ppm, 122.1 ppm, 123.5 ppm, 126.0 ppm, 126.8 ppm, 128.2 ppm, 128.9 ppm, 143.4 ppm, 144.6 ppm, 153.8 ppm, 159 ppm, 161.2 ppm and 162.1 ppm.

More specifically, the ^{13}C CP/MAS (Cross Polarization Magic Angle Spinning) spectra presented with the following peaks (expressed in ppm ± 0.2 ppm):

Peak no.	Chemical displacement (ppm)	Peak no.	Chemical displacement (ppm)
1	162.1	10	126.0
2	161.2	11	123.5
3	159.0	12	122.1
4	153.8	13	121.3
5	144.6	14	65.9
6	143.4	15	50.6
7	128.9	16	46.9
8	128.2	17	45.0
9	126.8	18	21.9

The invention also extends to the process for preparing crystalline form I of abexinostat tosylate, characterized by the fact that the abexinostat crystallizes in a polar medium in the presence of *para*-toluenesulfonic acid. The polar environment should preferably consist of one or more solvents chosen from among water, alcohols, ketones and esters, it being understood that:

- "alcohols" should be taken to mean C_1-C_6 alcohols such as methanol, ethanol, propanol, isopropanol, butanol, isobutanol, pentanol, 2-pentanol, 3-pentanol, isopentanol and hexanol;

- "ketones" should be taken to mean C_3-C_6 ketones such as acetone, methyl ethyl ketone, 2-pentanone, 3-pentanone, 3-methyl-2-butanone, 2-hexanone, 3-hexanone, ethyl isopropyl ketone, methyl isopropyl acetone and 2.2-dimethyl-3- butanone;

- "esters" should be taken to mean C_3-C_8 esters such as ethyl formate, isopropyl formate, ethyl acetate, propyl acetate, isopropyl acetate, butyl acetate, isobutyl acetate, tert-butyl acetate, pentyl acetate, isopentyl acetate and hexyl acetate.

The preferred alcohols are ethanol and isopropanol. Of the preferred solvents, acetone and methyl ethyl ketone (MEK) are preferable from among the ketones and ethyl acetate is preferable for the esters.

Alternatively, the polar environment can consist of a binary mixture, one of the constituents being water. Even more preferentially, the polar environment can consist of a binary mixture chosen from the following combination: acetone/water, ethanol/water, isopropanol/water and methyl ethyl ketone/water.

In the crystallization process according to the invention, abexinostat (free base) can be used that is obtained by any method.

The invention also covers another preparation method for the crystalline form I of abexinostat tosylate, in which crystallization is initiated by a very small quantity of abexinostat tosylate in crystalline form I.

In this second crystallization method, according to the invention, abexinostat (free base) can be used that is obtained by any method.

The advantage of obtaining abexinostat tosylate in crystalline form I is that it enables the preparation of pharmaceutical formulations having a constant and reproducible composition and presenting with good characteristics of dissolution and stability; this is particularly advantageous where the formulations are destined for oral administration. More specifically, the use of crystalline form I of abexinostat tosylate is of particular interest on an industrial scale, in view of its low hygroscopicity.

Crystalline form I of abexinostat tosylate is designed to treat cancer, and more especially the treatment of carcinoma, tumors, neoplasms, lymphoma, melanoma, glioma, sarcoma or blastoma.

The invention also extends to pharmaceutical compositions whose active principle is an abexinostat tosylate salt, and again more especially the crystalline form I of abexinostat tosylate, with one or more inert, non-toxic and appropriate excipients. Of the pharmaceutical compositions according to the invention, those that should be mentioned particularly are the most suitable for oral, parenteral (intravenous or subcutaneous) and nasal administration, simple or sugar-coated pills, granules, sub-lingual pills, gellules, tablets, suppositories, creams, ointments, dermal gels, injectable preparations, drinkable suspensions and chewing pastes.

Pharmaceutical compositions administered orally are preferable.

The effective dosage varies depending on the gender, age, and weight of the patient, the manner of administration, the nature of the cancer, and any associated treatments; the effective dosage varies between 20 mg and 480 mg of *N*-hydroxy-4-{2-[3-*(N,N*-dimethylaminomethyl) benzo-furan-2-ylcarbonylamino]ethoxy} benzamide expressed in free base per day.

The following examples illustrate the invention, but in no way restrict it.

Example 1: Process for obtaining crystalline form I of abexinostat tosylate

1.66 kg of abexinostat (free base) is placed in 9.48 kg of a mixture of isopropanol and water (50/50 mass/mass) at ambient temperature. P-toluene sulfonic acid monohydrate (0.83 kg) is added in 2.36 kg of water at ambient temperature. The medium is then heated to 75°C for 30 minutes before being cooled to

0°C. When crystallization is complete, the suspension is filtered at 20°C. After drying, the crystalline form I of abexinostat tosylate is obtained with a yield of about 85% and with a purity greater than 99%. The solid has been characterized by an X diffraction diagram on powder, details of the Raman spectrum and the NMR spectrum being shown in the following examples 3-6.

Example 2: Method for obtaining the crystalline form I of abexinostat tosylate (seeding)

33.9 kg of abexinostat (free base) are placed in 170 kg of a mixture of isopropanol and water (45.6/54.4 mass/mass) at ambient temperature. A solution is then added consisting of p-toluene sulfonic acid monohydrate (17.06 kg) in water (24.1 kg). The medium is then heated to 70-75°C, cooled and primed with 1.935 kg of crystalline form I of abexinostat tosylate. The suspension is then filtered at 20°C. After drying, crystalline form I of abexinostat tosylate is obtained with a yield of about 86% and a purity greater than 99%. The solid is characterized by diagram diffraction X on the powder. The Raman spectrum and NMR spectrum are specified in the following Examples 3-6.

Example 3: Crystalline form I of abexinostat tosylate (X diffraction diagram on powder)

The data were recorded on a PANalytical X'Pert Pro MPD diffractometer with an X'Celerator detector under the following conditions:

- Tension 45 kV, intensity 40 mA,
- Theta/theta mounting,
- Anode: copper,
- K alpha-1 wavelength: 1.54060 Å,
- K alpha-2 wavelength: 1.54443 Å,
- K alpha-2/ K alpha-1 ratio: 0.5
- Measurement method: continuous from 3° through 55° (Bragg angle 2 theta) with an incrementation of 0.017°,
- Measuring time per step: 35.53 secs.

The X diffraction diagram on powder of form I of abexinostat tosylate, obtained using the method outlined in Examples 1 or 2, is expressed in terms of the position of the ray (Bragg angle 2 theta, expressed in ±0.2°

degrees), the inter-reticular distance d (expressed in Å), and the relative intensity (expressed in percentages in relation to the most intense ray). The significant rays have been collected into the following table:

Ray no.	Angle 2-theta (degrees)	Inter-reticular distance (Å)	Relative intensity (%)
1	**6.50**	**13.581**	**75.6**
2	**9.94**	**8.894**	**58.4**
3	**11.35**	**7.789**	**19.1**
4	**12.33**	**7.173**	**23.7**
5	**14.08**	**6.285**	**33,1**
6	**18.95**	**4.683**	**100**
7	**19.61**	**4.526**	**53.9**
8	**19.96**	**4.449**	**50.9**
9	**21.08**	**4.215**	**93.5**
10	**22.82**	**3.897**	**28.5**
11	**23.61**	**3.768**	**32.6**
12	**27.05**	**3.296**	**16.0**

Example 4: Crystalline form I of abexinostat tosylate (crystalline mesh)

A solution of abexinostat tosylate saturated in 2,2,2-trifluoroethanol was prepared through agitation in suspension for 24 hours at ambient temperature, followed by filtration. Subsequently, 1 mL of this saturated solution was poured into an HPLC vial of 1.8 mL to which 0.25 mL water was added. The solution was maintained at ambient temperature for 75 minutes. After centrifugation then drying, the solid was isolated for analysis. From the crystals obtained, a crystal of sufficient quality was sampled for analysis by X diffraction on monocrystal.

The crystalline structure was determined on the previous monocrystal using a Bruker Kappa CCD diffractometer fitted with an FR590 generator having a molybdenum anticathode ((λMoKα1 = 0.7093 Å) and an angular field of between 2° and 27.5° in θ. The following settings were established:

- triclinic crystalline mesh,
- parameters of the mesh: a = 10.467 Å, b = 14.631 Å, c = 20.159 Å, α = 73.971°, β = 79.040°, γ = 72.683°
- space group: P-1

- number of molecules in the mesh: 4
- volume of the mesh: V_{mesh} = 2813,0 Å^3
- density: d = 1.345 g/cm^3.

Example 5: Crystalline form I of abexinostat tosylate (Raman spectrum)

Form I of abexinostat tosylate was characterized by Raman spectroscopy. The spectra were recorded in diffuse reflection mode (Raman Station 400, PerkinElmer) with a 785 nm laser. The signal was recorded using a CCD detector. The wavelength shift depends on the substance and is typical of it, thus enabling an analysis of the chemical composition and molecular arrangement of the sample studied. The spectra were acquired with maximum power (100% of the laser's capacity), using a 100 µm spotlight, twenty two-second exposures and a spectral resolution of 2 cm^{-1}. The spectral range explored ranged between 0 and 3278 cm^{-1}.

Significant peaks were observed in the following positions: 940 cm^{-1}, 1088 cm^{-1}, 1132 cm^{-1},1242 cm^{-1}, 1360 cm^{-1}, 1608 cm^{-1}.

Example 6: Crystalline form I of abexinostat tosylate (solid RMN spectrum)

Form I of abexinostat tosylate was also characterized by NRM spectroscopy in the solid state. ^{13}C NRM spectra were recorded at ambient temperature with the help of a Bruker SB Avance spectrometer using a type 4 mm CP/MAS SB VTN probe under the following conditions:

- Frequency: 125.76 MHz,
- Width of spectrum: 40 kHz,
- Magic-angle spinning speed: 10 kHz.
- Sequence of impulses: CP (Cross Polarization) with SPINAL64 decoupling (decoupling power of 80 kHz),
- Interval between repetitions: 10 s,
- Acquisition time: 35 ms,
- Contact time: 4 ms

- Number of scans: 4096.

An apodization function ("5 Hz line broadening") was applied to the signal received before the Fourier conversion. The spectra thus obtained were referenced in relation to a sample of adamantane (the highest frequency peak of adamantane has a chemical displacement of 38.48 ppm).

The peaks observed were collected into the following table (expressed in ppm ± 0,2 ppm) :

Peak no.	**Chemical displacement (ppm)**	**Peak no.**	**Chemical displacement (ppm)**
1	**162.1**	**10**	**126.0**
2	**161.2**	**11**	**123.5**
3	**159.0**	**12**	**122.1**
4	**153.8**	**13**	**121.3**
5	**144.6**	**14**	**65.9**
6	**143.4**	**15**	**50.6**
7	**128.9**	**16**	**46.9**
8	**128.2**	**17**	**45.0**
9	**126.8**	**18**	**21.9**

Example 7: Pharmaceutical Composition

The preparation formula for 1000 tablets dosed at 100 mg of abexinostat (expressed in the equivalent base):

Abexinostat tosylate..... 143.4 g

Lactose monohydrate..... 213.1 g

Magnesium stearate ..... 2.5 g

Maize starch..... 75 g

Maltodextrin..... 50 g

Anhydrous colloidal silica ..... 1 g

Carboxymethyl cellulose sodium..... 15 g

Example 8: Hygroscopy

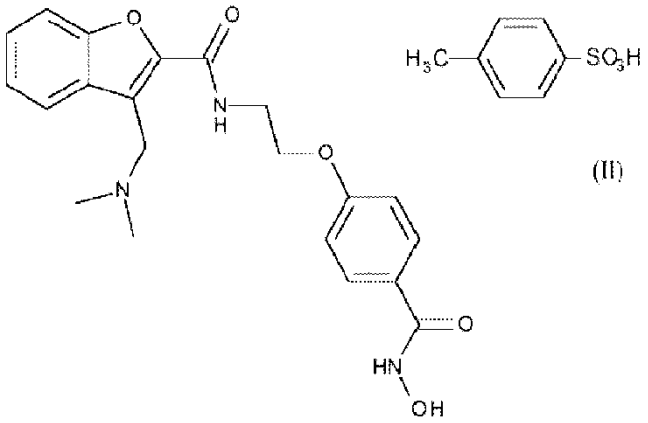
The hygroscopicity of form I of abexinostat tosylate was assessed by water vapor adsorption gravimetry (DVS - Dynamic Vapor Sorption). A sample of 5 to 10 mg of the medicinal substance, weighed accurately, was placed in a DVS sampling vessel operating at 25°C under controlled humidity. The variation in the mass was recorded during drying at 0 per cent RH (relative humidity) and during two subsequent cycles of linear increase and decrease in the relative humidity within a range of 0-90 percent RH at a speed of 10 percent per hour. The relative humidity was maintained constantly when it reached 0 i.e. 90 percent RH, until the variation in mass was less than 0.002 percent per minute, with a time limit of 15 hours.

An increase in weight of less than 0.5% was detected through DVS analysis after exposure of a sample to relative humidity of 0% through 90% at 25°C.

Patentkrav

1. *N*-hydroksy-4-{2-[3-(*N,N*-dimetylaminometyl)benzofuran-2-ylkarbonylamino]etoksy}benzamidtosylat eller en av dens solvater.

2. Salt ifølge krav 1 med formel (II):



(II)

3. Krystallinsk form I av abeksinostattosylat ifølge ett av kravene 1 eller 2, **karakterisert ved at** det har et røntgenpulverdiffraksjonsdiagram som har de følgende diffraksjonslinjene (Braggs-vinkel 2-theta, uttrykt i grader ±0,2°): 6,50; 9,94; 11,35; 12,33; 14,08; 18,95; 21,08; 27,05.

4. Krystallinsk form I av abeksinostattosylat ifølge krav 3, **karakterisert ved at** det har et røntgenpulverdiffraksjonsdiagram som har de følgende diffraksjonslinjene (Braggs vinkel 2-theta, uttrykt i grader ±0,2°): 6,50; 9,94; 11,35; 12,33; 14,08; 18,95; 19,61; 19,96; 21,08; 22,82; 23,61; 27,05.

5. Krystallinsk form I av abeksinostattosylat ifølge krav 3 eller 4, **karakterisert ved at** det har følgende røntgenpulverdiffraksjonsdiagram målt på et PANalytical X'Pert Pro MPD-diffraktometer med en X'Celeratordetektor og uttrykt i form av linjeposisjon (Braggs-vinkel 2-theta, uttrykt i grader ±0,2°) og interretikulær avstand d (uttrykt i Å):

Linje nr.	Vinkel-2-theta (grader)	Interretikulær avstand (Å)
1	6,50	13,581
2	9,94	8,894
3	11,35	7,789
4	12,33	7,173
5	14,08	6,285
6	18,95	4,683
7	19,61	4,526
8	19,96	4,449
9	21,08	4,215
10	22,82	3,897
11	23,61	3,768
12	27,05	3,296

6. Krystallinsk form I av abeksinostattosylat ifølge ett av kravene 3 til 5, **karakterisert ved at** det har et Raman-spektrum som har en signifikant topp ved posisjon 1608 cm^{-1}.

7. Krystallinsk form I av abeksinostattosylat ifølge ett av kravene 1 til 6, **karakterisert ved at** det har et Raman-spektrum som har signifikante topper ved posisjonene 940 cm^{-1}, 1088 cm^{-1}, 1132 cm^{-1}, 1242 cm^{-1}, 1360 cm^{-1}, 1608 cm^{-1}.

8. Krystallinsk form I av abeksinostattosylat ifølge ett av kravene 1 eller 2, **karakterisert ved at** det har et fast tilstands ^{13}C CP/MAS NMR-spektrum som har de følgende toppene (uttrykt i ppm ± 0,2 ppm): 121,2 ppm, 122,1 ppm, 123,5 ppm 126,0 ppm, 126,8 ppm, 128,2 ppm, 128,9 ppm, 143,4 ppm, 144,6 ppm, 153,8 ppm, 159 ppm, 161,2 ppm og 162,1 ppm.

9. Krystallinsk form I av abeksinostattosylat ifølge krav 8, **karakterisert ved at** det har et fast tilstands ^{13}C CP/MAS NMR-spektrum som har de følgende toppene (uttrykt i ppm ± 0,2 ppm):

Topp nr.	Kjemisk skift (ppm)	Topp nr.	Kjemisk skift (ppm)
1	162,1	10	126,0
2	161,2	11	123,5
3	159,0	12	122,1
4	153,8	13	121,3
5	144,6	14	65,9
6	143,4	15	50,6
7	128,9	16	46,9
8	128,2	17	45,0
9	126,8	18	21,9

10. Farmasøytisk sammensetning som inneholder abeksinostattosylat ifølge ett av kravene 1 eller 2 som aktiv bestanddel i forbindelse med én eller flere farmasøytisk akseptable eksipienser.

11. Farmasøytisk sammensetning som inneholder krystallinsk form I av abeksinostattosylat ifølge ett av kravene 3 til 9 som aktiv bestanddel i forbindelse med én eller flere farmasøytisk akseptable eksipienser.

12. Farmasøytisk sammensetning ifølge krav 10 eller 11 for anvendelse ved behandling av kreft.

13. Farmasøytisk sammensetning beregnet på å bli anvendt ifølge ett av kravene 10 til 12, der kreften er et karsinom, en tumor, et neoplasma, et lymfom, et melanom, et gliom, et sarkom eller et blastom.

14. Prosess for fremstilling av krystallinsk form I av abeksinostattosylat ifølge ett av kravene 3 til 9, der abeksinostatet krystalliseres i nærvær av paratoluensulfonsyre i et polært medium.

15. Prosess for fremstilling av krystallinsk form I av abeksinostattosylat ifølge krav 14, der det polare mediet er sammensatt av ett eller flere løsningsmidler valgt fra vann, alkoholer, ketoner

og estere.

16. Prosess for fremstilling av krystallinsk form I av abeksinostattosylat ifølge krav 15, der det polare mediet er en binær blanding, der én av bestanddelene er vann.

17. Prosess for fremstilling av krystallinsk form I av abeksinostattosylat ifølge krav 16, der det polare mediet er en binær blanding valgt fra: aceton/vann, etanol/vann, isopropanol/vann og metyletylketon/vann.

18. Prosess for fremstilling av krystallinsk form I av abeksinostattosylat ifølge ett av kravene 14 til 17, der krystallisasjonen aktiveres av en meget liten mengde av krystallinsk form I av abeksinostattosylat.