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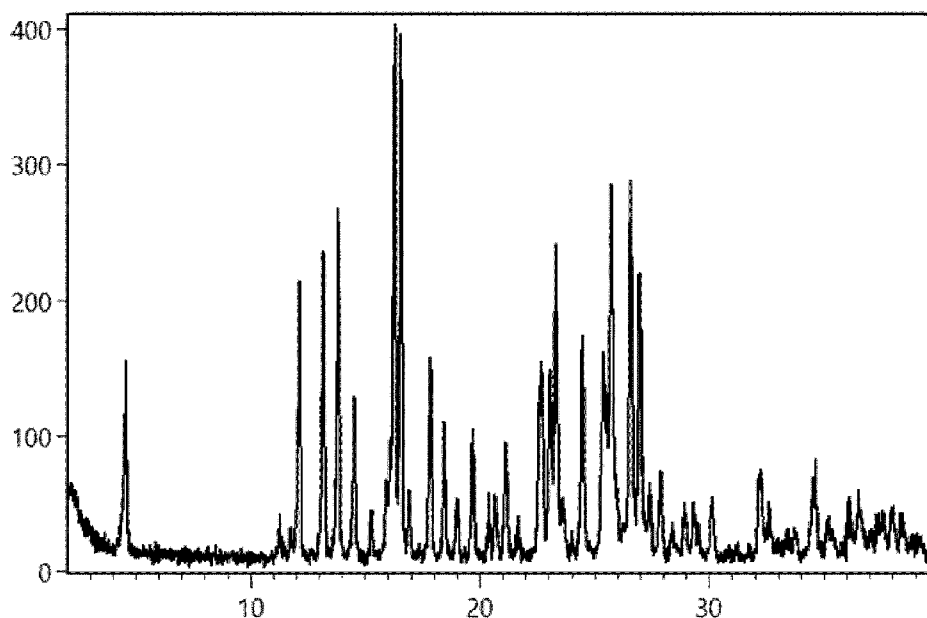
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(54) Title: CRYSTALLINE (S)-[3,4-DIFLUORO-2-(2-FLUORO-4-IODOPHENYLAMINO)PHENYL][3-HYDROXY-3-(PIPERIDIN-2-YL)AZETIDIN-1-YL]METHANONE HEMISUCCINATE

Figure 1



(57) Abstract: The present invention relates to crystalline cobimetinib hemisuccinate and a process for its preparation. The invention also relates to a pharmaceutical composition comprising crystalline cobimetinib hemisuccinate, preferably in a predetermined and/or effective amount and at least one pharmaceutically acceptable excipient. The pharmaceutical composition of the present invention can be used for the treatment of cancer, in particular for the treatment of melanoma.



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**CRYSTALLINE (*S*)-[3,4-DIFLUORO-2-(2-FLUORO-4-
IODOPHENYLAMINO)PHENYL][3-HYDROXY-3-(PIPERIDIN-2-
YL)AZETIDIN-1-YL]METHANONE HEMISUCCINATE**

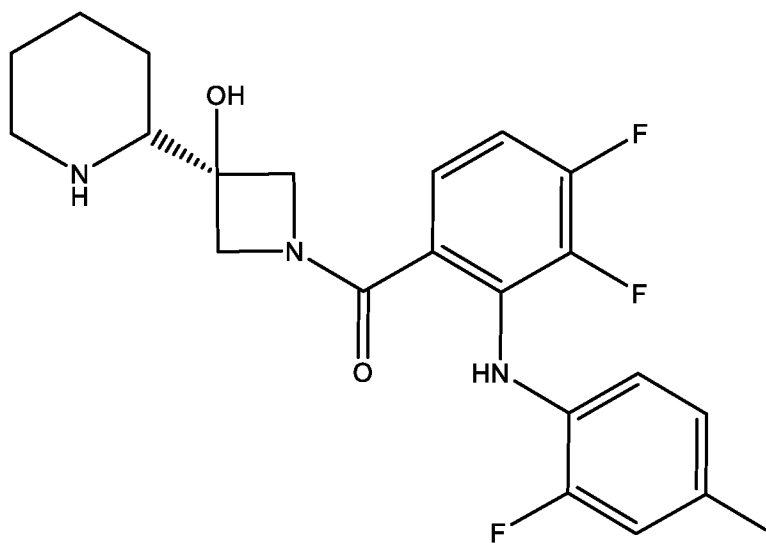
FIELD OF THE INVENTION

- 5 The present invention relates to crystalline cobimetinib hemisuccinate and a process for its preparation. The invention also relates to a pharmaceutical composition comprising crystalline cobimetinib hemisuccinate, preferably in a predetermined and/or effective amount and at least one pharmaceutically acceptable excipient. The pharmaceutical composition of the present invention can be used for the treatment of cancer, in particular for the treatment of melanoma.

10 **BACKGROUND OF THE INVENTION**

Cobimetinib is a kinase inhibitor indicated for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600 mutation, in combination with vemurafenib. It can be chemically designated as (*S*)-[3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl][3-hydroxy-3-(piperidin-2-yl)azetidin-1-yl]methanone and is represented by the following

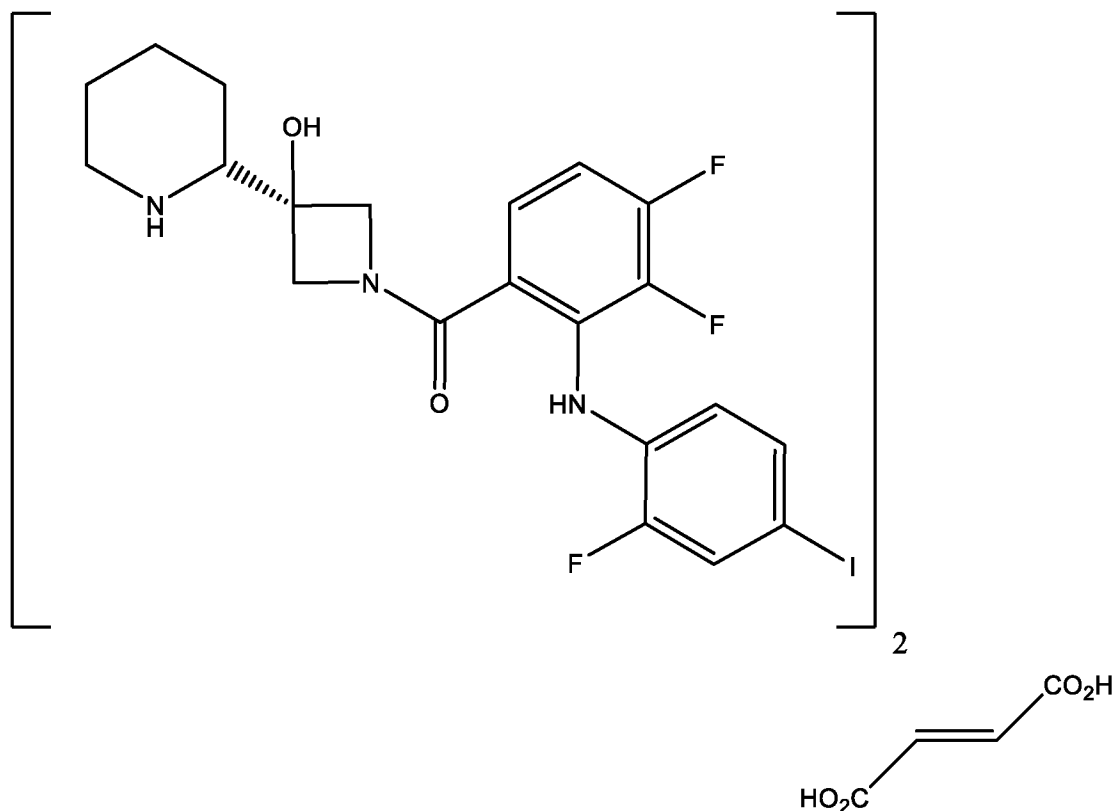
15 chemical structure according to Formula (I)



Formula (I).

- WO 2007/044515 A1 describes the synthesis of cobimetinib (Example 22b, page 231). WO 2008/076415 A1 discloses cobimetinib and pharmaceutically acceptable salts thereof, wherein a generic list of possible salts is given on page 28, paragraph [0103]. Cobimetinib is marketed in form of its hemifumarate salt in the United States, Europe, and elsewhere under
- 20

the brand name Cotellic[®]. Cobimetinib hemifumarate can be characterized by the following chemical structure according to Formula (II)



Formula (II).

- 5 The hemifumarate salt of cobimetinib is subject-matter of WO 2017/004393 A1. According to the teaching of WO 2017/004393 A1 the hemifumarate is the only salt which possesses properties appropriate for processing, manufacturing, storage stability and/or usefulness as a drug, whereas other salts than the hemifumarate were amorphous or a mixture of crystalline and amorphous materials and therefore not suitable for clinical development (see paragraphs
10 [0024] and [00147]).

SUMMARY OF THE INVENTION

Surprisingly, the inventors of the present invention now identified a crystalline salt form of cobimetinib other than the hemifumarate salt, which possesses excellent physicochemical properties allowing for the formulation of customized pharmaceutical drug products.

- 15 The crystalline cobimetinib hemisuccinate of the present invention is a non-solvated anhydrous highly crystalline salt form with low-hygroscopicity and high melting point. Advantageously, when compared with the known crystalline cobimetinib hemifumarate, the crystalline

hemisuccinate salt of the present invention shows improved aqueous solubility and water wettability.

Abbreviations

	PXRD	powder X-ray diffractogram
5	DSC	differential scanning calorimetry
	TGA	thermogravimetric analysis
	NMR	nuclear magnetic resonance
	DSA	drop shape analysis
	RH	relative humidity
10	w-%	weight percent
	ppm	parts per million

Definitions

In the context of the present invention the following definitions have the indicated meaning, unless explicitly stated otherwise:

- 15 As used herein the term “room temperature” refers to a temperature in the range of from 20 to 30 °C.

As used herein, the term “measured at a temperature in the range of from 20 to 30 °C” refers to a measurement under standard conditions. Typically, standard conditions mean a temperature in the range of from 20 to 30 °C, i.e. at room temperature. Standard conditions can mean a
20 temperature of about 22 °C. Typically, standard conditions can additionally mean a measurement under 20-80% relative humidity, preferably 30-70% relative humidity, more preferably 40-60% relative humidity and most preferably 50% relative humidity.

The term “reflection” with regards to powder X-ray diffraction as used herein, means peaks in an X-ray diffractogram, which are caused at certain diffraction angles (Bragg angles) by
25 constructive interference from X-rays scattered by parallel planes of atoms in solid material, which are distributed in an ordered and repetitive pattern in a long-range positional order. Such a solid material is classified as crystalline material, whereas amorphous material is defined as solid material which lacks long-range order and only displays short-range order, thus resulting in broad scattering. According to literature, long-range order e.g. extends over approximately
30 100 to 1000 atoms, whereas short-range order is over a few atoms only (see “*Fundamentals of*

Powder Diffraction and Structural Characterization of Materials” by Vitalij K. Pecharsky and Peter Y. Zavalij, Kluwer Academic Publishers, 2003, page 3).

The term “essentially the same” with reference to powder X-ray diffraction means that variabilities in reflection positions and relative intensities of the reflections are to be taken into account. For example, a typical precision of the 2-Theta values is in the range of $\pm 0.2^\circ$ 2-Theta, preferably in the range of $\pm 0.1^\circ$ 2-Theta. Thus, a reflection that usually appears at 4.6° 2-Theta for example can appear between 4.4° and 4.8° 2-Theta, preferably between 4.5° and 4.7° 2-Theta on most X-ray diffractometers under standard conditions. Furthermore, one skilled in the art will appreciate that relative reflection intensities will show inter-apparatus variability as well as variability due to degree of crystallinity, preferred orientation, sample preparation and other factors known to those skilled in the art and should be taken as qualitative measure only.

Crystalline cobimetinib hemisuccinate of the present invention may be referred to herein as being characterized by a powder X-ray diffractogram "as shown in" a figure. The person skilled in the art understands that factors such as variations in instrument type, response and variations in sample directionality, sample concentration, sample purity, sample history and sample preparation may lead to variations, for example relating to the exact reflection and peak positions and their intensities. However, a comparison of the graphical data in the figures herein with the graphical data generated for an unknown physical form and the confirmation that two sets of graphical data relate to the same crystal form is well within the knowledge of a person skilled in the art.

The term “solid-state form” as used herein refers to any crystalline and/or amorphous phase of a compound.

The term “anhydrous” as used herein refers to a compound where no water is cooperated in or accommodated by the crystal structure. An anhydrous compound may still contain residual water, which is not part of the crystal structure but may be adsorbed on the surface or absorbed in disordered regions of the crystal.

The term “non-solvated” as used herein refer to a compound where no organic solvent is cooperated in or accommodated by the crystal structure. A non-solvated compound may still contain residual organic solvent, which is not part of the crystal structure but may be adsorbed on the surface or absorbed in disordered regions of the crystal.

As used herein, the term “mother liquor” refers to the solution remaining after crystallization of a solid from said solution.

A “predetermined amount” as used herein with regard to crystalline cobimetinib hemisuccinate of the present invention refers to the initial amount of the crystalline cobimetinib hemisuccinate used for the preparation of a pharmaceutical composition having a desired dosage strength of cobimetinib.

The term “effective amount” as used herein with regard to crystalline cobimetinib hemisuccinate of the present invention encompasses an amount of crystalline cobimetinib hemisuccinate, which causes the desired therapeutic and/or prophylactic effect.

As used herein, the term “about” means within a statistically meaningful range of a value. Such a range can be within an order of magnitude, typically within 10%, more typically within 5%, even more typically within 1% and most typically within 0.1% of the indicated value or range. Sometimes, such a range can lie within the experimental error, typical of standard methods used for the measurement and/or determination of a given value or range.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1: illustrates a representative PXRD of crystalline cobimetinib hemisuccinate of the present invention. The x-axis shows the scattering angle in °2-Theta, the y-axis shows the intensity of the scattered X-ray beam in counts of detected photons.

Figure 2: illustrates a representative DSC curve of crystalline cobimetinib hemisuccinate of the present invention. The x-axis shows the temperature in degree Celsius (°C), the y-axis shows the heat flow rate in Watt per gram (W/g) with endothermic peaks going down.

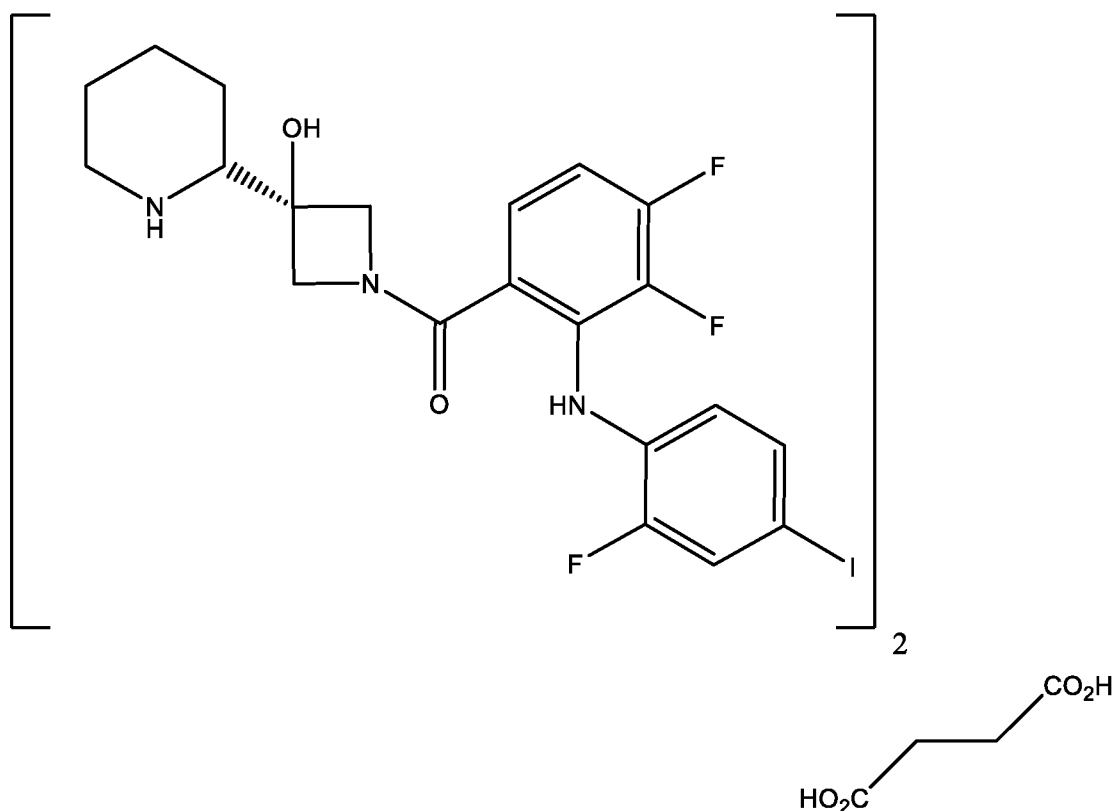
Figure 3: illustrates a representative TGA curve of crystalline cobimetinib hemisuccinate of the present invention. The x-axis shows the temperature in degree Celsius (°C), the y-axis shows the mass (loss) of the sample in weight percent (w-%).

Figure 4: illustrates a representative ¹H-NMR spectrum of crystalline cobimetinib hemisuccinate of the present invention. The x-axis shows the chemical shift in parts per million (ppm) relative to tetramethylsilane.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to crystalline (S)-[3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl][3-hydroxy-3-(piperidin-2-yl)azetidin-1-yl]methanone

hemisuccinate salt, herein also designated cobimetinib hemisuccinate. More precisely, the present invention relates to crystalline cobimetinib hemisuccinate characterized by the chemical structure according to Formula (III)



Formula (III).

The skilled person will appreciate that in the crystalline cobimetinib hemisuccinate of the present invention cobimetinib may be in protonated form (e.g. the piperidine nitrogen is protonated) while succinic acid may be in a deprotonated form.

The crystalline cobimetinib hemisuccinate salt of the present invention as defined in any one of the above described embodiments may be characterized by analytical methods well known in the field of the pharmaceutical industry for characterizing solids. Such methods comprise but are not limited to powder X-ray diffraction, differential scanning calorimetry, thermogravimetric analysis and gravimetric moisture sorption. It may be characterized by one of the aforementioned analytical methods or by combining two or more of them. In particular, the crystalline cobimetinib hemisuccinate of the present invention may be characterized by any one of the following embodiments or by combining two or more of the following embodiments.

The present invention relates to crystalline cobimetinib hemisuccinate characterized by having a PXRD comprising reflections at 2-Theta angles of:

$(4.6 \pm 0.2)^\circ$, $(13.8 \pm 0.2)^\circ$ and $(16.3 \pm 0.2)^\circ$; or

$(4.6 \pm 0.2)^\circ$, $(12.1 \pm 0.2)^\circ$, $(13.8 \pm 0.2)^\circ$ and $(16.3 \pm 0.2)^\circ$; or

5 $(4.6 \pm 0.2)^\circ$, $(12.1 \pm 0.2)^\circ$, $(13.2 \pm 0.2)^\circ$, $(13.8 \pm 0.2)^\circ$ and $(16.3 \pm 0.2)^\circ$; or

$(4.6 \pm 0.2)^\circ$, $(12.1 \pm 0.2)^\circ$, $(13.2 \pm 0.2)^\circ$, $(13.8 \pm 0.2)^\circ$, $(16.3 \pm 0.2)^\circ$ and $(16.6 \pm 0.2)^\circ$; or

$(4.6 \pm 0.2)^\circ$, $(12.1 \pm 0.2)^\circ$, $(13.2 \pm 0.2)^\circ$, $(13.8 \pm 0.2)^\circ$, $(14.5 \pm 0.2)^\circ$, $(16.3 \pm 0.2)^\circ$ and $(16.6 \pm 0.2)^\circ$; or

$(4.6 \pm 0.2)^\circ$, $(12.1 \pm 0.2)^\circ$, $(13.2 \pm 0.2)^\circ$, $(13.8 \pm 0.2)^\circ$, $(14.5 \pm 0.2)^\circ$, $(16.3 \pm 0.2)^\circ$, $(16.6 \pm 0.2)^\circ$

10 and $(17.8 \pm 0.2)^\circ$; or

$(4.6 \pm 0.2)^\circ$, $(12.1 \pm 0.2)^\circ$, $(13.2 \pm 0.2)^\circ$, $(13.8 \pm 0.2)^\circ$, $(14.5 \pm 0.2)^\circ$, $(16.3 \pm 0.2)^\circ$, $(16.6 \pm 0.2)^\circ$, $(17.8 \pm 0.2)^\circ$ and $(24.5 \pm 0.2)^\circ$; or

$(4.6 \pm 0.2)^\circ$, $(11.3 \pm 0.2)^\circ$, $(12.1 \pm 0.2)^\circ$, $(13.2 \pm 0.2)^\circ$, $(13.8 \pm 0.2)^\circ$, $(14.5 \pm 0.2)^\circ$, $(16.3 \pm 0.2)^\circ$, $(16.6 \pm 0.2)^\circ$, $(17.8 \pm 0.2)^\circ$ and $(24.5 \pm 0.2)^\circ$,

15 when measured at a temperature in the range of from 20 to 30 °C with Cu-K α _{1,2} radiation having a wavelength of 0.15419 nm.

Alternatively, the present invention relates to crystalline cobimetinib hemisuccinate characterized by having a PXRD comprising reflections at 2-Theta angles of:

$(4.6 \pm 0.1)^\circ$, $(13.8 \pm 0.1)^\circ$ and $(16.3 \pm 0.1)^\circ$; or

20 $(4.6 \pm 0.1)^\circ$, $(12.1 \pm 0.1)^\circ$, $(13.8 \pm 0.1)^\circ$ and $(16.3 \pm 0.1)^\circ$; or

$(4.6 \pm 0.1)^\circ$, $(12.1 \pm 0.1)^\circ$, $(13.2 \pm 0.1)^\circ$, $(13.8 \pm 0.1)^\circ$ and $(16.3 \pm 0.1)^\circ$; or

$(4.6 \pm 0.1)^\circ$, $(12.1 \pm 0.1)^\circ$, $(13.2 \pm 0.1)^\circ$, $(13.8 \pm 0.1)^\circ$, $(16.3 \pm 0.1)^\circ$ and $(16.6 \pm 0.1)^\circ$; or

$(4.6 \pm 0.1)^\circ$, $(12.1 \pm 0.1)^\circ$, $(13.2 \pm 0.1)^\circ$, $(13.8 \pm 0.1)^\circ$, $(14.5 \pm 0.1)^\circ$, $(16.3 \pm 0.1)^\circ$ and $(16.6 \pm 0.1)^\circ$; or

25 $(4.6 \pm 0.1)^\circ$, $(12.1 \pm 0.1)^\circ$, $(13.2 \pm 0.1)^\circ$, $(13.8 \pm 0.1)^\circ$, $(14.5 \pm 0.1)^\circ$, $(16.3 \pm 0.1)^\circ$, $(16.6 \pm 0.1)^\circ$ and $(17.8 \pm 0.1)^\circ$; or

$(4.6 \pm 0.1)^\circ$, $(12.1 \pm 0.1)^\circ$, $(13.2 \pm 0.1)^\circ$, $(13.8 \pm 0.1)^\circ$, $(14.5 \pm 0.1)^\circ$, $(16.3 \pm 0.1)^\circ$, $(16.6 \pm 0.1)^\circ$, $(17.8 \pm 0.1)^\circ$ and $(24.5 \pm 0.1)^\circ$; or

$(4.6 \pm 0.1)^\circ$, $(11.3 \pm 0.1)^\circ$, $(12.1 \pm 0.1)^\circ$, $(13.2 \pm 0.1)^\circ$, $(13.8 \pm 0.1)^\circ$, $(14.5 \pm 0.1)^\circ$, $(16.3 \pm 0.1)^\circ$, $(16.6 \pm 0.1)^\circ$, $(17.8 \pm 0.1)^\circ$ and $(24.5 \pm 0.1)^\circ$,

30 when measured at a temperature in the range of from 20 to 30 °C with Cu-K α _{1,2} radiation having a wavelength of 0.15419 nm.

In addition, the present invention relates to crystalline cobimetinib hemisuccinate characterized by having a PXRD comprising reflections at 2-Theta angles of $(12.1 \pm 0.2)^\circ$, $(13.2 \pm 0.2)^\circ$, $(13.8 \pm 0.2)^\circ$, $(16.3 \pm 0.2)^\circ$, $(16.6 \pm 0.2)^\circ$, $(23.3 \pm 0.2)^\circ$, $(24.5 \pm 0.2)^\circ$, $(25.7 \pm 0.2)^\circ$, $(26.6 \pm 0.2)^\circ$ and (27.0 ± 0.2) , when measured at a temperature in the range of from 20 to 30 °C with Cu-K $\alpha_{1,2}$ radiation having a wavelength of 0.15419 nm.

Alternatively, the present invention relates to crystalline cobimetinib hemisuccinate characterized by having a PXRD comprising reflections at 2-Theta angles of $(12.1 \pm 0.1)^\circ$, $(13.2 \pm 0.1)^\circ$, $(13.8 \pm 0.1)^\circ$, $(16.3 \pm 0.1)^\circ$, $(16.6 \pm 0.1)^\circ$, $(23.3 \pm 0.1)^\circ$, $(24.5 \pm 0.1)^\circ$, $(25.7 \pm 0.1)^\circ$, $(26.6 \pm 0.1)^\circ$ and (27.0 ± 0.1) , when measured at a temperature in the range of from 20 to 30 °C with Cu-K $\alpha_{1,2}$ radiation having a wavelength of 0.15419 nm.

The present invention also relates to crystalline cobimetinib hemisuccinate characterized by having a PXRD essentially the same as shown in Figure 1 of the present invention, when measured at a temperature in the range of from 20 to 30 °C with Cu-K $\alpha_{1,2}$ radiation having a wavelength of 0.15419 nm.

Furthermore, the present invention relates to crystalline cobimetinib hemisuccinate characterized by having a DSC curve comprising an endothermic peak having an onset at a temperature of $(188 \pm 5)^\circ\text{C}$, preferably of $(188 \pm 3)^\circ\text{C}$, even more preferably of $(188 \pm 2)^\circ\text{C}$ and most preferably of $(188 \pm 1)^\circ\text{C}$, when measured at a heating rate of 10 K/min.

In still another embodiment, the invention relates crystalline cobimetinib hemisuccinate, characterized by having a melting point onset at a temperature in the range of from $(188 \pm 5)^\circ\text{C}$, preferably of from $(188 \pm 3)^\circ\text{C}$, more preferably of from $(188 \pm 2)^\circ\text{C}$, even more preferably of from $(188 \pm 1)^\circ\text{C}$, for example having a melting point onset at a temperature of about 188 °C, when measured with DSC at a heating rate of 10 K/min.

The present invention also relates to crystalline cobimetinib hemisuccinate characterized by having a DSC curve comprising an endothermic peak having a peak maximum at a temperature of $(190 \pm 5)^\circ\text{C}$, preferably of $(190 \pm 3)^\circ\text{C}$, even more preferably of $(190 \pm 2)^\circ\text{C}$ and most preferably of $(190 \pm 1)^\circ\text{C}$, when measured a heating rate of 10 K/min.

In another embodiment, the present invention relates to crystalline cobimetinib hemisuccinate, characterized by having a TGA curve showing no mass loss, when heated from 30 to 190°C at a rate of 10 K/min.

Preferably, the crystalline cobimetinib hemisuccinate of the present invention as defined in any one of the embodiments described above is anhydrous.

Even more preferably, the crystalline cobimetinib hemisuccinate of the present invention as defined in any one of the embodiments described above is non-solvated.

- 5 The present invention further relates to crystalline cobimetinib hemisuccinate characterized by showing a mass change of not more than 1.0 w-%, based on the weight of the crystalline cobimetinib hemisuccinate, when measured with GMS during the sorption cycle at a relative humidity in the range of from 0 to 90% and a temperature of $(25.0 \pm 0.1)^{\circ}\text{C}$.

10 In another aspect, the invention relates to a process for the preparation of the crystalline cobimetinib hemisuccinate as defined in any one of the above described embodiments comprising:

- (a) reacting cobimetinib free base and succinic acid in the presence of a suitable solvent;
- (b) allowing for the crystallization of cobimetinib hemisuccinate;
- (c) separating at least a part of the crystals obtained in step (b);
- 15 (d) optionally washing the crystals obtained in step (c); and
- (e) drying the crystals obtained in step (c) or (d).

Cobimetinib may be prepared according to the synthesis disclosed in Example 22b of WO 2007/044515 A1 or according to the procedures set forth in WO 2014/059422 A1 or Examples 1 to 6 of WO 2017/004393 A1. Succinic acid is commercially available (e.g. from
20 Fluka[®], assay $\geq 99\%$).

In the first step (a) of the above described process cobimetinib free base is reacted with succinic acid in the presence of a suitable solvent. The suitable solvent may be selected from the group consisting of esters, ketones, alcohols and nitriles or any mixtures thereof. Preferably, the ester is selected from the group consisting of methyl acetate, ethyl acetate, *n*-propyl acetate, isopropyl
25 acetate, *n*-butyl acetate and isobutyl acetate or any mixtures thereof, the ketone is selected from the group consisting of acetone, methylethyl ketone and methylisobutyl ketone or any mixtures thereof, the alcohol is selected from isopropyl alcohol or isobutyl alcohol or a mixture thereof and the nitrile is acetonitrile. Most preferably, the suitable solvent is ethyl acetate or acetone.

The molar ratio of cobimetinib free base and succinic acid applied in step (a) is in the range of from 1.0: 0.55 – 1.00, preferably of from 1.0: 0.55 – 0.75 and most preferably of from 1.0: 0.55 – 0.65.

5 The cobimetinib free base concentration in relation to the applied solvent in step (a) is in the range of from 10 – 60 g/L, most preferably of from 15 – 30 g/L.

The reaction may be carried out at room temperature or at elevated temperature e.g. between room temperature and reflux temperature. For example, the reaction may be carried out at about 50-70°C, e.g. at 60°C. Preferably, temperature is selected such, that cobimetinib and succinic acid at least partially dissolve and most preferably both components dissolve completely.

10 Once the reaction is complete, cobimetinib succinate is allowed to crystallize from the mother liquor. Usually, the material crystallizes gradually upon stirring. The solution may also be cooled to room temperature in order to initiate crystallization. The obtained suspension may then be further stirred until plentiful crystallization occurs e.g. for a period in the range of from 0.5 to 120 hours, preferably of from 1 to 72 hours and most preferably of from 2 to 6 hours. In
15 order to increase the yield, the suspension may be further cooled e.g. to a temperature in the range of from 0 to 10 °C, e.g. of from 2 to 8 °C.

In the next step (c), at least a part of the crystals are separated from their mother liquor. Preferably, the crystals are separated from their mother liquor by any conventional method such as filtration, centrifugation, solvent evaporation or decantation, more preferably by filtration or
20 centrifugation and most preferably by filtration.

In an optional step (d), the isolated crystals may be washed with one or more suitable solvent(s). Suitable solvents, which may be used are selected from one or more esters. The one or more ethers may be selected from the group consisting of methyl acetate, ethyl acetate, *n*-propyl acetate, isopropyl acetate, *n*-butyl acetate and isobutyl acetate, wherein ethyl acetate is most
25 preferred. In one embodiment, the solvent used in step (d) is ethyl acetate.

Finally, the obtained crystals are dried, wherein drying may be performed at a temperature in the range of from about 20 to 120 °C, preferably of from about 20 to 100 °C , even more preferably of from about 30 to 60 °C. Drying may be performed at ambient pressure and/or under reduced pressure. Preferably, drying is performed at a pressure of about 100 mbar or less,
30 more preferably of about 50 mbar or less for example a vacuum of about 30 mbar or less. Drying

may be performed for a period in the range of from about 1 to 24 hours, preferably from about 1 to 12 hours and most preferably from about 2 to 6 hours.

In a further aspect the present invention relates to the use of the crystalline cobimetinib hemisuccinate of the present invention as defined in any one of the embodiments described
5 above for the preparation of a pharmaceutical composition.

In still a further aspect, the present invention relates to a pharmaceutical composition comprising crystalline cobimetinib hemisuccinate of the present invention as defined in any one of the embodiments described above, preferably in an effective and/or predetermined amount, and at least one pharmaceutically acceptable excipient. Preferably, the pharmaceutical
10 composition of the present invention is an oral solid dosage form, such as a tablet or a capsule. More preferably, the pharmaceutical composition of the present invention is a tablet e.g. a film-coated tablet. Most preferably, the pharmaceutical composition of the present invention is an immediate-release film-coated tablet.

The at least one pharmaceutically acceptable excipient, which is comprised in the
15 pharmaceutical composition of the present invention, is preferably selected from the group consisting of fillers, disintegrants, lubricants, coating materials and combinations thereof. In one embodiment all of these pharmaceutically acceptable excipients are comprised by the pharmaceutical composition of the present invention.

In a preferred embodiment, the at least one pharmaceutically acceptable excipient is selected
20 from the group consisting of microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, magnesium stearate and coating materials. In a preferred embodiment, all of these pharmaceutically acceptable excipients are comprised by the pharmaceutical composition of the present invention.

The present invention also relates to a pharmaceutical composition as defined in any one of the
25 embodiments described above, wherein the pharmaceutical composition comprises a tablet core and a film-coating. The tablet core comprises crystalline cobimetinib hemisuccinate of the present invention and at least one pharmaceutically acceptable excipient. Preferably, the at least one pharmaceutically acceptable excipient is selected from the group consisting of fillers, disintegrants and lubricants, preferably all of these pharmaceutically acceptable excipients are
30 comprised by the tablet core. For example, the tablet core comprises at least one

pharmaceutically acceptable excipient selected from the group consisting of microcrystalline cellulose, lactose monohydrate, croscarmellose sodium and magnesium stearate, preferably all of these pharmaceutically acceptable excipients are comprised by the tablet core. The film-coating may comprise at least one pharmaceutically acceptable excipient selected from the group consisting of polyvinyl alcohol, titanium dioxide, polyethylene glycol and talc, preferably all of these pharmaceutically acceptable excipients are comprised by the film-coating.

The pharmaceutical composition of the present invention can be produced by standard manufacturing processes, which are well-known to the skilled person including blending, granulation (wet or dry granulation), tablet compression and film-coating.

Preferably, the present invention relates to a pharmaceutical composition as describe above, wherein the predetermined and/or effective amount of crystalline cobimetinib hemisuccinate of the present invention is selected from the group consisting of 20 mg, 40 mg and 60 mg calculated as cobimetinib free base. Most preferably, the invention relates to a pharmaceutical composition as described above, wherein the predetermined and/or effective amount of crystalline cobimetinib hemisuccinate of the present invention is 20 mg calculated as cobimetinib free base.

The present invention also relates to a pharmaceutical composition as defined in any one of the above described embodiments, wherein the pharmaceutical composition is to be administered once-daily. Preferably, the once daily dose is 60 mg, e.g. trice 20 mg, once 60 mg or once 20 mg plus once 40 mg, each dose calculated as cobimetinib free base. Alternatively, the once daily dose is 40 mg, e.g. twice 20 mg, or once 40 mg, each dose calculated as cobimetinib free base. In another embodiment, the once daily dose is 20 mg once daily, e.g. once 20 mg, calculated as cobimetinib free base.

In a further aspect, the present invention relates to the pharmaceutical composition as defined in any one of the above described embodiments for use as a medicament.

Moreover, the present invention relates to the pharmaceutical composition as defined in any one of the above described embodiments for use in the treatment of cancer.

The present invention also relates to the pharmaceutical composition as defined in any one of the above described embodiments for use in the treatment of cancer selected from the group

consisting of melanoma (including BRAF V600 mutant melanoma), breast cancer, (including triple negative breast cancer), colorectal cancer (including KRAS mutant colorectal cancer), non-small cell lung cancer, acute myeloid leukemia and pancreatic cancer. Preferably, the invention relates to the pharmaceutical composition as defined in any one of the above described embodiments for use in the treatment of melanoma. Most preferably, the invention relates to the pharmaceutical composition as defined in any one of the above described embodiments for use in the treatment of BRAF V600 mutant melanoma.

In another embodiment, the present invention is directed to a method of treating cancer selected from the group consisting of melanoma (including BRAF V600 mutant melanoma), breast cancer, (including triple negative breast cancer), colorectal cancer (including KRAS mutant colorectal cancer), non-small cell lung cancer, acute myeloid leukemia and pancreatic cancer, said method comprising administering the pharmaceutical composition as defined in any one of the above described embodiments to a patient in need of such a treatment.

In another aspect the present invention relates to the pharmaceutical composition as defined in any one of the above described embodiments intended for the treatment of cancer in combination with one or more additional active pharmaceutical ingredient(s) selected from the group consisting of vemurafenib, dabrafenib and trametinib or mixtures thereof.

A treatment in combination with one or more additional active pharmaceutical ingredient(s) can mean the administration of a pharmaceutical dosage form comprising the crystalline cobimetinib hemisuccinate of the present invention and the one or more additional active pharmaceutical ingredient(s) in the same dosage form, for example as a fixed-dose combination.

Alternatively, a treatment in combination with one or more additional active pharmaceutical ingredient(s) can mean the administration of separate pharmaceutical dosage forms, one comprising the crystalline cobimetinib hemisuccinate of the present invention, and the other(s) comprising the one or more additional active pharmaceutical ingredient(s) in separate dosage form(s). Typically in such a combination treatment instructions are provided that the pharmaceutical dosage form comprising the crystalline cobimetinib hemisuccinate of the present invention is to be administered in combination with said separate dosage form(s) for the effective treatment of cancer.

EXAMPLES

The following non-limiting examples are illustrative for the disclosure and are not to be construed as to be in any way limiting for the scope of the invention.

Example 1: Preparation of crystalline cobimetinib hemisuccinate

- 5 Cobimetinib free base (2.70 g, 5.1 mmol) was dissolved in ethyl acetate (100 mL) by heating to around 60°C followed by addition of succinic acid (0.33 g, 2.8 mmol). Shortly after dissolution of both components crystallization was observed. The suspension was cooled from 60°C to 20°C in 30 minutes. The suspension was further stirred for three days at 20°C, filtered and the recovered solid vacuum dried at room temperature to obtain crystalline cobimetinib
10 hemisuccinate.

Example 2: Preparation of crystalline cobimetinib hemisuccinate

- Cobimetinib free base (17.9 mg, 0.034 mmol) and succinic acid (2.6 mg, 0.022 mmol) were dissolved in acetone (1 mL) at room temperature. The solution was stirred and crystallization was observed approximately one hour after dissolution. The suspension was further stirred for
15 one day at room temperature before the crystals were collected by filtration and vacuum dried at room temperature.

Example 3: Preparation of crystalline cobimetinib hemisuccinate

- Cobimetinib free base (17.9 mg, 0.034 mmol) and succinic acid (2.2 mg, 0.018 mmol) were dissolved in 1-butanol (1 mL) at room temperature. The solution was stirred for one day at room
20 temperature, whereat a suspension was obtained. The obtained crystals were collected by filtration and vacuum dried at room temperature.

Example 4: Preparation of crystalline cobimetinib hemisuccinate

- Cobimetinib free base (17.8 mg, 0.034 mmol) and succinic acid (2.3 mg, 0.019 mmol) were sonicated in acetonitrile (1 mL) at room temperature to obtain a solution. The solution was then
25 stirred for one day at room temperature to obtain a suspension. The obtained crystals were collected by filtration and vacuum dried at room temperature.

Example 5: Preparation of crystalline cobimetinib hemisuccinate

- Cobimetinib free base (179.0 mg, 0.034 mmol) and succinic acid (2.3 mg, 0.019 mmol) were sonicated in isopropylacetate (1 mL) at about 62°C to obtain a solution. Shortly after dissolution
30 crystallization was observed. The suspension was further stirred for one day at room

temperature before the obtained crystals were collected by filtration and vacuum dried at room temperature.

Example 6: Solid-state characterization of crystalline cobimetinib hemisuccinate

Powder X-ray diffraction

- 5 Powder X-ray diffraction was performed with a PANalytical Empyrean diffractometer equipped with a theta/theta coupled goniometer in transmission geometry, Cu-K α _{1,2} radiation (wavelength 0.15419 nm) with a focusing mirror and a solid state PIXcel detector. Diffractograms were recorded at a tube voltage of 45 kV and a tube current of 40 mA, applying a stepsize of 0.026° 2-Theta with 200s per step (255 channels) in the angular range of 2° to 40°
10 2-Theta at ambient conditions. A typical precision of the 2-Theta values is in the range of $\pm 0.2^\circ$ 2-Theta, preferably of $\pm 0.1^\circ$ 2-Theta.

A representative diffractogram of crystalline cobimetinib hemisuccinate is displayed in Figure 1 herein. The corresponding reflection list is provided in Table 1 below.

Reflection position [° 2-Theta]	Reflection position [° 2-Theta]	Reflection position [° 2-Theta]	Reflection position [° 2-Theta]
4.6	16.6	21.1	25.7
11.3	16.9	21.7	26.6
12.1	17.8	22.6	27.0
13.2	18.4	22.7	27.4
13.8	19.0	23.1	27.9
14.5	19.7	23.3	28.4
15.3	20.4	24.5	28.9
16.3	20.7	25.4	29.3

15 **Table 1:** PXRD reflections of crystalline cobimetinib hemisuccinate in the range of from 2 to 30° 2-Theta; A typical precision of the 2-Theta values is in the range of $\pm 0.2^\circ$ 2-Theta, preferably of $\pm 0.1^\circ$ 2-Theta.

Differential scanning calorimetry

- 20 DSC was performed on a Mettler Toledo DSC 3+ star system instrument. About 1.7 mg of the sample was heated in a 40 microliter aluminium pan with a closed aluminium lid from 30 to 350 °C at a rate of 10 K/min. Nitrogen (purge rate 100 mL/min) was used as purge gas.

The DSC curve of crystalline cobimetinib hemisuccinate shows an endothermic peak with an onset temperature of about 188 °C and a peak temperature of about 190 °C, which is due to the melting of the sample. Immediately, after melting the sample decomposes, which is indicated by a broad exothermic peak (see also Figure 2 herein).

5 Thermogravimetric analysis

TGA was performed on a Mettler TGA/DSC 1 instrument. About 0.8 mg of the sample was heated in a 40 microliter aluminum pan with a pierced aluminum lid. The sample was heated from 30 to 250 °C at a rate of 10 K/min. Nitrogen (purge rate 100 mL/min) was used as purge gas.

10 The TGA curve of crystalline cobimetinib hemisuccinate shows no mass loss from the beginning of the measurement at about 30°C until melting of the sample at about 190°C. Hence, it can be concluded that neither water nor organic solvents are part of the crystal structure. Only at temperatures above about 190°C, e.g. after melting a significant weight loss indicates decomposition (see also Figure 3 herein).

15 Nuclear Magnetic Resonance

¹H NMR spectra were acquired on a Bruker Avance III spectrometer at 500MHz in DMSO-d₆ at a temperature of 25°C. Shifts are reported in parts per million (ppm) relative to tetramethylsilane.

20 **Comparative Example 1:** Water wettability of crystalline cobimetinib hemisuccinate and hemifumarate

Tablet compacts of crystalline cobimetinib hemisuccinate and crystalline cobimetinib hemifumarate were prepared using a manual laboratory press (PW10, P/O Weber, D-Remshalden) equipped with force and displacement sensors (Hottinger Baldwin, D-Darmstadt). The water droplets were placed on each tablet surface. The contact angle of this sessile drops
25 at the moment of the first contact was measured using *Kruess DSA25E* (*Kruess, D-Hamburg, Germany*), equipped with illumination, a manual lift table (z-axis), video camera and software *Kruess Advance 1.6.2*.

Drop shape analysis (DSA) gives valuable information about the wetting behavior of the cobimetinib salts. The contact angles and wettability of the two salt forms are clearly different,
30 whereat a low contact angle means better wettability. In case of the cobimetinib hemisuccinate,

the water wettability is better than for cobimetinib hemifumarate. The results are summarized in Table 2 below:

	Contact angle (standard deviation)
Cobimetinib hemifumarate	90.6° (3.1°)
Cobimetinib hemisuccinate	79.3° (1.7°)

Table 2: Results of drop shape analysis

Comparative Example 2: Water solubility of crystalline cobimetinib hemisuccinate and hemifumarate

The equilibrium solubilities in water at $(24 \pm 1)^\circ\text{C}$ were determined by HPLC at 300 nm for crystalline cobimetinib hemisuccinate and crystalline cobimetinib hemifumarate, respectively. Cobimetinib hemisuccinate shows a more than 2-fold higher solubility in water compared to cobimetinib hemifumarate. The results are summarized in Table 3 below:

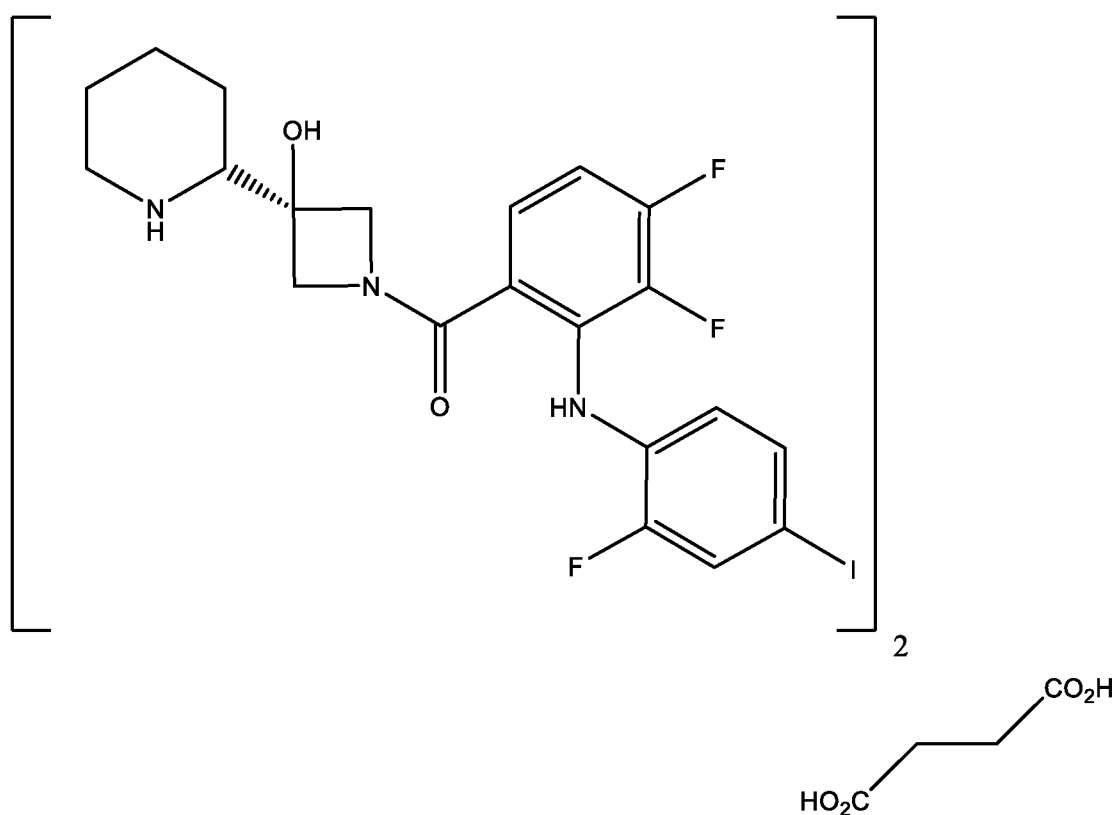
	Concentration in g/L
Cobimetinib hemifumarate	0.7
Cobimetinib hemisuccinate	1.6

Table 3: Results of solubility testing

CLAIMS

1) A crystalline hemisuccinate salt of (*S*)-[3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl][3-hydroxy-3-(piperidin-2-yl)azetidin-1-yl]methanone (cobimetinib).

5 2) The crystalline hemisuccinate salt of claim 1 characterized by the chemical structure according to Formula (III)



Formula (III).

3) The crystalline hemisuccinate salt according to claim 1 or 2 characterized by having a powder X-ray diffractogram comprising reflections at 2-Theta angles of $(4.6 \pm 0.2)^\circ$, $(13.8 \pm 0.2)^\circ$ and $(16.3 \pm 0.2)^\circ$, when measured at a temperature in the range of from 20 to 30 °C with Cu-Kalpha_{1,2} radiation having a wavelength of 0.15419 nm.

4) The crystalline hemisuccinate salt according to claim 3 characterized by having a powder X-ray diffractogram comprising additional reflections at 2-Theta angles of $(12.1 \pm 0.2)^\circ$ and $(13.2 \pm 0.2)^\circ$, when measured at a temperature in the range of from 20 to 30 °C with Cu-Kalpha_{1,2} radiation having a wavelength of 0.15419 nm.

- 5) The crystalline hemisuccinate salt as defined in any one of the preceding claims characterized by having a DSC curve comprising an endothermic peak having an onset at a temperature of $(188 \pm 5)^{\circ}\text{C}$, when measured at a heating rate of 10 K/min.
- 6) The crystalline hemisuccinate salt as defined in any one of the preceding claims
5 characterized by having a TGA curve showing no mass loss, when heated from 30 to 190°C at a rate of 10 K/min.
- 7) The crystalline hemisuccinate salt as defined in any one of the preceding claims characterized by showing a mass change of not more than 1.0 w-%, based on the weight of cobimetinib hemisuccinate, when measured with gravimetric moisture sorption
10 during the sorption cycle at a relative humidity in the range of from 0 to 90% and a temperature of $(25.0 \pm 0.1)^{\circ}\text{C}$.
- 8) Use of the crystalline hemisuccinate salt as defined in any one of the preceding claims for the preparation of a pharmaceutical composition.
- 9) A pharmaceutical composition comprising the crystalline hemisuccinate salt as defined
15 in any one of claims 1 to 7 and at least one pharmaceutically acceptable excipient.
- 10) The pharmaceutical composition of claim 9, wherein the pharmaceutical composition is an oral solid dosage form.
- 11) The pharmaceutical composition of claim 10, wherein the oral solid dosage form is a film-coated tablet.
- 20 12) The pharmaceutical composition as defined in any one of claims 9 to 11, comprising 20 mg of the crystalline hemisuccinate salt as defined in any one of claims 1 to 8, calculated as cobimetinib free base.
- 13) The pharmaceutical composition as defined in any one of claims 9 to 12 for use in the treatment of cancer.
- 25 14) The pharmaceutical composition as defined in any one of claims 9 to 12 for use in the treatment of melanoma (including BRAF V600 mutant melanoma).
- 15) The pharmaceutical composition as defined in any one of claims 9 to 12 in combination with vemurafenib for use in the treatment of BRAF V600 mutant melanoma.

Figure 1

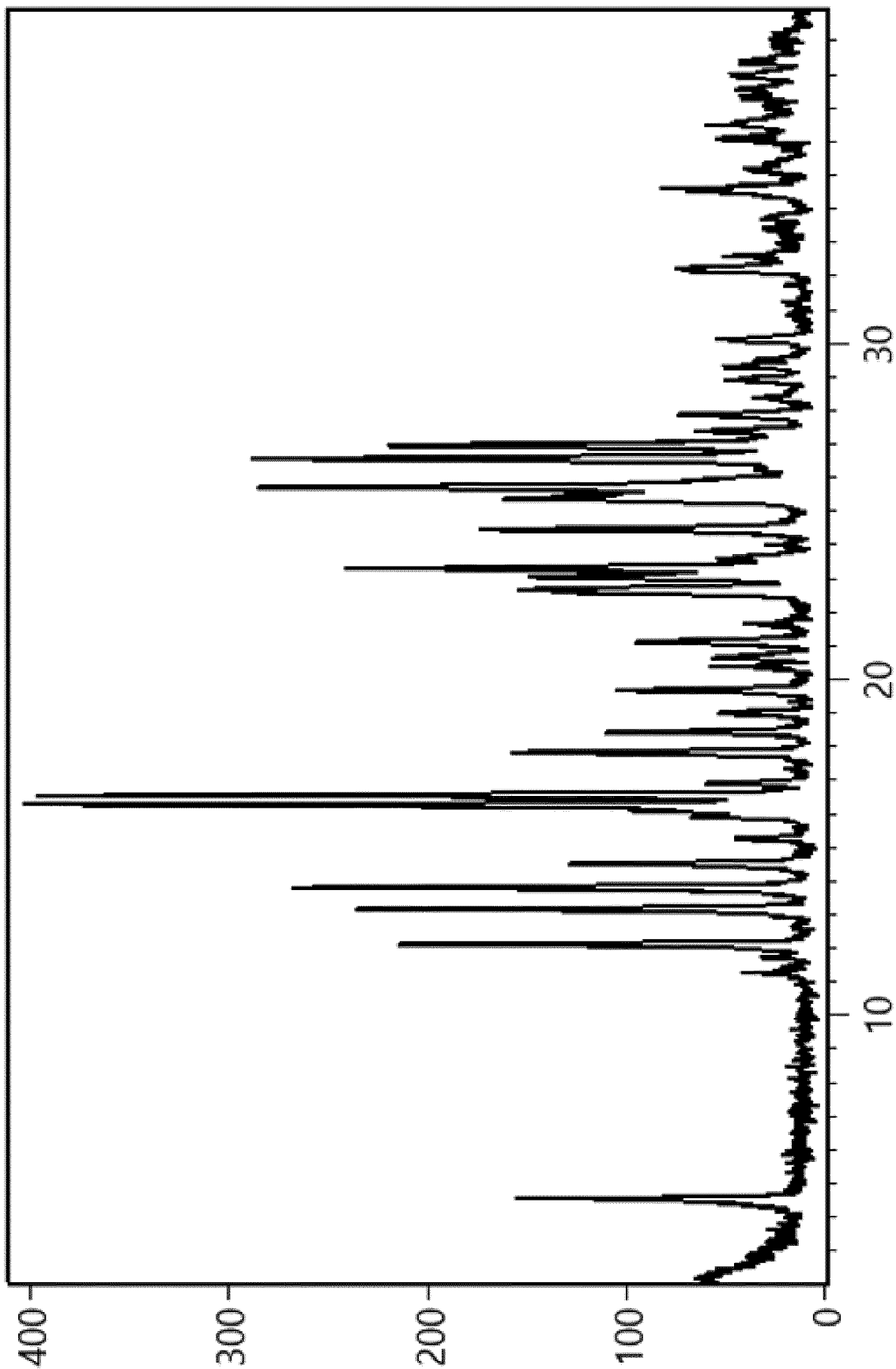


Figure 2

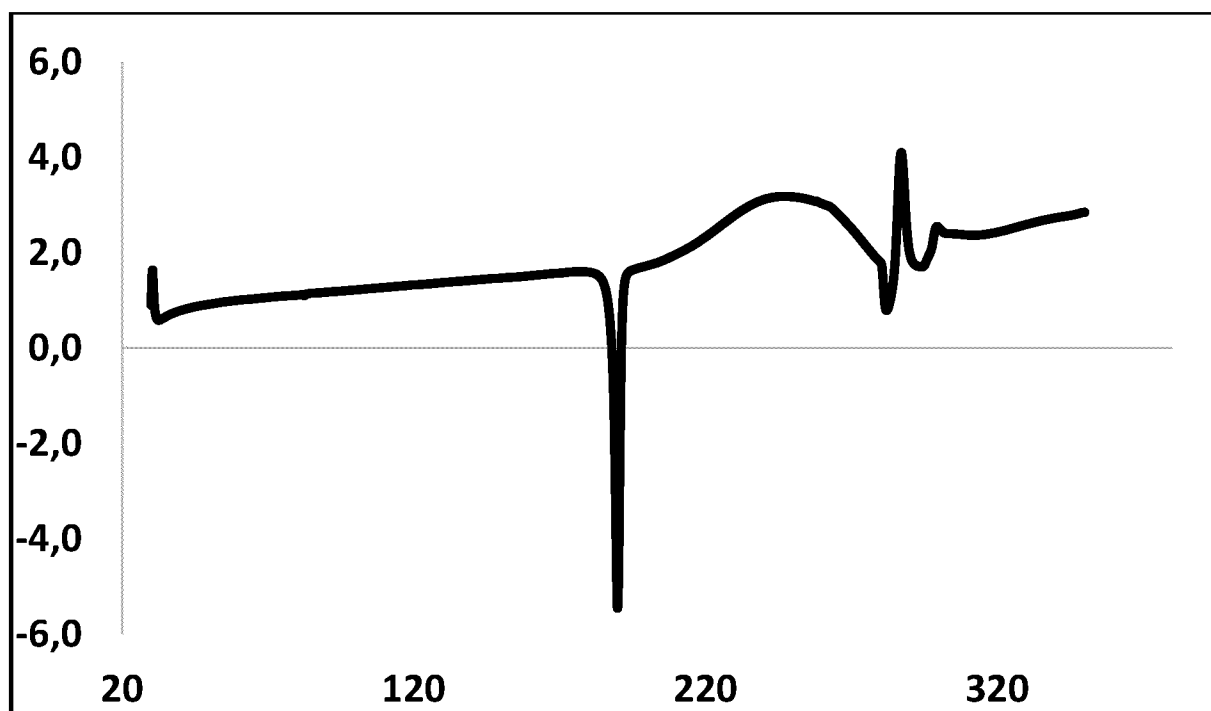


Figure 3

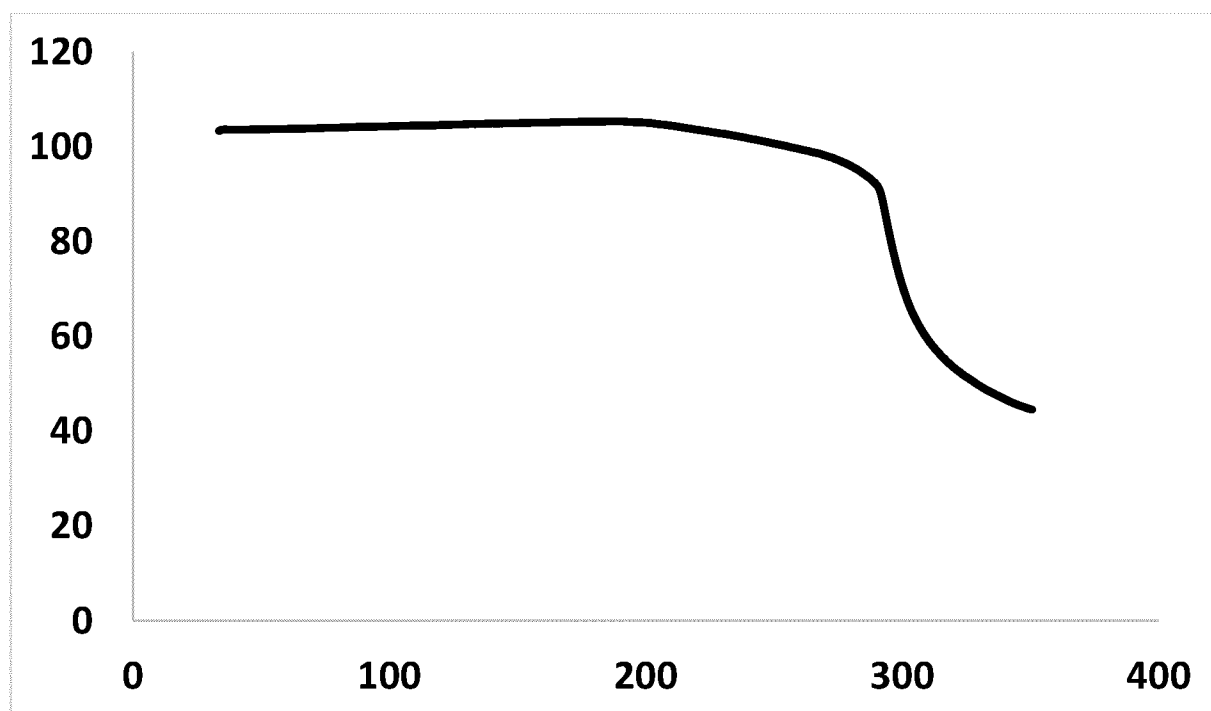
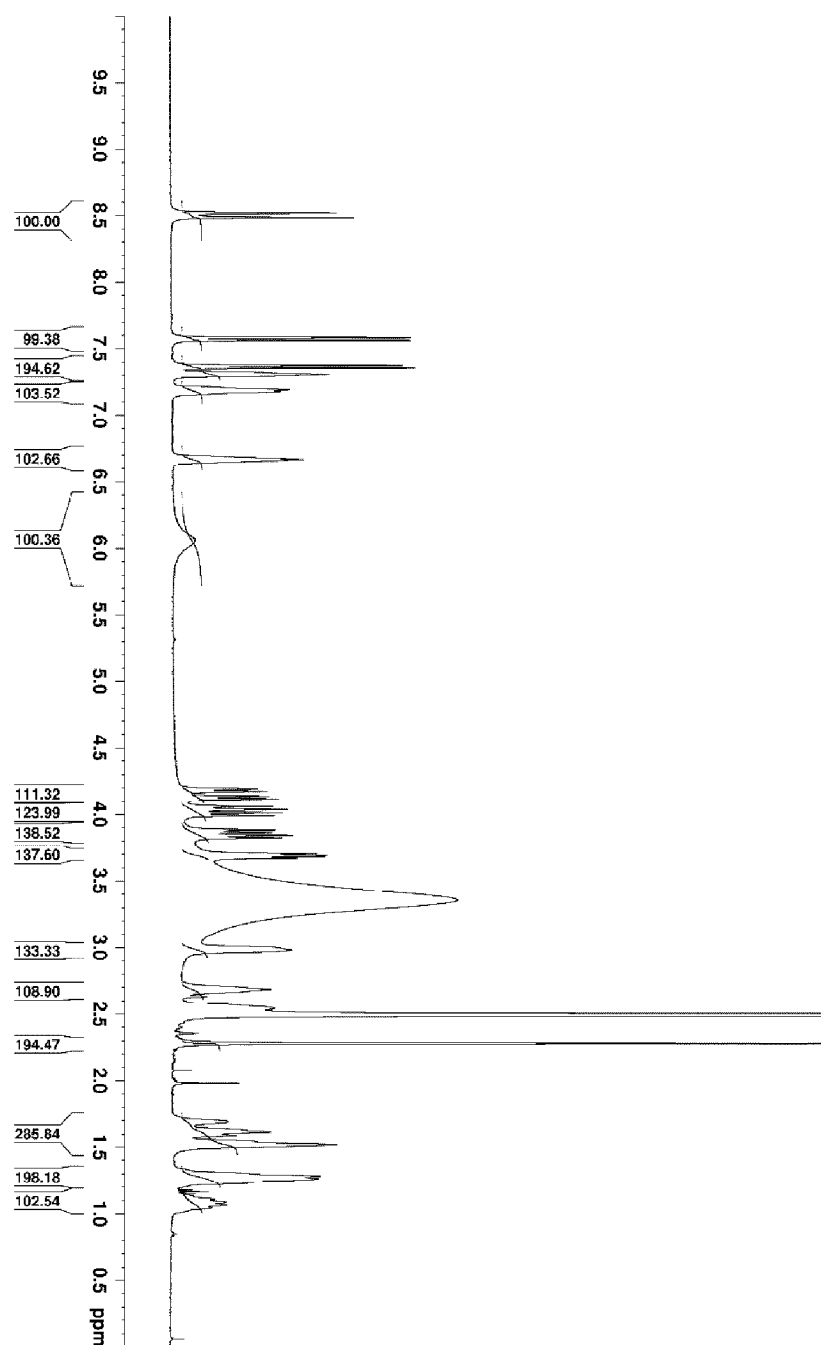


Figure 4



INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2020/056584

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D401/04 A61K31/4427 A61P35/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2017/004393 A1 (EXELIXIS INC [US]) 5 January 2017 (2017-01-05) cited in the application see the fumarate salt of cobimetinib -----	1-15



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

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"E" earlier application or patent but published on or after the international filing date

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

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Date of the actual completion of the international search

16 April 2020

Date of mailing of the international search report

30/04/2020

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2020/056584

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