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(54) Title: NOVEL POLYMORPH OF NILOTINIB MONOHYDROCHLORIDE MONOHYDRATE

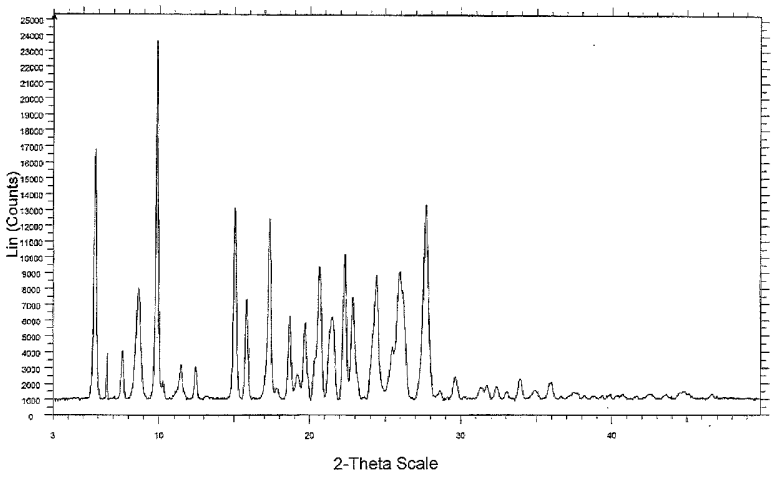

Figure 1

(57) Abstract: The present invention relates to a novel polymorph of 4-methyl-N-[3-(4-methyl-imidazol- 1-yl)-5-(trifluoromethyl)-phenyl]-3-[(4-pyridin-3-yl-pyrimidin-2-yl)amino] benzamide (nilotinib) monohydrochloride monohydrate, and to methods for preparing, pharmaceutical compositions comprising, and methods of treatment using said polymorph.

WO 2011/086541 A1

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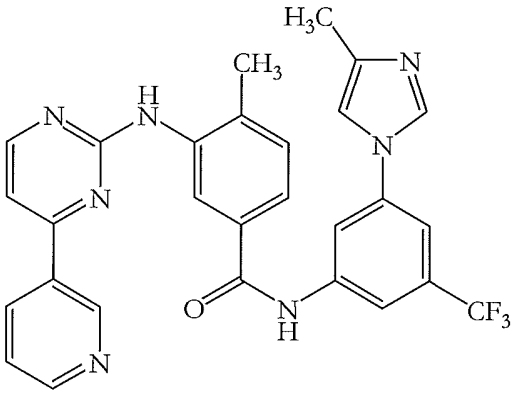
NOVEL POLYMORPH OF NILOTINIB MONOHYDROCHLORIDE MONOHYDRATE

Field of the invention

The present invention relates to a novel polymorph of 4-methyl-N-[3-(4-methyl-imidazol-1-yl)-5-(trifluoromethyl)-phenyl]-3-[(4-pyridin-3-yl-pyrimidin-2-yl)amino] benzamide monohydrochloride monohydrate, and to methods for preparing, pharmaceutical compositions comprising, and methods of treatment using said polymorph.

Background of the invention

4-Methyl-N-[3-(4-methyl-imidazol-1-yl)-5-(trifluoromethyl)-phenyl]-3-[(4-pyridin-3-yl-pyrimidin-2-yl)amino] benzamide having formula (I) was first disclosed in WO 2004/005281. This compound, also known as nilotinib, is a tyrosine kinase inhibitor and is indicated in the treatment of drug-resistant chronic myelogenous leukemia (CML). However, WO 2004/005281 does not disclose any salts or hydrates of nilotinib.



(I)

WO 2007/015871 is directed to various salts of nilotinib. Preferred embodiments include the hydrochloride, monophosphate, diphosphate, sulfate, methane sulfonate, ethane sulfonate, benzene sulfonate and p-toluene sulfonate salts of nilotinib. In relation to the hydrochloride salt in particular, the application only discloses forms A and B and further specifically discloses the preparation of the nilotinib monohydrochloride monohydrate by adding nilotinib free base to methanol and hydrochloric acid and recovering the hydrochloride salt after seeding. There are further references to the hydrochloride salt that

do not specify the monohydrochloride monohydrate form. It is not clear from the disclosure whether nilotinib hydrochloride form A is a hydrated form or an anhydrous form, however it is prepared using very similar solvents and conditions to those used to prepare form B, which is a form of nilotinib monohydrochloride monohydrate.

The marketed product, Tasigna®, is the monohydrochloride monohydrate salt described above. There is always a need to prepare alternate salts or salt forms which can either match or better the pharmacokinetic properties of such marketed products. These alternative salts and salt forms must also pass the quality and safety criteria set out by the various health authorities around the world and can themselves be marketed as equally efficacious and often more cost effective alternatives to patient groups and healthcare systems around the world.

Summary of the invention

The inventors have succeeded in preparing an alternative novel crystalline form of nilotinib monohydrochloride monohydrate to that disclosed in the prior art. Advantageously this novel form does not require seeding or separate exposure to moisture, thus overcomes any disadvantages that may be present with these techniques.

Accordingly, there is provided in a first aspect of the invention nilotinib monohydrochloride monohydrate having an X-ray diffraction pattern comprising major peaks at 5.70, 7.56, 9.82, 15.01, 17.31 and 27.68 ± 0.2 degrees 2-theta. A particularly preferred embodiment provides nilotinib monohydrochloride monohydrate having an X-ray diffraction pattern comprising further peaks at 8.60, 11.39, 12.41, 15.78, 18.64, 19.64, 20.27, 20.65, 21.48, 22.31, 22.84, 24.05, 24.40, 25.46, 25.94 and 29.64 ± 0.2 degrees 2-theta.

In an alternative embodiment according to the first aspect of the invention nilotinib monohydrochloride monohydrate is provided having an X-ray diffraction pattern substantially as shown in Figure 1.

In another alternative embodiment nilotinib monohydrochloride monohydrate is provided having a differential scanning calorimetry (DSC) thermogram with endothermic peaks at

about 95.8°C ± 0.5°C and about 258.8°C ± 0.5°C. Preferably the nilotinib monohydrochloride monohydrate has a differential scanning calorimetry thermogram substantially as shown in Figure 2.

A further alternative embodiment comprises nilotinib monohydrochloride monohydrate having a thermogravimetric analysis (TGA) thermogram substantially as shown in Figure 3.

A second aspect of the invention provides a process for preparing nilotinib monohydrochloride monohydrate according to the first aspect of the invention comprising:

(iv) heating nilotinib monohydrochloride salt in a high boiling point solvent system; and

(v) isolating the resulting nilotinib monohydrochloride monohydrate salt from the solvent system of step (iv).

It is currently believed that the heating of nilotinib monohydrochloride salt in a solvent system provides the new polymorphic form of the present invention. The heating is made possible by the use of a high boiling point solvent system. The nilotinib monohydrochloride salt used in step (iv) may be nilotinib monohydrochloride dihydrate.

In preferred embodiments the high boiling point solvent used in step (iv) has a boiling point of greater than 80°C, most preferably between 80°C and 150°C. In this regard, particularly preferred high boiling point solvents are selected from xylene, toluene and mixtures thereof.

In particularly preferred embodiments the heating in step (iv) is carried out at reflux temperatures, preferably for between about 2-10 hours, most advantageously for between about 3-4 hours.

A preferred embodiment of the second aspect of the present invention provides a process for preparing nilotinib monohydrochloride monohydrate according to the first aspect of the invention comprising:

(i) mixing nilotinib free base in an organic solvent system;

(ii) adding a solution of HCl in an organic solvent to the mixture from step (i) or adding the mixture from step (i) to a solution of HCl in an organic solvent;

(iii) separating the resulting nilotinib monohydrochloride salt from the mixture in step (ii);

(iv) heating the separated salt from step (iii) in a high boiling point solvent system; and

(v) isolating the resulting nilotinib monohydrochloride monohydrate salt from the solvent system of step (iv).

In certain preferred embodiments the organic solvent system from step (i) comprises N,N-dimethylacetamide, acetone, ethanol, n-butanol, N-methyl pyrrolidine, tetrahydrofuran or mixtures thereof. Further solvents that may be utilised comprise methanol, methanol-water, acetonitrile, isopropyl alcohol and dimethyl formamide or mixtures thereof. In one embodiment the organic solvent system from step (i) does not comprise methanol.

Preferably, in step (ii), a solution of HCl in an organic solvent is added to the mixture from step (i).

Preferably the solution of HCl used in step (ii) is prepared by passing HCl gas through an organic solvent. In preferred embodiments the organic solvent used in preparing the solution of HCl used in step (ii) is selected from the group comprising a C_{1-4} alcohol, ethyl acetate, tetrahydrofuran and acetonitrile or mixtures thereof. Most preferably, the C_{1-4} alcohol is one or more of methanol, ethanol, isopropanol and n-butanol.

In certain preferred embodiments an anti-solvent is added to the mixture from step (ii) to aid precipitation of the desired nilotinib monohydrochloride salt, most preferably the solvent/anti-solvent combination is as defined in the Table below:

Organic solvent system	Anti-solvent	HCl source
acetone	-	ethanol HCl
n-butanol	-	ethanol HCl
N,N-dimethylacetamide	ethyl acetate	acetonitrile HCl
n-butanol	-	n-butanol HCl
acetone	-	n-butanol HCl
ethanol	-	n-butanol HCl
N-methyl pyrrolidine (NMP)	water	tetrahydrofuran HCl
ethyl acetate	-	methanol HCl
acetone	-	methanol HCl
tetrahydrofuran	-	methanol HCl

Table

It is currently believed that the nilotinib monohydrochloride salt separated in step (iii) is nilotinib monohydrochloride dihydrate.

In further particularly preferred embodiments the high boiling point solvent used in step (iv) has a boiling point of greater than 80°C, most preferably between 80°C and 150°C. In this regard, particularly preferred high boiling point solvents are selected from xylene and/or toluene.

Preferably the process according to the second aspect of the present invention is carried out without any seeding.

A third aspect of the invention provides nilotinib monohydrochloride monohydrate according to the first aspect of the invention or prepared by a process according to the second aspect of the invention, having a chemical purity as determined by HPLC of greater than 95%, preferably greater than 99%, most preferably greater than 99.5%.

A fourth aspect of the invention provides nilotinib monohydrochloride monohydrate according to the first or third aspects of the invention or prepared by a process according to the second aspect of the invention, having a polymorphic purity as determined by X-ray crystallography of greater than 95%, preferably greater than 99%, most preferably greater than 99.5%.

Preferably the nilotinib monohydrochloride monohydrate according to the first, third or fourth aspects of the invention or prepared by a process according to the second aspect of the invention is suitable for use in medicine, preferably for the treatment of cancer, more preferably for the treatment of chronic myelogenous leukaemia (CML), more preferably for the treatment of adults with chronic phase or accelerated phase Philadelphia chromosome positive chronic myelogenous leukaemia (CML) with resistance or intolerance to prior therapy including imatinib.

A fifth aspect of the invention provides the use of nilotinib monohydrochloride monohydrate according to the first, third or fourth aspects of the invention or prepared by a process according to the second aspect of the invention, for the manufacture of a medicament for the treatment cancer, preferably for the treatment of chronic myelogenous leukaemia (CML), more preferably for the treatment of adults with chronic phase or accelerated phase Philadelphia chromosome positive chronic myelogenous leukaemia (CML) with resistance or intolerance to prior therapy including imatinib.

A sixth aspect of the invention provides a pharmaceutical composition comprising nilotinib monohydrochloride monohydrate according to the first, third or fourth aspects of the invention or prepared by a process according to the second aspect of the invention, and at least one pharmaceutically acceptable excipient. Preferably the pharmaceutical composition is suitable for use in the treatment of cancer, preferably for use in the treatment of chronic myelogenous leukaemia (CML), most preferably for use in the treatment of adults with chronic phase or accelerated phase Philadelphia chromosome positive chronic myelogenous leukaemia (CML) with resistance or intolerance to prior therapy including imatinib.

A seventh aspect of the invention provides a method of treating cancer, comprising administering to a patient in need thereof a therapeutically effective amount of nilotinib monohydrochloride monohydrate according to the first, third or fourth aspects of the invention or prepared by a process according to the second aspect of the invention, or a therapeutically effective amount of a pharmaceutical composition according to the sixth aspect of the invention. Preferably the patient is a mammal, preferably a human. Preferably

the method is for treating chronic myelogenous leukaemia (CML), more preferably for treating adults with chronic phase or accelerated phase Philadelphia chromosome positive chronic myelogenous leukaemia (CML) with resistance or intolerance to prior therapy including imatinib.

Brief description of the drawings

Figure 1 is a representative X-ray powder diffraction pattern of nilotinib monohydrochloride monohydrate according to the invention.

Figure 2 is a representative differential scanning calorimetry thermogram of nilotinib monohydrochloride monohydrate according to the invention.

Figure 3 is a representative thermogravimetry curve of nilotinib monohydrochloride monohydrate according to the invention.

Figure 4 is a comparison of the X-ray powder diffraction patterns of the prior art forms A and B of nilotinib monohydrochloride monohydrate as disclosed in WO 2007/015871.

Detailed description of the invention

The inventors have succeeded in preparing an alternative crystalline form of nilotinib monohydrochloride monohydrate to those disclosed in the prior art. Comparison of Figure 1 and Figure 4 clearly shows the differences between the nilotinib monohydrochloride monohydrate of the present invention and the prior art forms A and B as disclosed in WO 2007/015871. For example the 2-theta range between values 3 and 10 shows 5 prominent peaks in Figure 1 that are not present in the prior art forms A and B.

Alternative crystalline forms are desirable for a number of reasons. Preparing novel salt forms is always desirable, as it widens the repertoire available to the medicinal chemist or the pharmaceutical formulator. Cancer medication is traditionally very expensive. Any means by which the cost of such medication can be reduced is particularly advantageous to individuals and to health care providers. Providing alternative but equally efficacious salts

and polymorphs thereof that may be formulated into significantly cheaper drug products is a particularly advantageous and desirable goal. A further advantage may be that the novel alternative crystalline form according to the invention may have improved dissolution, bioavailability and/or processability over the prior art forms. Preparing such alternative salts or salt forms is not necessarily routine. There are a huge number of possible alternative salts, hydrates, polymorphs and pseudopolymorphs for any given drug, all, none or any proportion of which may be a suitable candidate. The present inventors have found that despite utilising similar solvents as disclosed in the prior art for preparing nilotinib monohydrochloride monohydrate, an alternative polymorph may be prepared.

Accordingly, there is provided in a first aspect of the invention nilotinib monohydrochloride monohydrate having an X-ray diffraction pattern comprising major peaks at 5.70, 7.56, 9.82, 15.01, 17.31 and 27.68 ± 0.2 degrees 2-theta. A particularly preferred embodiment provides nilotinib monohydrochloride monohydrate having an X-ray diffraction pattern comprising further peaks at 8.60, 11.39, 12.41, 15.78, 18.64, 19.64, 20.27, 20.65, 21.48, 22.31, 22.84, 24.05, 24.40, 25.46, 25.94 and 29.64 ± 0.2 degrees 2-theta.

In an alternative embodiment nilotinib monohydrochloride monohydrate is provided having an X-ray diffraction pattern substantially as shown in Figure 1.

In yet another alternative embodiment nilotinib monohydrochloride monohydrate is provided having a differential scanning calorimetry thermogram substantially as shown in Figure 2.

A further alternative embodiment comprises nilotinib monohydrochloride monohydrate having a thermogravimetric analysis thermogram substantially as shown in Figure 3.

A second aspect according to the invention provides a process for preparing nilotinib monohydrochloride monohydrate according to the first aspect of the invention comprising:

(i) mixing nilotinib free base in an organic solvent system;

(ii) adding a solution of HCl in an organic solvent to the mixture from step (i);

(iii) separating the resulting nilotinib monohydrochloride salt from the mixture in step (ii);

(iv) heating the separated salt from step (iii) in a high boiling point solvent system; and

(v) isolating the resulting nilotinib monohydrochloride monohydrate salt from the solvent system of step (iv).

For the purposes of the invention, the term "mixing" is meant to include any addition of nilotinib free base to an organic solvent system, this may include dissolving or suspending all or any proportion of the nilotinib free base in the solvent system. In certain embodiments the addition of the nilotinib free base to the solvent system may be a suspension or the free base may be dissolved completely or partially in the solvent system. In certain preferred embodiments the organic solvent system comprises N,N-dimethylacetamide, acetone, ethanol, n-butanol, N-methyl pyrrolidine, tetrahydrofuran or mixtures thereof. Further solvents that may be utilised comprise methanol, methanol-water, acetonitrile, isopropyl alcohol and dimethyl formamide or mixtures thereof. In one embodiment the organic solvent system from step (i) does not comprise methanol.

The inventors have found that addition of a solution of HCl in an organic solvent to the reaction mixture obtained in step (i), or vice versa, results in a nilotinib monohydrochloride salt. Preferably the solution of HCl used in step (ii) is prepared by passing HCl gas through the organic solvent. In preferred embodiments the organic solvent used in preparing the solution of HCl used in step (ii) is selected from the group comprising a C_{1-4} alcohol, ethyl acetate, acetonitrile, tetrahydrofuran or mixtures thereof. Most preferably, the C_{1-4} alcohol is one or more of methanol, ethanol, isopropanol and n-butanol.

The resultant nilotinib monohydrochloride salt in step (iii) is separated from the reaction mixture preferably by precipitation. In certain preferred embodiments an anti-solvent is added to the mixture from step (ii) in order to aid precipitation of the resultant nilotinib monohydrochloride salt. An anti-solvent can be added to a solvent system in order to reduce the solubility of a solute, in this case the nilotinib monohydrochloride salt, causing the solute to precipitate out of solution.

The inventors have found that the solvent/anti-solvent combinations shown in Table 1 are particularly advantageous.

Organic solvent system	Anti-solvent	HCl source	Preferred stirring time (h)
acetone	-	ethanol HCl	5
n-butanol	-	ethanol HCl	5
N,N-dimethylacetamide	ethyl acetate	acetonitrile HCl	48
n-butanol	-	n-butanol HCl	5
acetone	-	n-butanol HCl	5
ethanol	-	n-butanol HCl	5
N-methyl pyrrolidine (NMP)	water	tetrahydrofuran HCl	24
ethyl acetate	-	methanol HCl	5
acetone	-	methanol HCl	5
tetrahydrofuran	-	methanol HCl	5

Table 1

Table 1 also shows approximate advantageous mixing times. Of course the skilled person will realise, these times are not limiting and may be varied within the scope of the invention. Further, it is within the skillset of one of ordinary skill in the art to determine suitable amounts of solvent to be used, as well as suitable reaction temperatures.

In certain embodiments the reaction mixture in step (ii) is stirred until the precipitate forms. The precipitate may form spontaneously or the reaction mixture may be cooled to facilitate the formation of the desired precipitate. The inventors have found that stirring the reaction mixture to form the precipitate is particularly advantageous. In this regard the stirring times shown in Table 1 are particularly advantageous.

In certain embodiments the formation of the desired precipitate may cause the reaction mixture to become increasingly viscous. In these embodiments additional solvent may be added to loosen the mixture. Most preferably the same solvent system utilised in step (i) is added to loosen the mixture. It will be apparent to the skilled person that in those embodiments where an anti-solvent is utilised, the addition of solvent may cause the nilotinib monohydrochloride salt to redissolve. In such situations the skilled person would realise that additional anti-solvent may be added to cause the desired nilotinib monohydrochloride salt to precipitate from the solution.

It is currently believed that the nilotinib monohydrochloride salt separated in step (iii) is nilotinib monohydrochloride dihydrate.

The separated solid from step (iii) is then heated in an organic solvent system comprised of high boiling point solvent(s). In particularly preferred embodiments the high boiling point solvent(s) has a temperature greater than 80°C, most advantageously between 80°C and 150°C. The inventors have found a solvent system comprising xylene and/or toluene to be a particularly advantageous high boiling point solvent system. In particularly preferred embodiments the heating in step (iv) is carried out at reflux temperatures, preferably for between about 2-10 hours, most advantageously for between about 3-4 hours. Of course the skilled person will realise that the separated solid from step (iii) may be in the form of a wet cake or may be dried by any suitable means for example by vacuum drying.

The desired nilotinib monohydrochloride monohydrate salt may then be obtained in step (v) by any of a number of suitable means. Most advantageously the heated mixture is preferably allowed to cool to obtain the desired nilotinib monohydrochloride monohydrate salt. The salt may then be further isolated by filtration and in particularly preferred embodiments is further dried.

Most preferably the filtered nilotinib monohydrochloride monohydrate according to the invention is dried under conditions of reduced pressure. The inventors have found that drying under vacuum or near vacuum until a constant weight is achieved is particularly preferred. Accordingly, in particularly advantageous embodiments the filtered nilotinib monohydrochloride monohydrate salt is dried in a vacuum oven, preferably in conditions that do not cause dissociation or degradation of the nilotinib monohydrochloride monohydrate salt. The inventors have found drying between about 55-65°C, most preferably between about 60-65°C, to be particularly advantageous. Further preferred embodiments provide drying in a vacuum oven at between about 500-600 mmHg pressure and further embodiments still provide drying for between about 5-20 hours, most preferably for about 10-15 hours.

A third aspect of the invention provides nilotinib monohydrochloride monohydrate according to the first aspect of the invention or prepared by a process according to the

second aspect of the invention, having a chemical purity as determined by HPLC of greater than 95%, preferably greater than 99%, most preferably greater than 99.5%.

A fourth aspect of the invention provides nilotinib monohydrochloride monohydrate according to the first or third aspects of the invention or prepared by a process according to the second aspect of the invention, having a polymorphic purity as determined by X-ray crystallography of greater than 95%, preferably greater than 99%, most preferably greater than 99.5%.

In a sixth aspect a pharmaceutical composition is provided comprising a therapeutically effective amount of nilotinib monohydrochloride monohydrate according to the first, third or fourth aspects or prepared by a process according to the second aspect of the present invention, and at least one pharmaceutically acceptable excipient. The pharmaceutical composition is preferably suitable for use in the treatment of cancer, preferably for use in the treatment of chronic myelogenous leukaemia (CML), most preferably for use in the treatment of adults with chronic phase or accelerated phase Philadelphia chromosome positive chronic myelogenous leukaemia (CML) with resistance or intolerance to prior therapy including imatinib.

Examples

The following non-limiting examples illustrate specific embodiments of the present invention. They are not intended to limit the scope of the present invention in any way.

Example 1

Nilotinib free base (2 g, 3.76 mmol) was completely dissolved or suspended in acetone (30 ml, 15 volumes). Hydrogen chloride gas in ethanol (3.76 mmol) at 24-30°C was added and the reaction mixture stirred for 5 hours until a precipitate formed. The precipitated solid was then filtered through a Buchner funnel and washed with acetone. The wet solid was transferred to another flask and refluxed with xylene (40 ml, 20 volumes) for 3-4 hours. After cooling to room temperature, the precipitated solid was filtered through a Buchner funnel, dried for 10-15 minutes and subjected to drying in a vacuum oven at 60-65°C for 15 hours at approximately 600 mmHg pressure to yield a light yellow coloured solid. The

dried solid was subjected to XRPD, KF, HCl content and chloride content analyses, confirming that the obtained solid was nilotinib monohydrochloride monohydrate according to the invention.

Yield: 1.06 g (58%)

HPLC Purity: 98.72%

Polymorphic Purity: XRPD confirmed the absence of other polymorphic forms.

Example	Reaction solvent (volume [ml])	Anti-solvent (volume [ml])	HCl source	Stirring time (h)
1	acetone (15)	-	ethanol HCl	5
2	n-butanol (15)	-	ethanol HCl	5
3	N,N-dimethylacetamide (15)	ethyl acetate (25)	acetonitrile HCl	48
4	n-butanol (15)	-	n-butanol HCl	5
5	acetone (15)	-	n-butanol HCl	5
6	ethanol (15)	-	n-butanol HCl	5
7	N-methyl pyrrolidine (NMP) (15)	water (8)	tetrahydrofuran HCl	24
8	ethyl acetate (20)	-	methanol HCl	5
9	acetone (20)	-	methanol HCl	5
10	tetrahydrofuran (20)	-	methanol HCl	5

Table 2

The same procedure was followed using the solvent system, anti-solvent where indicated, HCl source and stirring time as shown for examples 2-10 in Table 2. The reaction solvent and anti-solvent amounts given in Table 2 are relative to 1 gram of nilotinib free base.

The HPLC purity of nilotinib monohydrochloride monohydrate prepared according to examples 2-10 was >98.5%. The nilotinib monohydrochloride monohydrate was also polymorphically pure; XRPDs confirmed the absence of other polymorphic forms.

The solids obtained from each example were all subjected to XRPD analysis using a Bruker D8 Advance instrument (using as radiation source copper radiation with a wavelength of 1.54 Å); DSC analysis using a Perkin Elmer instrument (heating rate 25-300°C at 10°C/min, open or closed crucible, closed aluminium pan with pinhole); TGA analysis using a Perkin Elmer instrument (heating rate 25-300°C at 10°C/min, open or closed

crucible, open ceramic pan); KF analysis; HCl content analysis; and chloride content analysis; confirming they were nilotinib monohydrochloride monohydrate according to the invention.

It will be understood that the present invention has been described above by way of example only. The examples are not intended to limit the scope of the invention. Various modifications and embodiments can be made without departing from the scope and spirit of the invention, which is defined by the following claims only.

Claims

1. Nilotinib monohydrochloride monohydrate having an X-ray diffraction pattern comprising peaks at 5.70, 7.56, 9.82, 15.01, 17.31 and 27.68 ± 0.2 degrees 2-theta.

2. Nilotinib monohydrochloride monohydrate according to claim 1, having an X-ray diffraction pattern comprising further peaks at 8.60, 11.39, 12.41, 15.78, 18.64, 19.64, 20.27, 20.65, 21.48, 22.31, 22.84, 24.05, 24.40, 25.46, 25.94 and 29.64 ± 0.2 degrees 2-theta.

3. Nilotinib monohydrochloride monohydrate according to claim 1 or 2, having an X-ray diffraction pattern substantially as shown in Figure 1.

4. Nilotinib monohydrochloride monohydrate according to any preceding claim, having a differential scanning calorimetry thermogram with endothermic peaks at about 95.8°C ± 0.5°C and about 258.8°C ± 0.5°C.

5. Nilotinib monohydrochloride monohydrate according to claim 4, having a differential scanning calorimetry thermogram substantially as shown in Figure 2.

6. Nilotinib monohydrochloride monohydrate according to any preceding claim, having a thermogravimetric analysis thermogram substantially as shown in Figure 3.

7. A process for preparing nilotinib monohydrochloride monohydrate according to any preceding claim, comprising:

(iv) heating nilotinib monohydrochloride salt in a high boiling point solvent system; and

(v) isolating the resulting nilotinib monohydrochloride monohydrate salt from the solvent system of step (iv).

8. A process for preparing nilotinib monohydrochloride monohydrate according to any preceding claim, comprising:

(i) mixing nilotinib free base in an organic solvent system;

(ii) adding a solution of HCl in an organic solvent to the mixture from step (i) or adding the mixture from step (i) to a solution of HCl in an organic solvent;

(iii) separating the resulting nilotinib monohydrochloride salt from the mixture in step (ii);

(iv) heating the separated salt from step (iii) in a high boiling point solvent system; and

(v) isolating the resulting nilotinib monohydrochloride monohydrate salt from the solvent system of step (iv).

9. A process according to claim 8, wherein the organic solvent system in step (i) comprises N,N-dimethylacetamide, acetone, ethanol, n-butanol, N-methyl pyrrolidine, tetrahydrofuran or mixtures thereof.

10. A process according to claim 8 or 9, wherein the solution of HCl used in step (ii) is prepared by passing HCl gas through an organic solvent.

11. A process according to claim 10, wherein the solvent used in preparing the organic solution of HCl used in step (ii) is selected from the group comprising a C_{1-4} alcohol, ethyl acetate, tetrahydrofuran and acetonitrile or mixtures thereof.

12. A process according to claim 11, wherein the C_{1-4} alcohol is one or more of methanol, ethanol, isopropanol and n-butanol.

13. A process according to any one of claims 8 to 12, wherein an anti-solvent is added to the mixture from step (ii) in order to help precipitate the desired nilotinib monohydrochloride salt.

14. A process according to claim 13, wherein the solvent/anti-solvent combination is as defined in the Table below:

Organic solvent system	Anti-solvent	HCl source
acetone	-	ethanol HCl
n-butanol	-	ethanol HCl
N,N-dimethylacetamide	ethyl acetate	acetonitrile HCl
n-butanol	-	n-butanol HCl
acetone	-	n-butanol HCl
ethanol	-	n-butanol HCl
N-methyl pyrrolidine (NMP)	water	tetrahydrofuran HCl
ethyl acetate	-	methanol HCl
acetone	-	methanol HCl
tetrahydrofuran	-	methanol HCl

Table

15. A process according to any one of claims 7 to 14, wherein the high boiling point solvent used in step (iv) has a boiling point of greater than 80°C.

16. A process according to claim 15, wherein the high boiling point solvent used in step (iv) has a boiling point of between 80°C and 150°C.

17. A process according to claim 16, wherein the high boiling point solvent is selected from xylene and/or toluene.

18. Nilotinib monohydrochloride monohydrate according to any one of claims 1 to 6, or prepared by a process according to any one of claims 7 to 17, having a chemical purity as determined by HPLC of:

(i) greater than 95%; and/or

(ii) greater than 99%; and/or

(iii) greater than 99.5%.

19. Nilotinib monohydrochloride monohydrate according to any one of claims 1 to 6 or 18, or prepared by a process according to any one of claims 7 to 17, having a polymorphic purity as determined by X-ray crystallography of:

(i) greater than 95%; and/or

(ii) greater than 99%; and/or

(iii) greater than 99.5%.

20. Nilotinib monohydrochloride monohydrate according to any one of claims 1 to 6 or 18 or 19, or prepared by a process according to any one of claims 7 to 17, for use in medicine.

21. Nilotinib monohydrochloride monohydrate according claim 20, for the treatment of:

(i) cancer; and/or

(ii) chronic myelogenous leukaemia (CML); and/or

(iii) adults with chronic phase or accelerated phase Philadelphia chromosome positive chronic myelogenous leukaemia (CML) with resistance or intolerance to prior therapy including imatinib.

22. Use of nilotinib monohydrochloride monohydrate according to any one of claims 1 to 6 or 18 to 21, or prepared by a process according to any one of claims 7 to 17, for the manufacture of a medicament for treating cancer.

23. The use according to claim 22, wherein the medicament is for the treatment of:

(i) chronic myelogenous leukaemia (CML); and/or

(ii) adults with chronic phase or accelerated phase Philadelphia chromosome positive chronic myelogenous leukaemia (CML) with resistance or intolerance to prior therapy including imatinib.

24. A pharmaceutical composition comprising nilotinib monohydrochloride monohydrate according to any one of claims 1 to 6 or 18 to 21, or prepared by a process according to any one of claims 7 to 17, and at least one pharmaceutically acceptable excipient.

25. A pharmaceutical composition according to claim 24, for the treatment of:

(i) cancer; and/or

(ii) chronic myelogenous leukaemia (CML); and/or

(iii) adults with chronic phase or accelerated phase Philadelphia chromosome positive chronic myelogenous leukaemia (CML) with resistance or intolerance to prior therapy including imatinib.

26. A method of treating cancer, comprising administering to a patient in need thereof a therapeutically effective amount of nilotinib monohydrochloride monohydrate according to any one of claims 1 to 6 or 18 to 21, or prepared by a process according to any one of claims 7 to 17, or a therapeutically effective amount of a pharmaceutical composition according to claim 24 or 25.

27. A method according to claim 26, wherein the method is for treating:

(i) chronic myelogenous leukaemia (CML); and/or

(ii) adults with chronic phase or accelerated phase Philadelphia chromosome positive chronic myelogenous leukaemia (CML) with resistance or intolerance to prior therapy including imatinib.

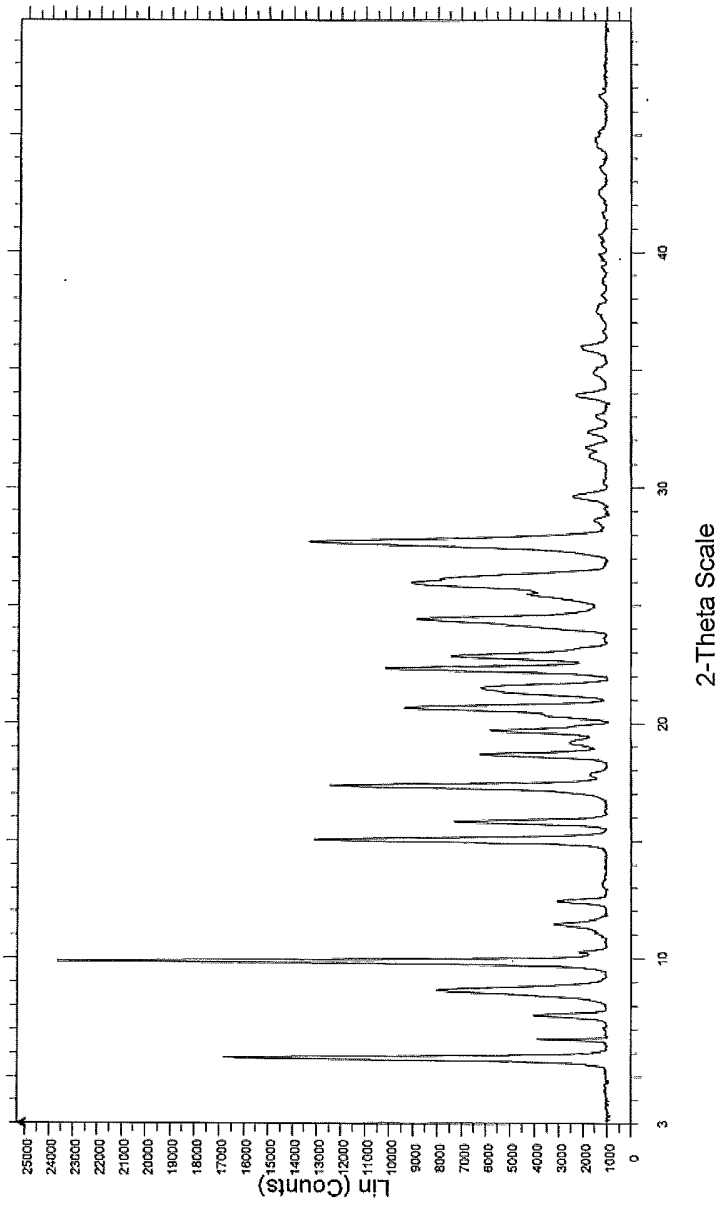

Lin (Counts)
25000
24000
23000
22000
21000
20000
19000
18000
17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
3
10
20
30
40
2-Theta Scale

Figure 1

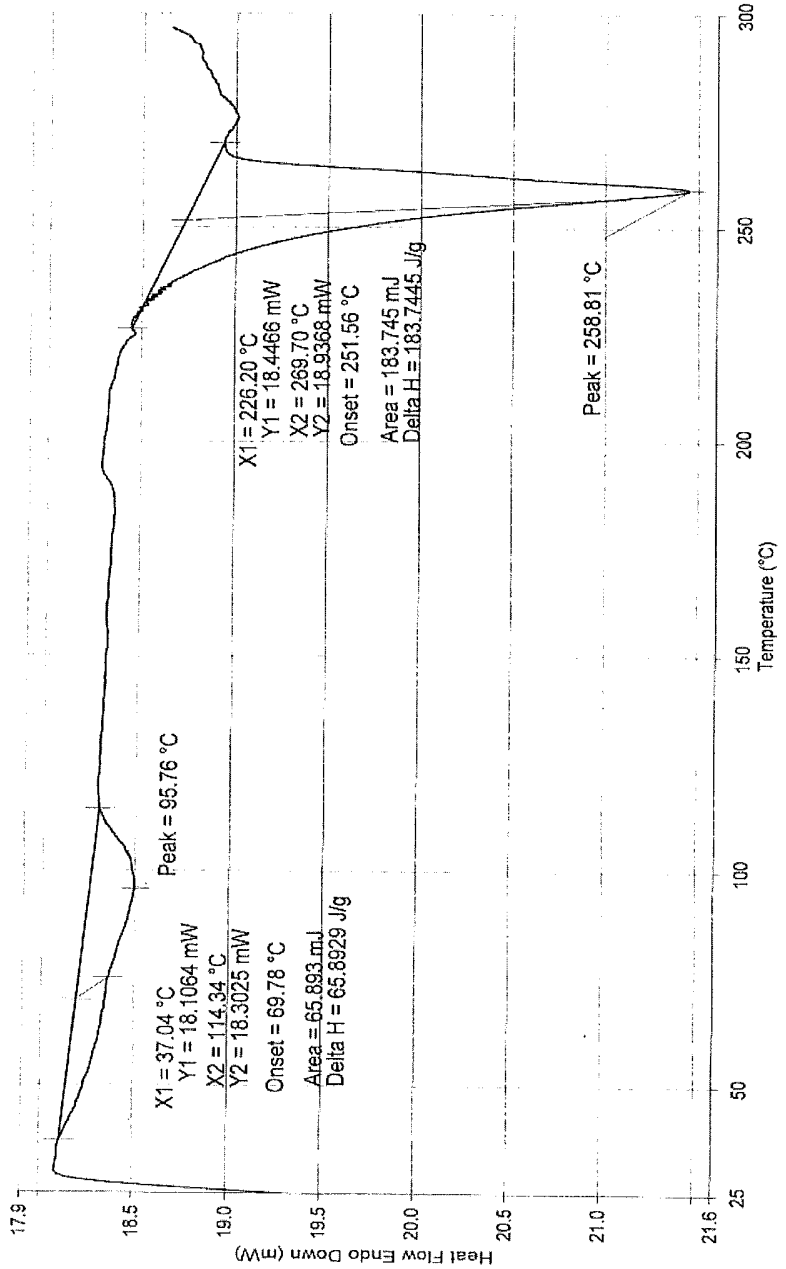

Heat Flow Endo Down (mW)
Temperature (°C)
X1 = 37.04 °C
Y1 = 18.1064 mW
Peak = 95.76 °C
X2 = 114.34 °C
Y2 = 18.3025 mW
Onset = 69.78 °C
Area = 65.893 mJ
Delta H = 65.8929 J/g
X1 = 226.20 °C
Y1 = 18.4466 mW
X2 = 269.70 °C
Y2 = 18.9368 mW
Onset = 251.56 °C
Area = 183.745 mJ
Delta H = 183.7445 J/g
Peak = 258.81 °C

Figure 2

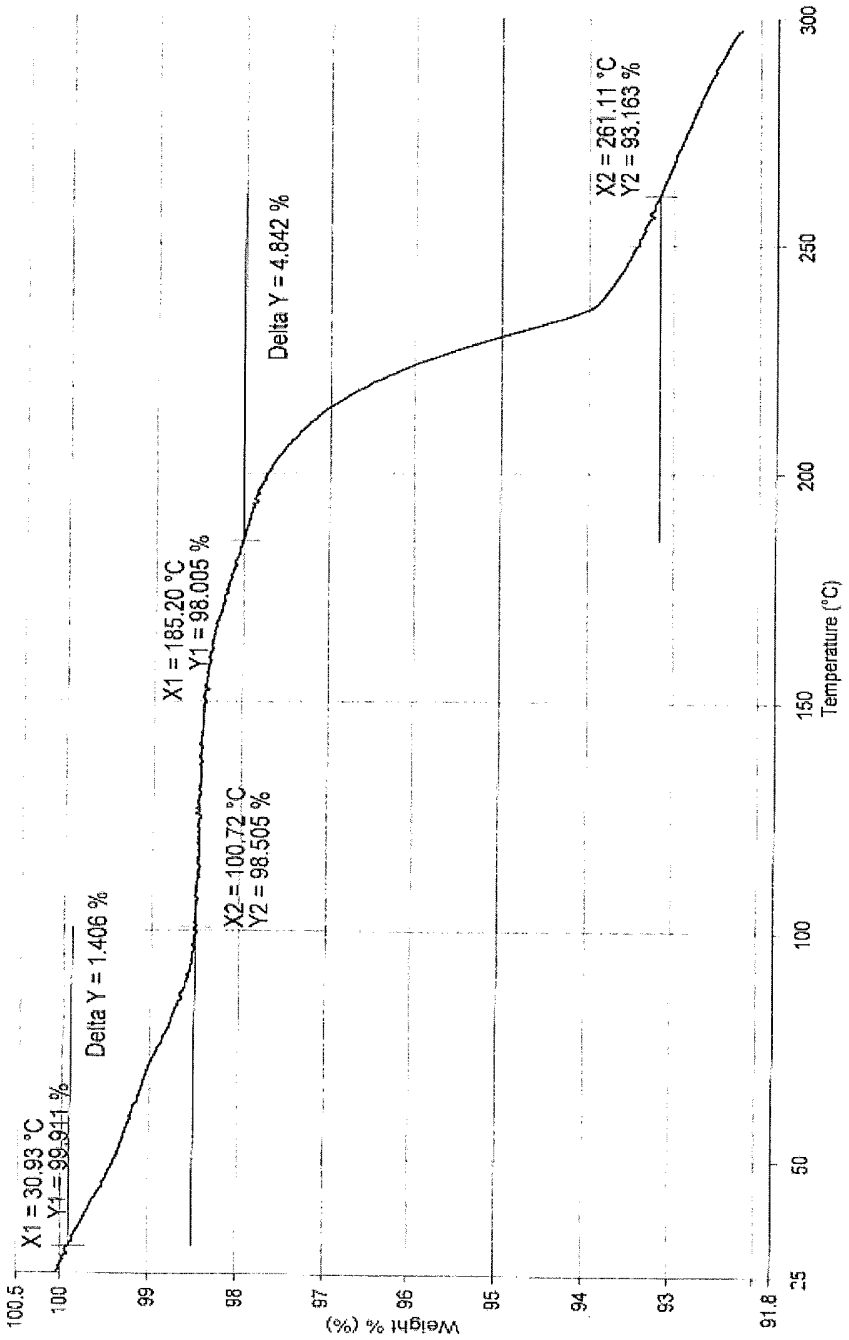

X1 = 30.93 °C
Y1 = 99.911 %
Delta Y = 1.406 %
X1 = 185.20 °C
Y1 = 98.005 %
X2 = 100.72 °C
Y2 = 98.505 %
Delta Y = 4.842 %
X2 = 261.11 °C
Y2 = 93.163 %
Weight % (%)
Temperature (°C)
100.5
100
99
98
97
96
95
94
93
91.8
25
50
100
150
200
250
300

Figure 3

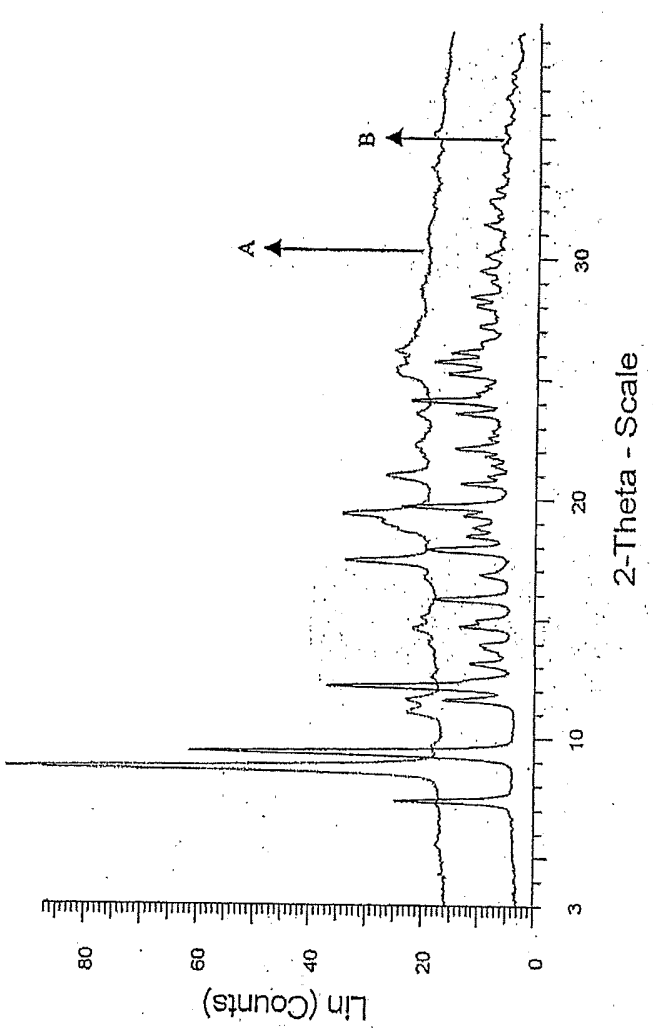


Figure 4

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2011/050822

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D401/14 A61K31/506 A61P35/02
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 A61K A61P

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 practical, search terms used)
EPO-Internal, WPI Data, BIOSIS, EMBASE, 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,P	WO 2010/054056 A2 (TEVA PHARMA [IL]; TEVA PHARMA [US]; STERIMBAUM GRETA [IL]; LEVI SIGALI) 14 May 2010 (2010-05-14) the whole document in particular form T17, claims 1-16, figures 19-20, paragraphs 38-43, 175-202 and examples 23-32	1-27
Y	WO 2007/015870 A2 (NOVARTIS AG [CH]; NOVARTIS PHARMA GMBH [AT]; MANLEY PAUL W [CH]; SHIEH) 8 February 2007 (2007-02-08) the whole document in particular claims 11-14, 19-22, 35-38 and 47-49, figures 6, 8, 15 and 20, paragraphs 44-46, 49-53, examples 2-5, 16, 21, 25-29 and paragraphs 107-113.	1-27

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"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

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"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.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 April 2011	28/04/2011

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Papathoma, Sofia

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2011/050822

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Y	CAIRA M R: "CRYSTALLINE POLYMORPHISM OF ORGANIC COMPOUNDS", TOPICS IN CURRENT CHEMISTRY, SPRINGER, BERLIN, DE, vol. 198, 1 January 1998 (1998-01-01), pages 163-208, XP001156954, ISSN: 0340-1022, DOI: DOI:10.1007/3-540-69178-2_5 ISBN: 978-3-540-36760-4 the whole document in particular pages 164-166.	1-27

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2011/050822

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		PE 02142007 A1	02-04-2007
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