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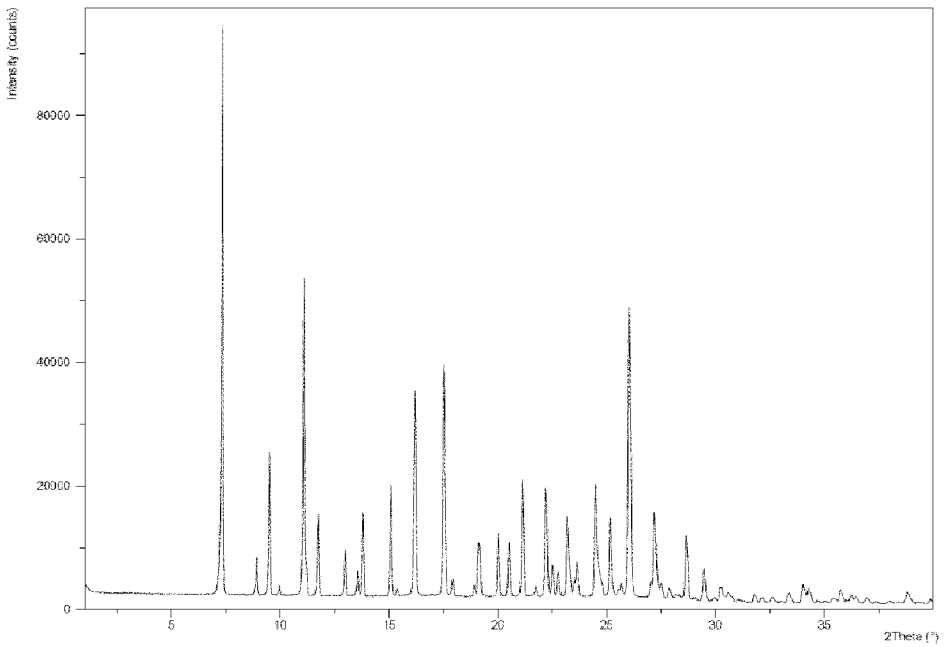
(54) Title: PHARMACEUTICAL COMPOSITIONS OF APREMILAST

FIG. 1



(57) Abstract: A pharmaceutical composition comprising Apremilast or pharmaceutically acceptable salts thereof, at least one filler and at least one disintegrant, wherein the active ingredient has a particle size volume distribution with D90 between 10 and 50 um. A process for manufacturing a pharmaceutical composition according to any one of the preceding claims, comprising the following steps: a) preparing a pre-mixture comprising Apremilast or a pharmaceutically acceptable salt thereof, a first part of the filler, disintegrant, and glidant; b) mixing the pre-mixture obtained in step (a) with the remaining part of the filler; c) adding the lubricant to the mixture obtained in step (b); d) compressing the mixture obtained in step (c) to form tablets; and e) optionally, coating the tablets obtained in step (d). Said composition for use in the treatment of psoriasis, psoriatic arthritis or oral ulcers associated with Behcet's disease.

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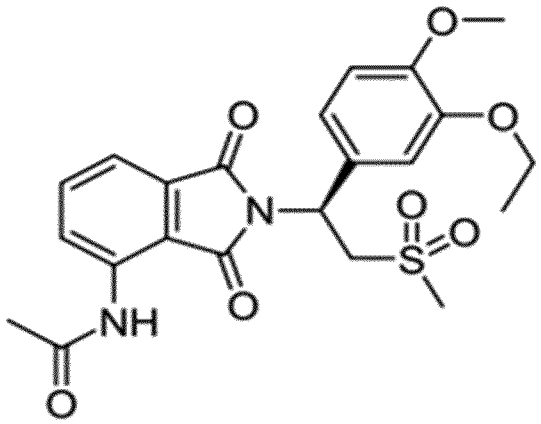
Pharmaceutical compositions of Apremilast

Field of the invention

The present invention relates to pharmaceutical compositions comprising Apremilast or a pharmaceutically acceptable salt or solvate thereof and to processes for the manufacture of said pharmaceutical compositions.

Background of the invention

Apremilast is a PDE4 inhibitor chemically known as N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-1,3-dioxoisoindol-4-yl]acetamide. Its empirical formula is $C_{22}H_{24}N_2O_7S$ and the molecular weight is 460.5. The chemical structure is shown below:



It is indicated for the treatment of adult patients with moderate to severe plaque psoriasis, active psoriatic arthritis or oral ulcers associated with Behçet's disease and available in the market as oral tablets under the trade name OTEZLA® in 10 mg, 20 mg and 30 mg strengths.

WO2007079182 discloses tablets, capsules, ampoules, ointment, paste and spray of Apremilast and processes for manufacturing Apremilast tablets by wet granulation.

WO2013101810 discloses Apremilast coated tablets. WO2019073331 discloses Apremilast disintegrant free tablets.

However, there are still lacking pharmaceutical compositions that allow for easy manufacture of oral solid dosage forms and, in the best of cases, are suitable for all kind of

patients in need of Apremilast. There is also a need for a reliable process that results in robust tablets that do not break easily and have an excellent dissolution behaviour so to allow for its application in psoriasis, psoriatic arthritis or Behçet's disease treatments.

Summary of the invention

The present invention in one aspect refers to a pharmaceutical composition comprising Apremilast, at least one filler and at least one disintegrant, wherein the active ingredient has a particle size volume distribution with D90 between 10 and 50 µm when measured by laser diffraction analysis.

In a preferred aspect, the pharmaceutical composition is lactose-free.

In another aspect, this invention refers to oral solid dosage forms obtained from said pharmaceutical composition.

In another aspect, this invention refers to a process of manufacturing the pharmaceutical composition.

In another aspect, this invention refers to the use of said pharmaceutical composition in treatments comprising, inter alia, psoriasis, psoriatic arthritis or Behçet's disease.

Brief description of the drawings

Figure 1. shows the PXRD of the crystalline anisaldehyde solvate of Apremilast

Figure 2. shows the PXRD of the crystalline 3-phenylpropanaldehyde solvate of Apremilast

Figure 3. shows the PXRD of the crystalline 3-methyl-2-cyclohexenone solvate of Apremilast

Figure 4. shows the PXRD of the crystalline 6-methyl-5-hepten-2-one solvate of Apremilast

Description of the invention

The present invention provides pharmaceutical compositions of Apremilast as well as a manufacturing process thereof.

The pharmaceutical compositions of the present invention comprise Apremilast or a pharmaceutically acceptable salt or solvate thereof, at least one filler and at least one disintegrant, wherein the active ingredient has a particle size volume distribution with D90 between 10 and 50 µm when measured by laser diffraction analysis. Optionally, the pharmaceutical composition may also comprise a glidant, a lubricant, or any other pharmaceutically acceptable additives.

The pharmaceutical composition may be used to manufacture oral solid dosage forms, such as tablets. The obtained tablets may be further coated with Opadry®-type coatings and then packaged in standard pharmaceutical packaging like bottles or blisters.

The manufacture of the pharmaceutical compositions comprises blending Apremilast or a pharmaceutically acceptable salt or solvate thereof with at least one filler and at least one disintegrant and then using direct compression to obtain oral solid dosage forms. Hence, the pharmaceutical compositions of the invention allow for an easy and straightforward manufacturing process using the minimum of resources, while achieving excellent dissolution behaviour for therapeutic applications and resulting in oral solid dosage forms that are durable due to a very low friability.

In a preferred embodiment, the pharmaceutical composition of the first aspect may comprise between 7 and 15 % by weight of Apremilast or a pharmaceutically acceptable salt or solvate thereof, in respect of the total weight of the pharmaceutical composition. In a more preferred embodiment, the pharmaceutical composition of the first aspect comprises between 8.5 and 12.5 % by weight of Apremilast or pharmaceutically acceptable salts or solvate thereof, in respect of the total weight of the pharmaceutical composition. The amount of Apremilast is used in such quantities to obtain oral dosage forms that may contain 10 mg, 20 mg or 30 mg of Apremilast.

Apremilast may be used in any solid form. For example, amorphous or crystalline Apremilast may be employed in the composition. Preferably, crystalline Apremilast is used. Any solid crystalline form described in WO 2009120167 can be used here. More preferably, form B is used, wherein form B of Apremilast is characterized by XRPD peaks located at positions: 10.1º, 12.4º, 13.5º, 15.7º, 16.3º, 18.1º, 20.7º, 22.5º, 24.7º, 26.2º, 26.9º, 29.1º ± 0.2º 2-theta.

Other crystalline forms that can be used are the crystalline anisaldehyde solvate of Apremilast, the crystalline 3-phenylpropanaldehyde solvate of Apremilast, the crystalline 3-methyl-2-cyclohexenone solvate of Apremilast or the crystalline 6-methyl-5-hepten-2-one solvate of Apremilast.

The crystalline anisaldehyde solvate of Apremilast is characterised by an X-ray powder diffractogram comprising at least the peaks at diffraction 2-theta angle 7.40, 11.15 and 26.10° 2θ ± 0.2° 2θ. Preferably, the X-ray powder diffractogram comprises at least the peaks at diffraction 2-theta angle 7.40, 11.15, 26.10, 17.59 and 16.25° 2θ ± 0.2° 2θ. More preferably, the X-ray powder diffractogram comprises at least the peaks at diffraction 2-theta angles 7.40, 8.99, 9.58, 10.02, 11.15, 11.81, 13.05, 13.62, 13.87, 15.15, 15.44, 16.25,

17.06, 17.59, 18.00, 19.00, 19.20, 20.09, 20.58, 21.21, 21.82, 22.28, 22.58, 22.86, 23.25, 23.72, 24.55, 24.83, 25.23, 25.40, 25.60, 25.75, 26.10, 27.09, 27.28, 27.59, 27.96, 28.24, 28.45, 28.72, 29.09, 29.53, 30.04, 30.29, 30.65, 30.84, 31.10, 31.40, 31.85, 32.27, 32.65, 33.06, 33.39, 33.51, 34.09, 34.34, 34.74, 35.45, 35.82, 36.29, 36.54, 37.02, 37.42, 38.04, 38.49 and 38.86° 2θ ± 0.2° 2θ, also shown in figure 1.

The crystalline 3-phenylpropanaldehyde solvate of Apremilast is characterised by an X-ray powder diffractogram comprising at least the peaks at diffraction 2-theta angle 7.31, 11.08, 25.96 and 11.75° 2θ ±0.2° 2θ. Preferably, X-ray powder diffractogram comprises at least the peaks at diffraction 2-theta angle 7.31, 11.08, 25.96, 11.75, 16.14, 17.47 and 25.08° 2θ ± 0.2° 2θ. More preferably, the X-ray powder diffractogram comprises at least the peaks at diffraction 2-theta angles 7.31, 8.91, 9.49, 9.93, 11.08, 11.75, 12.96, 13.55, 13.76, 15.04, 15.33, 16.14, 17.47, 17.90, 18.92, 19.10, 19.96, 20.44, 21.10, 21.74, 22.14, 22.45, 22.78, 23.12, 23.65, 24.41, 24.73, 25.08, 25.52, 25.64, 25.96, 26.96, 27.13, 27.51, 27.84, 28.09, 28.35, 28.57, 29.36, 30.11, 30.37, 30.53, 30.74, 30.94, 31.21, 31.69, 32.03, 32.48, 32.96, 33.24, 33.44, 33.94, 34.16, 34.55, 35.32, 35.64, 35.77, 36.14, 36.42, 36.87, 37.23, 37.85, 38.66 and 39.74° 2θ ± 0.2° 2θ, shown in figure 2.

The crystalline 3-methyl-2-cyclohexenone solvate of Apremilast is characterised by an X-ray powder diffractogram comprising at least the peaks at diffraction 2-theta angle 7.41, 11.17, 26.16 and 17.61° 2θ ± 0.2° 2θ. Preferably, the X-ray powder diffractogram comprises at least the peaks at diffraction 2-theta angle 7.41, 11.17, 26.16, 17.61, 22.33, 24.60, 21.21, 16.29, 25.29 and 23.30° 2θ ± 0.2° 2θ. More preferably, the X-ray powder diffractogram comprises at least the peaks at diffraction 2-theta angles 7.41, 9.00, 9.60, 10.04, 11.16, 11.82, 13.07, 13.63, 13.90, 15.19, 15.47, 16.29, 17.61, 18.02, 19.02, 19.24, 20.13, 20.62, 21.24, 21.52, 21.84, 22.33, 22.62, 22.88, 23.30, 23.73, 24.60, 24.85, 25.29, 25.63, 26.16, 27.15, 27.34, 27.61, 28.01, 28.30, 28.45, 28.77, 29.23, 29.60, 30.04, 30.45, 30.70, 30.86, 31.38, 31.91, 32.32, 32.68, 33.11, 33.50, 34.15, 34.42, 34.82, 35.17, 35.53, 35.87, 36.15, 36.36, 36.59, 37.11, 37.51, 38.13, 38.51, 38.96 and 39.55° 2θ ± 0.2° 2θ, shown in figure 3.

The crystalline 6-methyl-5-hepten-2-one solvate of Apremilast is characterised by an X-ray powder diffractogram comprising at least the peaks at diffraction 2-theta angle 11.25, 7.40, 26.10, 17.61and 17.80° 2θ ± 0.2° 2θ. Preferably, the X-ray powder diffractogram comprising at least the peaks at diffraction 2-theta angle 11.25, 7.40, 26.10, 11.99, 16.27, 17.61 and 17.80° 2θ ± 0.2° 2θ. More preferably, the X-ray powder diffractogram comprises at least the

peaks at diffraction 2-theta angles 7.40, 9.04, 9.56, 10.02, 11.25, 11.99, 13.13, 13.85, 15.12, 16.27, 16.46, 17.61, 17.80, 18.09, 19.15, 20.08, 20.55, 21.19, 21.35, 22.09, 22.27, 22.64, 23.12, 23.28, 23.58, 24.07, 24.62, 25.03, 25.22, 25.92, 26.10, 27.32, 27.68, 27.97, 28.21, 28.80, 29.50, 30.28, 30.52, 30.92, 31.17, 31.91, 32.43, 32.78, 33.49, 33.98, 34.28, 34.55, 34.69, 35.38, 35.60, 35.95, 36.06, 36.41, 36.81, 37.27, 38.08, 38.80 and 39.28° 2θ ± 0.2° 2θ, shown in figure 4.

The aforementioned crystalline solvates of Apremilast may be prepared using a process which comprises the steps of:

1) dissolving or suspending Apremilast in a solvent selected from an organic solvent and/or water,

2) adding, as a cosolvent, the solvent for forming the solvate selected from the group consisting of anisaldehyde, 3-phenylpropanaldehyde, 3-methyl-2-cyclohexenone or 6-methyl-5-hepten-2-one,

3) optionally, heating the mixture of step (2) at a temperature of from 50 to 85ºC, and

4) isolating the respective solvate of Apremilast.

For example, form B of Apremilast may be used in step 1).

Suitable solvents used in step 1) may be an organic solvent selected from a ketone solvent, an ester solvent, an ether solvent, a hydrocarbon solvent and/or water or mixtures thereof. Suitable ketone solvent may be selected from acetone, methyl ethyl ketone or 2-butanone, methyl isobutyl ketone, cyclohexanone, cyclopentanone and 3-pentanone or mixtures thereof. Suitable ester solvent may be selected from ethyl formate, methyl acetate, ethyl acetate, isopropyl acetate, butyl acetate, isobutyl acetate and ethyl malonate or mixtures thereof. Suitable ether solvent may be selected from diethyl ether, dipropyl ether, diphenyl ether, isopropyl ether, tert-butyl methyl ether, tetrahydrofuran and 1,4-dioxane or mixtures thereof. Suitable hydrocarbon solvent may be selected from n-pentane, n-hexane, n-heptane, n-octane, cyclohexane and methylcyclohexane or mixtures thereof. Preferably, the solvent used in step 1) is an organic solvent selected from a ketone solvent, a hydrocarbon solvent and/or water. More preferably, the solvent of step 1) is acetone, cyclohexane and/or water.

The amount of either anisaldehyde, 3-phenylpropanaldehyde, 3-methyl-2-cyclohexenone or 6-methyl-5-hepten-2-one used in step 2) may be of from 0.1 to 5.0 (v/v), preferably of

from 0.1 to 4.0 (v/v), more preferably of from 0.1 to 3.0 (v/v), and even more preferably of from 0.1 to 2.0 (v/v) with respect to the solvent used in step 1).

In the present invention, the Apremilast is used with a specific particle size distribution (PSD), specifically D90 from about 10 to 50 µm. The PSD may have influence in the dissolution of Apremilast and thus may be controlled. Preferably, the particle size distribution D90 ranges from about 10 to 40 µm, more preferably from about 12 to 35 µm, and even more preferably from 14 to 30 µm. In one specific example, Apremilast has a PSD D90 of 15 µm. In another specific example, Apremilast has a PSD D90 of 28 µm. When Apremilast having a PSD D90 ranging from 10 to 50 µm is used in the composition, the dissolution profile at pH 6.8 is excellent and achieves an Apremilast release as good as the innovator's product. If the PSD D90 is lower than 10 µm, the release may be too fast, whereas when the PSD D90 is more than 50 µm, the release may be too slow. The term "particle size" refers to the size of the particles measured in µm. The measurement was performed with an appropriate apparatus by conventional analytical techniques such as laser diffraction. In the present invention the particle size was measured by a Mastersizer 3000 particle size analyzer. Such apparatus uses a technique of laser diffraction to measure the size of particles. It operates by measuring the intensity of light scattered, as a laser beam passes through a dispersed particles sample. This data is then analyzed using the general-purpose model to calculate the size of the particles that created the scattering pattern, assuming a spherical particle shape.

The terms "particle size distribution" or "PSD" have the same meaning and are used interchangeably. They refer to the percentage of the particles within a certain size range. The term "D90" refers to the value of particle size distribution where at least 90% of the particles have a size less or equal to the given value. Thus, a particle size distribution D90 from about 10 to 50 µm means that 90% of the particles of Apremilast have a size less or equal to the given value within the range from about 10 to 50 µm.

The pharmaceutical composition as herein disclosed comprises at least one or more fillers. Preferably, the total amount of filler or fillers present in the pharmaceutical composition ranges from 60 % to 93 % by weight in respect of the total amount of the pharmaceutical composition. More preferably, the total amount of filler or fillers present in the pharmaceutical composition ranges from 70 % to 90 % by weight in respect of the total amount of the pharmaceutical composition. Even more preferably, the total amount of filler or fillers present in the pharmaceutical composition ranges from 80 % to 88 % by weight in respect of the total amount of the pharmaceutical composition.

The term “filler” as used herein refers to pharmaceutically acceptable excipients which are added to the bulk volume of the active agent making up the solid composition. As a result, the size of the solid composition increases, which makes its size suitable for handling. Fillers are convenient when the dose of drug per solid composition is low and the solid composition would otherwise be too small. In a preferred embodiment of the pharmaceutical composition as herein disclosed, said pharmaceutical composition comprises at least one filler wherein said filler may be selected from the group comprising or consisting of microcrystalline cellulose, lactose, powdered cellulose, dibasic calcium phosphate, tribasic calcium phosphate, starch, pregelatinized starch, dextrose, mannitol, sucrose and sorbitol or any combination thereof. The lactose may be lactose monohydrate, anhydrous lactose and combinations thereof. Preferably, anhydrous lactose is used. In a preferred embodiment, the filler is a combination of microcrystalline cellulose and lactose. In another preferred embodiment, the filler is microcrystalline cellulose. In a more preferred embodiment, the filler does not comprise any lactose and is thus lactose-free. Lactose-free formulations avoid possible gastrointestinal disorders resulting from lactose intolerance. These alterations are becoming more common among the population and avoiding this excipient prevents any intolerance issues and allows its use for any kind of patients.

As used herein, “lubricant” means a substance that reduces friction between the composition of the present invention and the surfaces of the apparatus used to compact the composition into a compressed form. In a preferred embodiment of the pharmaceutical composition as herein disclosed, said pharmaceutical composition comprises at least one lubricant. Preferably, the total amount of lubricant or lubricants present in the pharmaceutical composition ranges from 0.1 to 2 % by weight in respect of the total amount of the pharmaceutical composition. More preferably, the total amount of lubricant or lubricants present in the pharmaceutical composition ranges from 0.5 to 1.5 % by weight in respect of the total amount of the pharmaceutical composition. Even more preferably, the total amount of lubricant or lubricants present in the pharmaceutical composition ranges from 0.5 to 1 % by weight in respect of the total amount of the pharmaceutical composition. In a preferred embodiment of the pharmaceutical composition as herein disclosed, said pharmaceutical composition comprises at least one lubricant selected from stearic acid, magnesium stearate, polyethylene glycol, sodium stearyl fumarate, sodium benzoate and mixtures thereof. Preferably, the pharmaceutical composition comprises at least one lubricant selected from magnesium stearate, stearic acid, sodium stearyl fumarate or

mixtures thereof, more preferably the pharmaceutical composition comprises magnesium stearate.

As used herein, “disintegrant” means a substance or a mixture of substances added to a tablet to facilitate its breakup or disintegration after administration. The pharmaceutical composition as herein disclosed comprises at least one disintegrant. Preferably, the total amount of disintegrant or disintegrants present in the pharmaceutical composition ranges from 1 to 10 % by weight in respect of the total amount of the pharmaceutical composition. More preferably, the total amount of disintegrant or disintegrants present in the pharmaceutical composition ranges from 2 to 7 % by weight in respect of the total amount of the pharmaceutical composition. Even more preferably, the total amount of disintegrant or disintegrants present in the pharmaceutical composition ranges from 3 to 5 % by weight in respect of the total amount of the pharmaceutical composition. The use of a disintegrant in a formulation helps to the proper dissolution of the tablet, making the Apremilast more easily available for the absorption in the gastrointestinal tract.

In a preferred embodiment of the pharmaceutical composition as herein disclosed, said pharmaceutical composition comprises at least one disintegrant selected from water-soluble disintegrants, such as starch, pregelatinized starch, sodium carboxymethyl cellulose, croscarmellose sodium, crosslinked polyvinylpyrrolidone, low-substituted hydroxypropyl cellulose and mixtures thereof. Preferably, the pharmaceutical composition comprises croscarmellose sodium.

As used herein, "glidant" means a substance which improves the flow characteristics of powder mixtures in the dry state. In a preferred embodiment of the pharmaceutical composition as herein disclosed, said pharmaceutical composition comprises at least one glidant. Preferably, the total amount of glidant or glidants present in the pharmaceutical composition ranges from 0.1 to 2.0 % by weight in respect of the total amount of the pharmaceutical composition. More preferably, the total amount of glidant or glidants present in the pharmaceutical composition ranges from 0.2 to 1.0 % by weight in respect of the total amount of the pharmaceutical composition. Even more preferably, the total amount of glidant or glidants present in the pharmaceutical composition ranges from 0.3 to 0.8 % by weight in respect of the total amount of the pharmaceutical composition.

In a preferred embodiment of the pharmaceutical composition as herein disclosed, said pharmaceutical composition comprises at least one glidant selected from the group consisting of colloidal silicon dioxide, talc, starch, starch derivatives, and mixtures thereof. Preferably, the pharmaceutical composition comprises colloidal silicon dioxide.

Another aspect of the invention refers to a process for the preparation of the compositions of the invention in the form of tablets. In an embodiment, the process for the preparation of the tablets of the present invention comprises:

a) preparing a pre-mixture comprising Apremilast or a pharmaceutically acceptable salt or solvate thereof, a first part of the filler, disintegrant, and glidant;

b) mixing the pre-mixture obtained in step a) with the remaining part of the filler;

c) adding the lubricant to the mixture obtained in step b);

d) compressing the mixture obtained in step c) to form tablets; and

e) optionally, coating the tablets obtained in step d).

This is a very straightforward manufacturing process which avoids wet granulation and thus is more economical and requires less resources. Also, the use of direct compression is a more reliable and provide robust tablets having good dissolution properties.

Preferably, the addition of the filler in step a) is done in two steps, meaning that first about of 10-20% of the total amount of the filler is added first, then Apremilast, disintegrant and glidant are added and finally about another 10-20% of the total amount of the filler is added and then altogether is homogenized to obtain the pre-mixture.

Preferably, step b) is carried out by adding a third part of the filler first, then mixing this with the obtained pre-mixture of step a) and then adding a fourth part of the filler. The so obtained blend is then homogenized.

Optionally, the pre-mixture obtained in step a) as well as the third and fourth parts of the filler needed in step b) may each be sieved using a sieve having a sieve diameter from 750 to 1250 µm.

Optionally, the lubricant before adding it to the manufacturing process, may be sieved using a sieve having a sieve diameter from 225 to 275 µm.

The filler in this process is added in different portions as explained above, in order to ensure the homogenization of the mixtures during pre-blending and blending steps. Otherwise, a loss of uniformity may be observed. In a specific example, when a combination of two fillers is used, then the first filler is added in form of the first part and the second part while the second filler is added as the third part and the fourth part. So, when a combination of microcrystalline cellulose and lactose are used as fillers, it is preferred to add microcrystalline cellulose as the first part and the second part during step a) and then add lactose as the third part and the fourth part during step b).

In one aspect, the composition mentioned herein is other than a combination of Apremilast and anhydrous lactose, microcrystalline cellulose, polyvinylpyrrolidone, stearic acid, colloidal anhydrous silica and gelatin. Among others, polyvinylpyrrolidone is not desired,

since it is known to undergo degradation more easily due to the high content of peroxides and this will affect eventually the oral solid dosage forms with respect to purity, dissolution behaviour and other aspects. The pharmaceutical composition of the present invention may be used to manufacture oral solid dosage forms such as tablets. The resulting tablets may then be stored in bulk or packaged into standard containers in the pharmaceutical industry, such as bottles, sachets or blisters. Known blisters comprise materials such as Alu/Alu (aluminium/aluminium), PVC/Alu (Polyvinylchloride/aluminium), PVC/PCTFE/Alu (Polyvinylchloride/ Polychlorotrifluoroethylene/aluminium), Polyamide/Alu/PVC-Alu (Polyamide/Aluminium/Polyvinyl chloride-aluminium) or PVC/PVDC/Alu (Polyvinylchloride/ Polyvinylidene chloride/aluminium). Bottles may be made, without limitations, from glass, or plastic material, for example HDPE (High-density polyethylene), LDPE (Low-density polyethylene), or PET (Polyethylene terephthalate).

EXAMPLES

The present invention will be described in more detail by way of the following illustrative examples, which are not intended to limit the scope of the present invention.

Example 1:

Composition comprising 30 mg Apremilast and tablet preparation.

Ingredients	mg	% by weight
Apremilast (D90 20 microns)	30.000	10.00
Microcrystalline cellulose	254.250	84.75
Sodium croscarmellose	12.000	4.00
Colloidal silicon dioxide	1.500	0.50
Magnesium stearate	2.250	0.75
Total uncoated tablet	300.0	100

To a 1L double cone blender were added 15.73% by weight of the microcrystalline cellulose (a first part of the filler) (pre-sieved through 1 mm sieve), Apremilast with particle size distribution D90 of 20 microns (crystalline form B as described in WO 2009120167), sodium croscarmellose, the colloidal silicon dioxide and a second portion of the microcrystalline cellulose (13.47% by weight; a second part of the filler) in the order mentioned. This mixture was homogenized in a universal mixer MIBL for 20 minutes at 23rpm to arrive at the pre-

mixture. Then, to a 2L doble cone blender were added 35.40% by weight of the microcrystalline cellulose (a third part of the filler), the pre-mixture and another 35.40% by weight of the filler (a fourth part of the filler) and the mixture was homogenized in a MIBL for 20 minutes at 23 rpm. Then magnesium stearate was added and the mixture homogenized during 5 minutes at 23 rpm. The obtained mixture was then compressed with 3 rounded punches resulting in tablets having a friability under 0.5% showing that there is a very low tendency of the obtained tablets to break under duress or contact. Optionally, the tablets were film-coated using Opadry.

The resulting tablets were submitted to a dissolution test according to the USP II dissolution test (paddle) at pH 6.8 with 0.15% of a lauryl sulfate solution and at rotation speed of 60 rpm. Testing 4 samples, the following average dissolution values, in percentage, at defined time points were obtained and compared to the dissolution profile of the reference product Otezla®.

t(minutes)	Example 1 (%)	Otezla® (%)
0	0.00	0.00
5	52.15	50.67
10	65.04	63.33
15	71.08	69.99
20	74.75	74.97
30	79.66	81.09
45	83.34	85.40
60	87.66	87.78
75	90.11	89.69

These results show an excellent dissolution profile compared to the innovator product.

Example 2:

Composition comprising 30 mg Apremilast and tablet preparation.

Ingredients	**mg**	**% by weight**
Apremilast (D90 29 microns)	30.000	10.00
Microcrystalline cellulose	251.250	83.75
Sodium Croscarmellose	15.000	5.00

Colloidal Silicon Dioxide	1.500	0.50
Magnesium Stearate	2.250	0.75
Total uncoated tablet	300.0	100

Example 2 was prepared following the procedure applied in example 1, the differences being the particle size of Apremilast, and the quantity of disintegrant, in this example 1% more, compensated with 1% less of the diluent.

The resulting tablets were submitted to a dissolution test according to the USP II dissolution test (paddle) at pH 6.8 with 0.15% of a lauryl sulfate solution and at rotation speed of 60 rpm. Testing 4 samples, the following average dissolution values, in percentage, at defined time points were obtained and compared to the dissolution profile of the reference product Otezla®

t(minutes)	Example 2 (%)	Otezla® (%)
0	0.00	0.00
5	49.54	50.67
10	62.28	63.33
15	68.19	69.99
20	71.92	74.97
30	76.45	81.09
45	80.90	85.40
60	84.70	87.78
75	97.29	89.69

These results show an excellent dissolution profile compared to the innovator product.

Example 3:

Composition comprising 30 mg Apremilast and tablet preparation.

Ingredients	**mg**	**% by weight**
Apremilast (D90 13 microns)	30.000	10.00
Microcrystalline cellulose	251.250	83.75
Sodium Croscarmellose	15.000	5.00

Colloidal Silicon Dioxide	1.500	0.50
Magnesium Stearate	2.250	0.75
Total uncoated tablet	300.0	100
Opadry® II 85F17424 Beige	9.000	
Total coated tablets	309.0	

Example 3 was prepared following the procedure applied in example 1, the differences being the particle size of Apremilast, and the quantity of disintegrant, in this example 1% more, compensated with 1% less of the diluent.

500.0g of the tablets obtained were coated using a STE RLab coater with a capacity of 1kg using a Opadry® II 85F17424 Beige (supplied by Colorcon).

Both the coated and non-coated tablets were submitted to a dissolution test according to the USP II dissolution test (paddle) at pH 6.8 with 0.15% of a lauryl sulfate solution and at rotation speed of 60 rpm. Testing 4 samples, the following average dissolution values, in percentage, at defined time points were obtained and compared to the dissolution profile of the reference product Otezla®

t(minutes)	Example 3 cores (%)	Example 3 coated tablets (%)	Otezla® (%)
0	0.0	0.0	0.0
5	49.5	39.6	50.7
10	61.8	53.9	63.3
15	69.2	62.3	70.0
20	73.9	68.8	75.0
30	80.8	75.6	81.1
45	86.6	82.4	85.4
60	89.9	87.0	87.8

These results show an excellent dissolution profile compared to the innovator product. The coated tablets have a bit slower dissolution profile than the non-coated tablets, but the dissolution profile is comparable to the innovator product nonetheless.

Example 4:

Composition comprising 30 mg Apremilast and tablet preparation.

Ingredients	mg	% by weight
Apremilast (D90 20 microns)	30.000	9.9
Microcrystalline cellulose	77.250	25.50
Anhydrous Lactose	180.000	59.41
Sodium Croscarmellose	12.000	3.96
Colloidal Silicon Dioxide	1.500	0.49
Magnesium Stearate	2.250	0.74
Total uncoated tablet	303.0	100

Example 4 was prepared like example 1, adding the two fillers microcrystalline cellulose and anhydrous lactose in 4 parts. The first and second parts, used for preparing the pre-mixture, were only microcrystalline cellulose. The third and fourth parts, to be added to the obtained pre-mixture, were only anhydrous lactose.

Example 5:

Ingredients	mg	% by weight
Apremilast	30.000	10.00
Microcrystalline cellulose	77.250	25.75
Anhydrous Lactose	180.000	60.00
Sodium Croscarmellose	9.000	3.00
Colloidal Silicon Dioxide	1.500	0.50
Magnesium Stearate	2.250	0.75
Total uncoated tablet	300.0	100

Example 5 was prepared like example 4. The obtained mixture was then compressed with 3 rounded punches resulting in tablets having a friability under 0.5% showing that there is a very low tendency of the obtained tablets to break under duress or contact.

The resulting tablets were submitted to a dissolution test according to the USP II dissolution test (paddle) at pH 6.8 with 0.15% of a lauryl sulfate solution and at rotation speed of 60 rpm. Testing 4 samples, the following average dissolution values, in percentage, at defined time points were obtained and compared to the dissolution profile of the reference product Otezla®

t(minutes)	Example 2 (%)	Otezla® (%)
0	0.00	0.00
5	40.1	50.7
10	58.8	63.3
15	68.3	70.0
20	73.5	75.0
30	79.8	81.1
45	85.1	85.4
60	88.4	87.8
75	90.8	89.7

These results show an excellent dissolution profile compared to the innovator product.

Example 6: Synthesis of an anisaldehyde solvate of Apremilast

Apremilast (12g, 26mmol) and anisaldehyde (24mL) were charged into a 50mL round-bottom flask, and the mixture was stirred at 75-80ºC for 3h. Once the reaction was completed, the reaction was cooled down to RT and then to 0-5ºC and stirred for 2h. The product was filtered and washed with cyclohexane. The solid was dried under vacuum at 45°C until constant weight, to obtain 10.59 g of the product.

The product was characterized by PXRD as it can be seen in figure 1.

Example 7: Synthesis of a 3-phenylpropanaldehyde solvate of Apremilast

Apremilast (12g, 26mmol) and 3-phenylpropanaldehyde (15mL) were charged into a 50mL round-bottom flask, and the mixture was stirred at 75-80ºC for 3h. Once the reaction was completed, the reaction was cooled down to RT and then to 0-5ºC and stirred for 2h. The product was filtered and washed with cyclohexane. The solid was dried under vacuum at 25°C until constant weight, to obtain 13.96 g of the product.

The product was characterized by PXRD as it can be seen in figure 2.

Example 8: Synthesis of a 3-methyl-2-cyclohexenone solvate of Apremilast

Apremilast (12g, 26mmol) and 3-Methyl-2-cyclohexenone (36mL) were charged into a 50mL round-bottom flask, and the mixture was stirred at RT for 3h. Cyclohexane (36 mL) was added to the solution, and then seeded. The mixture was stirred overnight, cooled to 0-5ºC, and stirred for 2 additional hours. The final solid was filtered and was washed with cyclohexane. The product was dried under vacuum at 45ºC until constant weight (12.72g). The product was characterized by PXRD as it can be seen in figure 3.

Example 9: Synthesis of a 6-methyl-5-hepten-2-one solvate of Apremilast

Apremilast (12g, 26mmol) and 6-Methyl-5-hepten-2-one (24mL) were charged into a 50mL round-bottom flask, and the mixture was stirred at 75-80ºC overnight. Once the reaction was completed, the reaction was cooled down to RT and then to 0-5ºC and stirred for 2 h. The product was filtered and washed with MTBE (36mL). The solid was dried under vacuum at 45°C until constant weight, to obtain 13.11g of the product.

The product was characterized by PXRD as it can be seen in figure 4.

Example 10: Preparation of a 3-phenylpropanaldehyde solvate of Apremilast in acetone

Apremilast (5 g, 10.86 mmol) and acetone (10 mL) were charged into a 50 mL round-bottom flask, and the resulting mixture was stirred at room temperature for 1 hour. Then, 3-phenylpropanaldehyde (3 mL) was added and the resulting mixture was stirred at reflux temperature for 3 hours, cooled down to room temperature for 24 hours and then to 0-5ºC and stirred for 2 hours at 0-5ºC. The solid obtained was filtered off, washed with acetone and dried under vacuum at 45-50°C until constant weight. Yield: 63%.

Example 11: Preparation of a 3-methyl-2-cyclohexenone solvate of Apremilast in water and cyclohexane

Apremilast (5 g, 10.86 mmol) and water (20 mL) were charged into a 50 mL round-bottom flask, and the resulting mixture was stirred at room temperature for 1 hour. Then, 3-methyl-2-cyclohexenone (5 mL) was added and the resulting mixture was stirred at room temperature for 3 hours. Afterwards, cyclohexane (15 mL) was added and the resulting mixture was stirred at room temperature for 24 hours, cooled down to 0-5ºC and stirred for 2 hours at 0-5ºC. The solid obtained was filtered off, washed with cyclohexane and dried under vacuum at 45-50°C until constant weight. Yield: 68%.

Methods

PSD measurement method:

- Determination of the particle size distribution (PSD) of Apremilast by laser diffraction

2 mg of sample were taken to measure the PSD of every API sample

Instrument conditions

Instrument: Malvern Laser Diffraction Masterizer 3000

Accesory: Dry Sampler Aero S

Measuring range: 0.001-3500µm

Sensitivity: Normal

Particle Type: Non-spherical

Material Refraction Index: 1.59

Material Absorption Index: 0.01

Dispersant: Air

Dispersant Air Pressure: 2 bar

Background measuring time: 5 seconds

Sample measuring time: 5 seconds

Number of measurements: 3

Obscuration Range: 1-5%

Feed rate: 30%

Hoper opening: 2.5

Analytical conditions for Powder X-Ray Diffraction (PXRD) analysis:

Sample preparation: the powder samples were sandwiched between films of polyester of 3.6 microns of thickness.

Equipment: PANalytical X'Pert PRO MPD q/q powder diffractometer of 240 millimetres of radius, in a configuration of convergent beam with a focalizing mirror and a transmission geometry with flat samples sandwiched between low absorbing films.

- Cu Ka radiation (l = 1.5418 Å).
- Work power: 45 kV – 40 mA.
- Incident beam slits defining a beam height of 0.4 millimetres.
- Incident and diffracted beam 0.02 radians Soller slits.
- PIXcel detector: Active length = 3.347º.
- 2q/q scans from 1 to 40º 2q with a step size of 0.026º 2q and a measuring time of 300 seconds per step.

Data acquisition: Powder diffraction pattern were acquired on a Bruker D8 Advance Series 2Theta/Theta powder diffraction system using CuKα1-radiation in transmission geometry. The system is equipped with a VÅNTEC-1 single photon counting PSD, a Germanium monochromator, a ninety positions auto-changer sample stage, fixed divergence slits and a radial soller.

Programs used: Data collection with DIFFRAC plus XRD Commander V.2.5.1, and evaluation with Diffrac.EVA V.5.0.0.22.

- Measurement conditions: The samples were measured in a range from 4 to 40º in 2θ in a 1 hour measurement using an angular step of 0.026º and a time per step of 300 s.

Dissolution profile method:

Reagents:

- Trifluoroacetic acid, HPLC/MS grade

- Water, HPLC grade

- Acetonitrile, HPLC grade

- Diluent mixture: Acetonitrile : Water (50:50)

Mix in a beaker the volume of acetonitrile, measured using a cylinder, with the volume of water, measured using another cylinder. Homogenize magnetically and sonicate for about 10 min. Allow the dissolution mixture to stand for a minimum of 3-4 hours before use.

- Dissolution medium: pH = 6.8 + 0.15% SLS

Monobasic sodium phosphate buffer pH = 6.8 + 0.15% SLS (sodium lauryl sulphate):

Dissolve 6.0 g of Monobasic Sodium Phosphate (NaH_2PO_4) into a 1000 mL volumetric flask containing 500 mL of water, HPLC grade. Stir and add 112 mL of 0.2M sodium hydroxide (1) and complete to volume with water, HPLC grade. Add 1.5 g of sodium lauryl sulphate and stir until complete dissolution.

(1) 0.2M Sodium Hydroxide Solution: 8.4 g of sodium hydroxide (pellets) are dissolved in one liter of MilliQ water.

Chromatographic conditions:

- Column: Acquity UPLC BEH C18 1.7 µm (100 x 2.1 mm) or equivalent

- Mobile phase: Acetonitrile + 0.05% TFA / Water + 0.05% TFA

Aqueous mobile phase: Trifluoroacetic acid 0.05% (Add 0.5 mL trifluoroacetic acid to 900 mL MilliQ water, stir and make up to 1000 mL).

Organic mobile phase: Acetonitrile + Trifluoroacetic acid 0.05% (Add 0.5 mL trifluoroacetic acid to 900 mL Acetonitrile HPLC grade, stir and make up to 1000 mL).

- Flow: 0.4 mL/min
- Detection wavelength: 230 nm
- Injection volume: 2 µL
- Sample temperature: 15 ºC
- Column temperature: 40 ºC
- Run time: 3 minutes
- Retention time: Apremilast: 1.2 min, approximately
- Mobile phase isocratic: (50:50) Water (TFA 0.05%) / Acetonitrile (TFA 0.05%)
- Purge solvent / Weak wash solvent (3600 µL): Acetonitrile / Water (5:95)
- Seal wash: Acetonitrile / Water (5:95)

CLAIMS

1. A pharmaceutical composition comprising Apremilast or a pharmaceutically acceptable salt or solvate thereof, at least one filler and at least one disintegrant, wherein the active ingredient has a particle size volume distribution with D90 between 10 and 50 µm, preferably between 10 and 40 µm, more preferably between 12 and 35 microns, and even more preferably between 14 and 30 µm, when measured by laser diffraction analysis.

2. The pharmaceutical composition of the preceding claim, wherein said composition is lactose free.

3. The pharmaceutical composition of claim 1, wherein said filler comprises microcrystalline cellulose and lactose, preferably microcrystalline cellulose and anhydrous lactose

4. The pharmaceutical composition of any one of the preceding claims, wherein the total amount of filler or fillers present in the pharmaceutical composition ranges from 60 to 93 % by weight in respect of the total amount of the pharmaceutical composition, preferably, the total amount of filler or fillers present in the pharmaceutical composition ranges from 70 to 90 % by weight in respect of the total amount of the pharmaceutical composition, more preferably, the total amount of filler or fillers present in the pharmaceutical composition ranges from 80 to 88 % by weight in respect of the total amount of the pharmaceutical composition.

5. The pharmaceutical composition of any one of the preceding claims, wherein the disintegrant is selected from pregelatinized starch, sodium carboxymethyl cellulose, sodium alginate, sodium starch glycolate, polyvinylpyrrolidone and combinations thereof, preferably the disintegrant comprises sodium carboxymethyl cellulose, more preferably the disintegrant is sodium carboxymethyl cellulose.

6. The pharmaceutical composition of any one of the preceding claims, wherein the total amount of disintegrant or disintegrants present in the pharmaceutical composition ranges from 1 to 10 % by weight in respect of the total amount of the pharmaceutical composition, preferably, the total amount of disintegrant or disintegrants present in the pharmaceutical composition ranges from 2 to 7 % by weight in respect of the total amount of the pharmaceutical composition, more preferably, the total amount of disintegrant or disintegrants present in the pharmaceutical composition ranges from 3 to 5 % by weight in respect of the total amount of the pharmaceutical composition.

7. The pharmaceutical composition of any one of the preceding claims, further comprising at least one lubricant, preferably the total amount of lubricant or lubricants

present in the pharmaceutical composition ranges from 0.1 to 2 % by weight in respect of the total amount of the pharmaceutical composition, more preferably, the total amount of lubricant or lubricants present in the pharmaceutical composition ranges from 0.5 to 1.5 % by weight in respect of the total amount of the pharmaceutical composition, even more preferably, the total amount of lubricant or lubricants present in the pharmaceutical composition ranges from 0.5 to 1 % by weight in respect of the total amount of the pharmaceutical composition.

8. The pharmaceutical composition of the preceding claim, wherein the lubricant or lubricants is selected from stearic acid, magnesium stearate, polyethylene glycol, sodium stearyl fumarate, sodium benzoate and mixtures thereof, preferably the lubricant is magnesium stearate.

9. The pharmaceutical composition of any one of the preceding claims, further comprising at least one glidant, preferably the total amount of glidant or glidants present in the pharmaceutical composition ranges from 0.1 to 2 % by weight in respect of the total amount of the pharmaceutical composition, more preferably, the total amount of glidant or glidants present in the pharmaceutical composition ranges from 0.2 to 1 % by weight in respect of the total amount of the pharmaceutical composition, even more preferably, the total amount of glidant or glidants present in the pharmaceutical composition ranges from 0.3 to 0.8 % by weight in respect of the total amount of the pharmaceutical composition.

10. The pharmaceutical composition of the preceding claim, wherein the glidant or glidants is selected from colloidal silicon dioxide, talc, starch, starch derivatives, and mixtures thereof, preferably the glidant is colloidal silicon dioxide.

11. The pharmaceutical composition of any one of the preceding claims, wherein said composition is in form of a tablet, preferably an immediate release tablet, more preferably an immediate release tablet manufactured by direct compression.

12. The pharmaceutical composition of claim 11, further comprising a coating.

13. A process for manufacturing a pharmaceutical composition according to any one of the preceding claims, comprising the following steps:

a) preparing a pre-mixture comprising Apremilast or a pharmaceutically acceptable salt or solvate thereof, a first part of the filler, disintegrant, and optionally glidant;

b) mixing the pre-mixture obtained in step a) with the remaining part of the filler;

c) adding the lubricant to the mixture obtained in step b);

d) compressing the mixture obtained in step c) to form tablets; ande) optionally, coating the tablets obtained in step d).

14. The pharmaceutical composition of any one of claims 1 to 12, for use in the treatment of psoriasis, psoriatic arthritis or oral ulcers associated with Behçet's disease, preferably severe chronic plaque psoriasis in adult patients who failed to respond to or who have a contraindication to, or are intolerant to other systemic therapy including cyclosporine, methotrexate or psoralen and ultraviolet-A light, or psoriatic arthritis in adult patients who have had an inadequate response or who have been intolerant to a prior disease-modifying antirheumatic drug therapy.

FIGURES

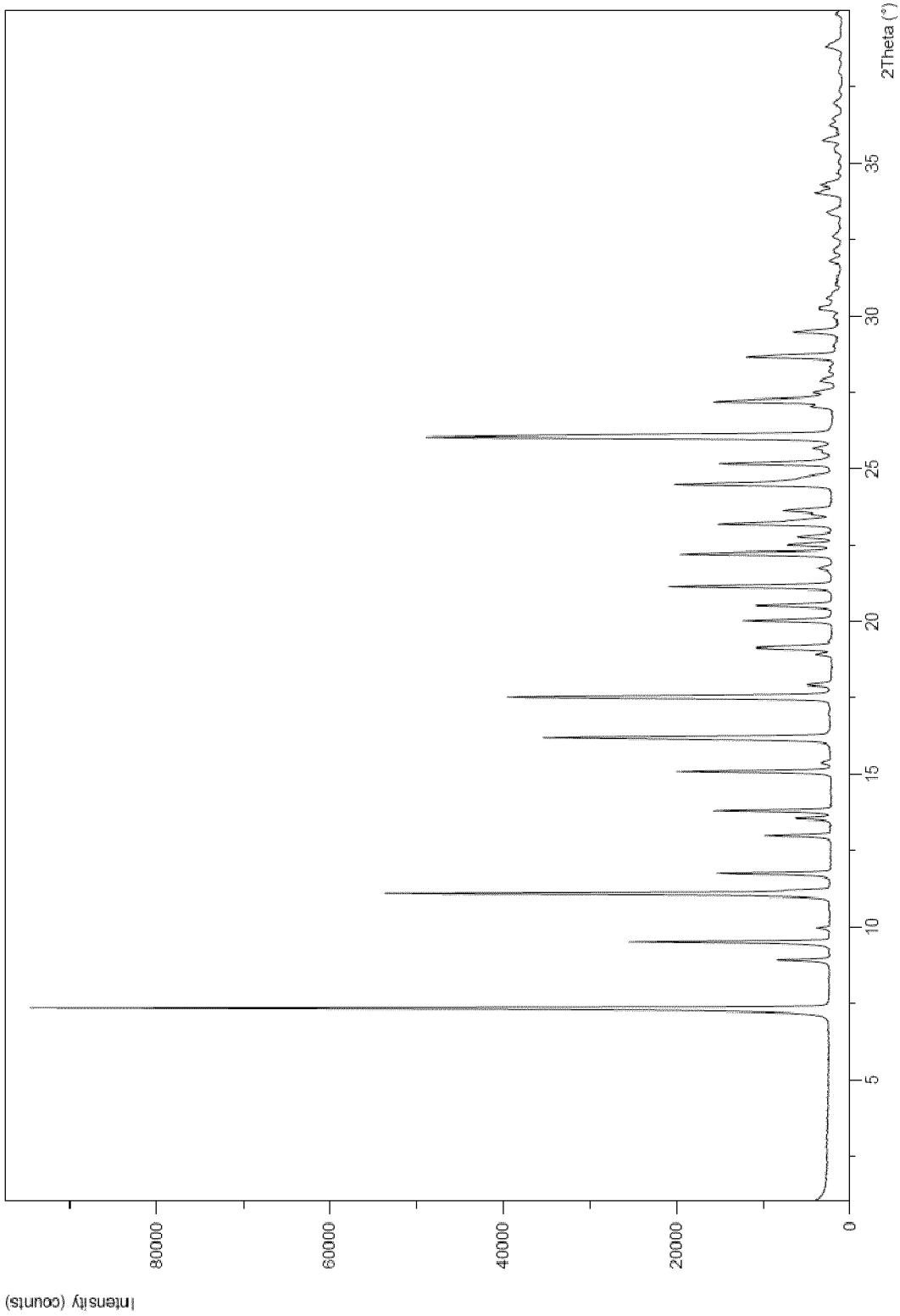
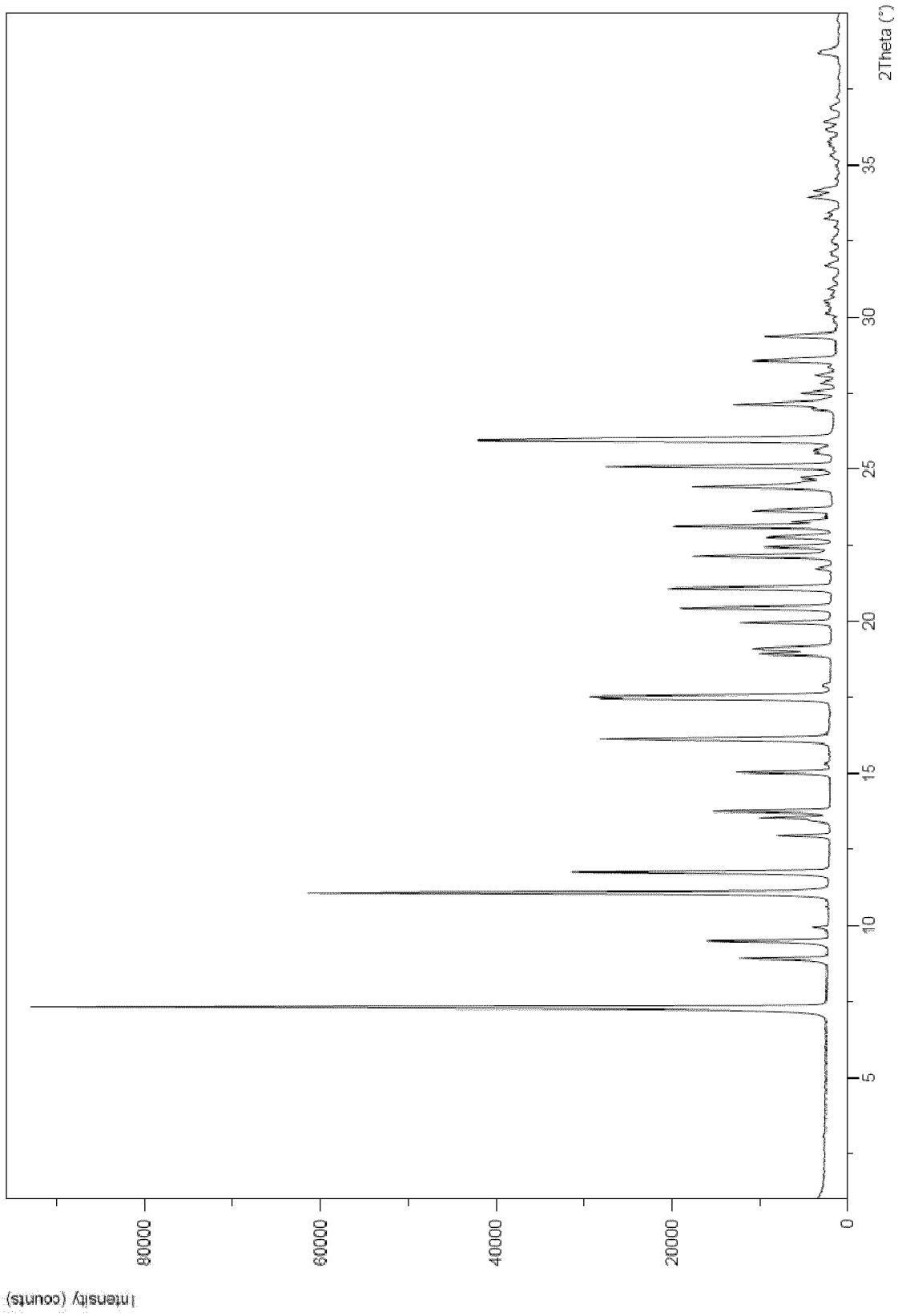


FIG. 1


2Theta (°)
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20
25
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40000
60000
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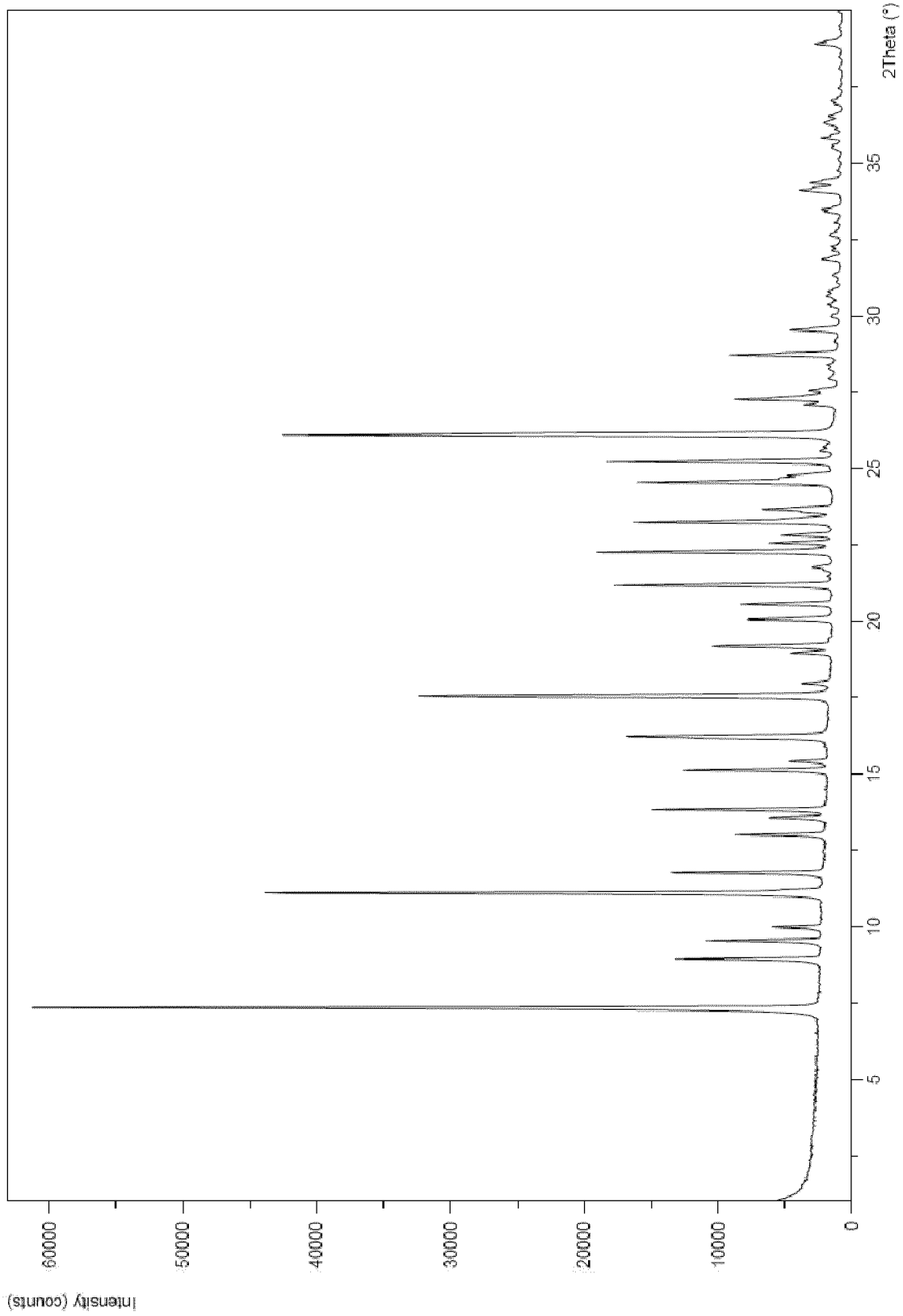
Intensity (counts)

FIG. 2


2Theta (°)
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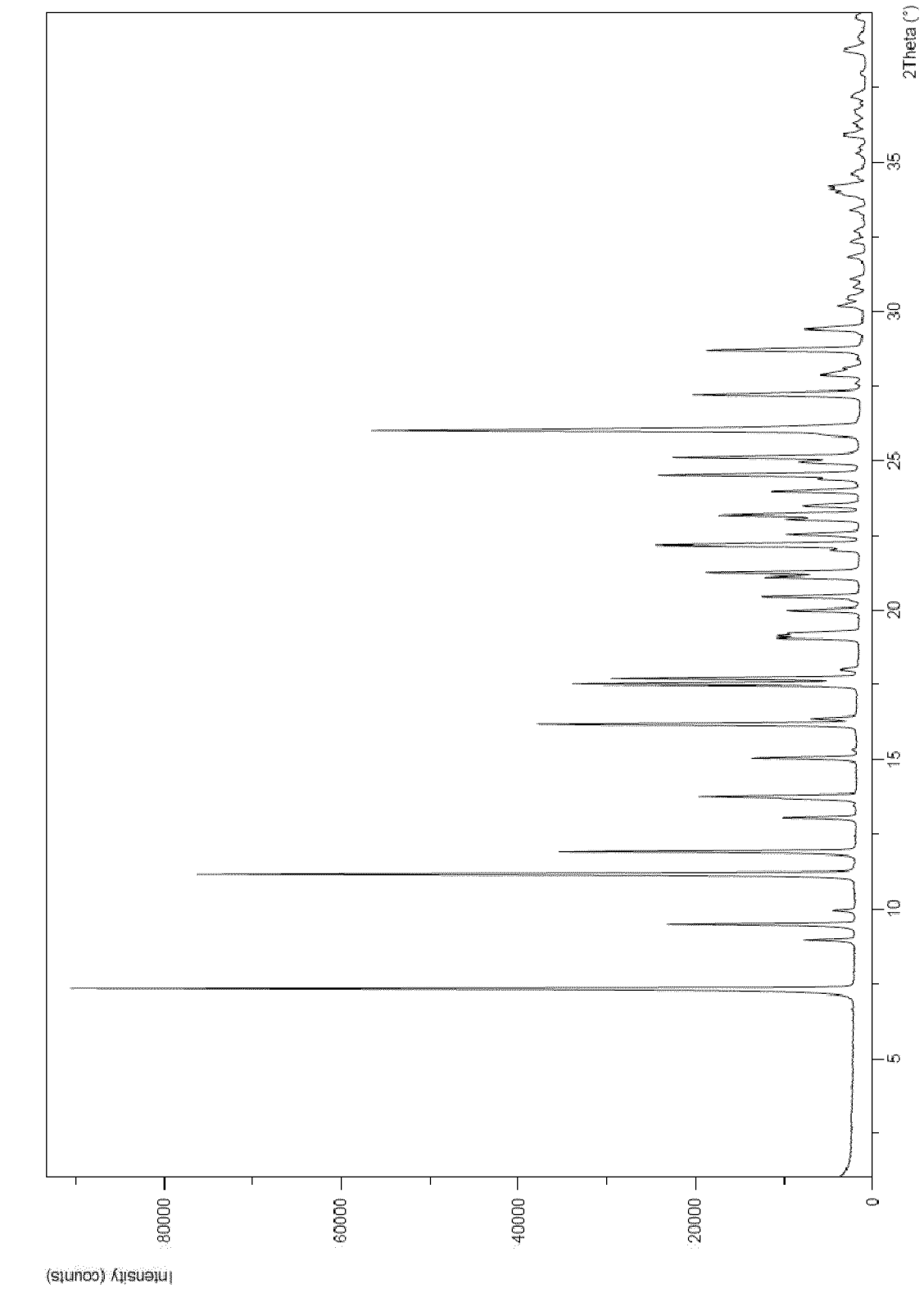
60000

FIG. 3


Intensity (counts)
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60000
40000
20000
0
5
10
15
20
25
30
35
2Theta (°)

FIG. 4

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2022/086847

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/4035 A61K9/20 A61P17/06 A61P17/02 A61P19/02
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)
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 practicable, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2019/073477 A1 (MANKIND PHARMA LTD [IN]) 18 April 2019 (2019-04-18) page 9, line 24 - line 26 page 11, line 4 - line 11 page 13, line 14 - page 14, line 20 page 16 - page 23; examples 1-10	1-14
Y	EP 2 651 400 B1 (CELGENE CORP [US]) 7 August 2019 (2019-08-07) paragraphs [0095] - [0100] paragraph [0108] paragraphs [0130] - [0144]; claim 1; examples 1-10	1-14

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

[x] See patent family annex.

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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

"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

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Date of the actual completion of the international search	Date of mailing of the international search report
20 March 2023	29/03/2023

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	Cetinkaya, Murat

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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2022/086847

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	WO 2017/118447 A1 (ZENTIVA KS [CZ]) 13 July 2017 (2017-07-13) page 5, line 13 - line 19 page 8, line 14 - page 9, line 19; examples 6-7	1-14
Y	WO 2013/119607 A2 (CELGENE CORP [US]) 15 August 2013 (2013-08-15) paragraph [0057] paragraphs [0119] - [0120] paragraphs [0121] - [0125] paragraphs [0129] - [0139] paragraphs [0155] - [0158]; claim 1; compounds I-XV	1-14
X	EP 2 695 616 A1 (CELGENE CORP [US]) 12 February 2014 (2014-02-12)	1-14
Y	paragraph [0066]; claim 1 paragraphs [0282] - [0285]; examples 13-14 paragraphs [0118], [0125], [0132], [0139], [0146], [0153], [0160]	1-14
Y	CN 104 892 486 A (JINAN TRIO PHARMATECH CO LTD) 9 September 2015 (2015-09-09) paragraphs [0089] - [0094]; table 3	1-14

1

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