(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
08 February 2018 (08.02.2018)

WIPO | PCT

(10) International Publication Number
WO 2018/024646 A1

(51) International Patent Classification:
A61K 9/48 (2006.01) *A61K 31/454* (2006.01)

(21) International Application Number:
PCT/EP2017/069242

(22) International Filing Date:
28 July 2017 (28.07.2017)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
16182389.3 02 August 2016 (02.08.2016) EP

(71) Applicant: **SYNTHON B.V.** [NL/NL]; Microweg 22, 6545 CM Nijmegen (NL).

(72) Inventors: **GARCIA JIMENEZ, Sonia**; Synthon Hispania S.L., Castello 1, Poligono Las Salinas, 08830 Sant Boi de Llobregat (ES). **NOGUEIRAS NIETO, Luis**; Synthon Hispania S.L., Castello 1, Poligono Las Salinas, 08830 Sant Boi de Llobregat (ES). **ÁLVAREZ FERNÁNDEZ, Lisardo**; Synthon Hispania S.L., Castello 1, Poligono Las Salinas, 08830 Sant Boi de Llobregat (ES). **VELADA CALZADA, Jose**; Synthon B.V., Microweg 22, 6545 CM Nijmegen (NL).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:
— *with international search report (Art. 21(3))*

WO 2018/024646 A1

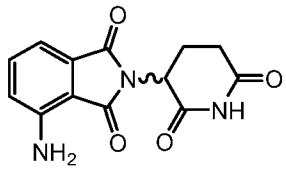
(54) Title: PHARMACEUTICAL COMPOSITION COMPRISING POMALIDOMIDE

(57) Abstract: The present invention relates to a pharmaceutical composition comprising pomalidomide, maltodextrin and a filler, wherein the weight ratio of maltodextrin to filler ranges from 1:1 to 1:2. The invention further relates to the use of said pharmaceutical composition as medicament in the treatment of multiple myeloma.

PHARMACEUTICAL COMPOSITION COMPRISING POMALIDOMIDE

BACKGROUND OF THE PRESENT INVENTION

Pomalidomide, chemically 4-amino-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione of formula (I),



(I)

is an anti-angiogenic and also acts as an immunomodulator in the treatment of multiple myeloma. Pomalidomide is marketed by Celgene under the brand names Imnovid® and Pomalyst®. Imnovid® and Pomalyst® are supplied for oral administration, as immediate-release hard gelatin capsules in four different strengths: 1, 2, 3 and 4 mg.

Pomalidomide is a BCS class IV product, having low permeability and low solubility. The drug substance is practically insoluble in water.

WO2010135396 discloses the marketed formulation of Imnovid® and Pomalyst® containing, besides pomalidomide, pregelatinized starch, mannitol and sodium stearyl fumarate. It contains pomalidomide polymorph A. The primary packaging of the capsules is polyvinyl chloride (PVC)/polychlorotrifluoroethylene (PCTFE) blisters with push through aluminium foil. These blisters provide a high moisture barrier, but are expensive.

According to the information published by the EMA in the European Public Assessment Report (EPAR), the capsule strengths use two common blends comprising the same excipients, varying in the proportion of drug substance and the two excipients mannitol and sodium stearyl fumarate. The capsules comprising 1 and 2 mg of pomalidomide are dose

proportional and utilize a common blend. The capsules comprising 3 and 4 mg of pomalidomide are dose proportional and use another common blend.

CN104042590 discloses capsule formulations comprising pomalidomide, anhydrous lactose, dextrin, cross-linked sodium carboxymethyl cellulose and polyethylene glycol 4000. It describes the use of two common blends: one blend for the 1 and 2 mg capsules and a second common blend for the 3 and 4 mg capsules. The capsules show good stability at 25°C/60% RH in non-specified packaging material.

CN104224723 discloses pomalidomide nanoparticles comprising 0.5 to 1.5% by weight of pomalidomide. To obtain the nanoparticles, specific equipment is needed which is not present in most pharmaceutical production plants. No stability data of the obtained compositions is presented.

CN104523692 discloses complexes of pomalidomide and cyclodextrins, obtained by freeze-drying. The technique of freeze-drying requires specific equipment and is rather expensive.

In view of the prior art cited above, there is still a need for pharmaceutical compositions comprising pomalidomide, which exhibit excellent long term stability and which are suitable for production on commercial scale by applying techniques and equipment commonly used in industry. It would be advantageous if, in addition, these compositions would require the use of just one common blend for the proposed capsule strengths.

BRIEF DESCRIPTION OF THE PRESENT INVENTION

The present invention provides a pharmaceutical composition comprising pomalidomide, maltodextrin and a filler, wherein the weight ratio of maltodextrin to filler ranges from 1:1 to 1:2.

It also provides a process to prepare said composition in the form of a capsule by blending pomalidomide and excipients followed by encapsulation.

Said pharmaceutical composition may be used as medicament in the treatment of multiple myeloma.

DETAILED DESCRIPTION OF THE PRESENT INVENTION

The marketed formulation of Imnovid® and Pomalyst® contains, besides pomalidomide, pregelatinized starch, mannitol and sodium stearyl fumarate. According to the information published by the EMA in the European Public Assessment Report (EPAR), several formulations were evaluated during development. The first formulation developed contained anhydrous lactose, microcrystalline cellulose, croscarmellose sodium and magnesium stearate. In an effort to improve processing, anhydrous lactose was replaced with anhydrous dibasic calcium phosphate and other excipients were changed accordingly. The revised formulation contained pomalidomide, anhydrous dibasic calcium phosphate, pregelatinized starch, croscarmellose sodium and sodium stearyl fumarate. However, this formulation gave rise to instability at accelerated and room temperature conditions. To overcome the instability of the formulation, additional formulations were studied, resulting in the selection of the currently marketed formulation. The problems ran into during the development of Imnovid® and Pomalyst® show that selection of excipients for this product is a difficult task. Pomalidomide exhibits potential reactivity towards fillers like maltose, lactose, trehalose or glucose, *e.g.* mono- or disaccharides, via a Maillard reaction. In addition, it seems that pomalidomide is prone to reaction with nucleophiles like calcium phosphate and sodium bicarbonate by a type of Gabriel reaction.

The primary packaging of the marketed capsules is polyvinyl chloride (PVC)/polychlorotrifluoroethylene (PCTFE) blisters with push through aluminium foil.

These blisters provide a high moisture barrier, but are expensive. It would be advantageous to have a pharmaceutical composition that does not require such expensive high moisture barrier blister pack material, but that does show sufficient long term stability in less protective packaging material.

The marketed formulation is available as immediate-release hard gelatin capsules in four different strengths: 1, 2, 3 and 4 mg. The capsule strengths are manufactured using two common blends comprising the same excipients, varying in the proportion of drug substance and the two excipients mannitol and sodium stearyl fumarate. The capsules comprising 1 and 2 mg of pomalidomide are dose proportional and utilize one single common blend. The capsules comprising 3 and 4 mg of pomalidomide are dose proportional and use another common blend. It would be advantageous to have a pharmaceutical composition comprising pomalidomide enabling the use of just one blend for all capsule strengths.

It was surprisingly found that a pharmaceutical composition comprising pomalidomide, maltodextrin and a filler, wherein the weight ratio of maltodextrin to filler ranges from 1:1 to 1:2 does not require high moisture barrier packaging material. The compositions of the present invention are more stable in less protective packaging material when compared to the marketed pomalidomide capsules.

Maltodextrin is a saccharide mixture of polymers that consist of D-glucose units, with a dextrose equivalent (DE) less than 20. The solubility, hygroscopicity and compressibility of maltodextrin increase as the DE increases. In principle, any maltodextrin can be used in accordance with the present invention. In a preferred embodiment of the present invention, maltodextrin with a DE of 11 to 14 is selected because of its good flow properties and acceptable bulk density. A typical example of such a grade of maltodextrin is Glucidex 12 or Glucidex IT12.

The pharmaceutical composition of the present invention comprises, besides pomalidomide and maltodextrin, a filler. The weight ratio of maltodextrin to the filler ranges from 1:1 to 1:2. More preferably, the weight ratio of maltodextrin to the filler ranges from 1:1.2 to 1:1.5. Preferably, the filler is selected from microcrystalline cellulose and calcium lactate. Calcium lactate can exist in a number of hydration states. In pharmaceutical compositions, calcium lactate is preferably used in its pentahydrated form as filler. More preferably, the filler used in accordance with the present invention is microcrystalline cellulose. Different grades of microcrystalline cellulose can be used. Most preferably, a type of microcrystalline cellulose with increased bulk density is used, allowing a reduction in blend volumes. A typical example of such a grade of microcrystalline cellulose is Vivapur® 301 or Vivapur® 302. By using the specific weight ratios of maltodextrin to the selected fillers, stable formulations are obtained that are able to mimic the dissolution profile of the Imnovid® and Pomalyst® capsules.

Preferably, the amount of pomalidomide in the pharmaceutical composition in accordance with the present invention is more than 2% by weight based on the total weight of the composition. By using this amount of API in combination with the specified excipients, the pharmaceutical composition according to the present invention requires just one single blend for all capsule strengths while the same capsule size as the Imnovid® and Pomalyst® capsules can be employed. The production process is simpler and the costs are reduced in case all capsule strengths are dose proportional.

In order to mimic the dissolution profile of the Imnovid® and Pomalyst® capsules, Pomalidomide in accordance with the present invention has a particle size distribution D_{90} equal to or less than 15 µm. With increasing D_{90} values, the dissolution is slowing down rapidly.

The pharmaceutical composition of the present invention comprising pomalidomide, maltodextrin and a filler, further comprises one or more pharmaceutically acceptable excipients. The excipients to be used in accordance with the present invention are well-known and are those excipients which are conventionally used by the person skilled in the art. Depending on the dosage form chosen for the pharmaceutical composition, the person skilled in the art will be able to select suitable pharmaceutically acceptable excipients. Preferably, the pharmaceutical composition is in the form of a capsule. Most preferably, the capsule is a hard gelatin capsule.

The pharmaceutical composition of the present invention further comprises, besides pomalidomide, maltodextrin and a filler, a lubricant and optionally a disintegrant.

The lubricant to be used in accordance with the present invention may be any lubricant known to a person of ordinary skill in the art. Sodium stearyl fumarate is a particularly preferred lubricant.

Whether the use of disintegrant in the composition is required depends upon the choice of filler. Some fillers, like microcrystalline cellulose, do possess disintegrating properties. In case such a filler is used, there is no need to include a disintegrant in the pharmaceutical composition. On the other hand, in the event that calcium lactate is used as filler, a disintegrant is required. The disintegrant to be used in accordance with the present invention may be any disintegrant known to a person of ordinary skill in the art. Suitable disintegrants to be used in accordance with the present invention are selected from the group consisting of croscarmellose sodium, crospovidone or sodium starch glycolate. Croscarmellose sodium is a particularly preferred disintegrant.

The pharmaceutical composition in accordance with the present invention exhibits a dissolution rate of at least 65% in 15 minutes and at least 90% in 45 minutes when tested in aqueous hydrochloric acid 0.1 N in a USP apparatus II at 50-100 rpm, 37°C.

The pharmaceutical composition of the present invention exhibits excellent long term stability. It is significantly less sensitive to moisture than the commercial products Imnovid® and Pomalyst® and therefore does not require expensive high moisture barrier packaging material like polyvinyl chloride (PVC)/polychlorotrifluoroethylene (PCTFE) blisters. The capsules of the present invention show excellent stability in *e.g.* the cheaper triplex (polyvinyl chloride (PVC)/polyethylene (PE)/polyvinylidene chloride (PVDC)) blisters. Even after 6 months at 40°C/75% RH in triplex blisters, the dissolution profile of the capsules mimic the profile of the Imnovid® and Pomalyst® capsules. Moreover, the pharmaceutical composition of the present invention is very suitable for production on commercial scale making use of equipment and techniques commonly used in industry.

The pharmaceutical composition of the present invention in the form of a capsule is obtained by a process comprising blending pomalidomide and excipients followed by encapsulation, using equipment and methods well-known in the art.

The pharmaceutical composition in accordance with the present invention may be used as a medicament. The pharmaceutical composition typically may be used in the treatment of multiple myeloma.

The following examples are intended to illustrate the scope of the present invention but not to limit it thereto.

EXAMPLES

Reference example 1: Pharmaceutical composition Imnovid®/Pomalyst®

Imnovid®/Pomalyst® capsules have the composition as given in table 1.

Table 1

Component	**Quantity (mg/capsule)**	**Quantity (mg/capsule)**	**Quantity (mg/capsule)**	**Quantity (mg/capsule)**
Pomalidomide	1.000	2.000	3.000	4.000
Pregelatinized starch	70.00	140.00	100.80	134.40
Sodium stearyl fumarate	0.32	0.64	0.45	0.60
Spray dried mannitol	53.68	107.36	75.75	101.00
Capsule content weight	**125.00**	**250.00**	**180.00**	**240.00**
Capsule size	Size 4	Size 2	Size 2	Size 2

The pomalidomide and mannitol were sieved through a suitable mesh sieve for deagglomeration and mixed in a suitable tumbling mixer. Pregelatinized starch was sieved through a suitable mesh sieve for deagglomeration, added to the blend and mixed in the tumbling mixer. Sodium stearyl fumarate was sieved through a suitable mesh sieve to deagglomerate, added to the blend and mixed in the tumbling mixer. The homogeneous blend was encapsulated using a dosator capsule filling machine. The hard gelatin capsules were packed and stored at 40°C/75% RH.

Example 1: Pharmaceutical composition comprising pomalidomide, microcrystalline cellulose and maltodextrin

The capsules comprising pomalidomide, microcrystalline cellulose and maltodextrin have the composition as given in table 2.

Table 2

Component	**Quantity (mg/capsule)**	**Quantity (mg/capsule)**	**Quantity (mg/capsule)**	**Quantity (mg/capsule)**
Pomalidomide	1.000	2.000	3.000	4.000
Microcrystalline cellulose	26.600	53.200	79.800	106.400
Maltodextrin	19.781	39.563	59.344	79.125
Sodium stearyl fumarate	0.119	0.238	0.356	0.475
Capsule content weight	**47.500**	**95.000**	**142.500**	**190.000**
Capsule size	Size 4	Size 2	Size 2	Size 2

The pomalidomide and microcrystalline cellulose were sieved through a suitable mesh sieve for deagglomeration and mixed in a suitable tumbling mixer. Maltodextrin (Glucidex IT12) was sieved through a suitable mesh sieve for deagglomeration, added to the blend and mixed in the tumbling mixer. Sodium stearyl fumarate was sieved through a suitable mesh sieve to deagglomerate, added to the blend and mixed in the tumbling mixer. The homogeneous blend was encapsulated using a dosator capsule filling machine. The hard gelatin capsules were packed and stored at 40ºC/75% RH.

The capsules obtained exhibited a dissolution rate of at least 65% in 15 minutes and at least 90% in 45 minutes when tested in aqueous hydrochloric acid 0.1 N in a USP apparatus II at 100 rpm, 37ºC. The dissolution profile of the capsules is similar to the profile of Imnovid®/Pomalyst®.

The capsules obtained are bioequivalent to the Imnovid®/Pomalyst® capsules.

Example 2: Pharmaceutical composition comprising pomalidomide, calcium lactate and maltodextrin

The capsules comprising of pomalidomide, calcium lactate and maltodextrin have the composition as given in table 3.

Table 3

Component	**Quantity (mg/capsule)**	**Quantity (mg/capsule)**	**Quantity (mg/capsule)**	**Quantity (mg/capsule)**
Pomalidomide	1.000	2.000	3.000	4.000
Calcium lactate pentahydrate	25.89	51.78	77.66	103.550
Maltodextrin	19.07	38.14	57.21	76.275
Croscarmellose sodium	1.425	2.850	4.275	5.700
Sodium stearyl fumarate	0.119	0.238	0.356	0.475
Capsule content weight	**47.500**	**95.000**	**142.500**	**190.000**
Capsule size	Size 4	Size 2	Size 2	Size 2

The pomalidomide, maltodextrin (Glucidex IT12), calcium lactate pentahydrate and croscarmellose sodium were sieved through a suitable mesh sieve for deagglomeration and mixed in a suitable tumbling mixer. Sodium stearyl fumarate was sieved through a suitable mesh sieve to deagglomerate, added to the blend and mixed in the tumbling mixer. The homogeneous blend was encapsulated using a dosator capsule filling machine. The hard gelatin capsules were packed and stored at 40°C/75% RH.

The capsules obtained exhibited a dissolution rate of at least 65% in 15 minutes and at least 90% in 45 minutes when tested in aqueous hydrochloric acid 0.1 N in a USP apparatus II at 50 rpm, 37°C. The dissolution profile of the capsules is similar to the profile of Imnovid®/Pomalyst®.

Example 4: Stability results

Table 4: Stability results at 40ºC/75% RH for Imnovid®/Pomalyst® capsules composition (4 mg/capsule) prepared according to Reference example 1 in different packaging materials

Packaging material			**PVC/Al blister**				**HDPE bottle/PP cap**		**Al/Al blister**			
Time (months)	0		3		6		6		3		6	
Water content – KF (%)	5.2		7.0		7.3		6.7		5.0		5.7	
Dissolution (%)*	Avg.	RSD	Avg.	RSD	Avg.	RSD	Avg.	RSD	Avg.	RSD	Avg.	RSD
- in 5 min	11	39.8	12	63.1	1	141.4	8	29.2	9	29.8	10	17.6
- in 10 min	51	23.7	44	18.0	8	42.0	37	10.0	49	17.0	47	1.3
- in 15 min	73	12.3	67	12.2	19	27.3	59	12.2	73	5.1	70	0.6
- in 20 min	82	8.8	77	7.0	30	16.1	71	11.4	85	3.7	81	0.5
- in 30 min	90	6.4	86	4.9	42	7.0	81	7.6	91	1.0	90	0.6
- in 45 min	95	5.0	90	4.5	55	8.4	88	5.0	96	0.9	95	0.9
- Final spin 250 rpm – 10 min	98	3.7	96	2.8	86	3.3	93	3.2	99	1.1	98	0.3

*) 0.1 N HCl USP II 50 rpm, 37ºC

Table 5: Stability results at 40ºC/75% RH for capsules (4 mg/capsule) prepared according to example 1 (comprising pomalidomide, microcrystalline cellulose and maltodextrin) in different packaging materials

Packaging material			**PVC/Al blister**				**HDPE bottle/PP cap**		**Al/Al blister**			
Time (months)	0		3		6		6		3		6	
Water content – KF (%)	6.3		8.2		N.P.		6.7		5.8		5.8	
Dissolution (%)*	Avg.	RSD	Avg.	RSD	Avg.	RSD	Avg.	RSD	Avg.	RSD	Avg.	RSD
- in 5 min	51	6.1	40	11.5	34	19.4	38	5.8	49	6.8	40	2.4
- in 10 min	76	2.5	64	1.2	56	17.6	67	4.5	71	2.7	68	1.7
- in 15 min	84	2.9	73	1.6	65	16.1	77	4.0	79	3.1	78	3.0
- in 20 min	89	2.3	78	1.4	69	15.8	84	4.2	84	2.7	84	3.7
- in 30 min	93	2.9	83	1.5	73	15.1	89	4.2	89	2.9	89	4.1
- in 45 min	96	2.4	86	0.6	76	15.0	93	5.0	92	3.3	93	4.6
- Final spin 250 rpm – 10 min	98	2.7	90	1.3	81	14.8	95	4.8	94	3.6	94	5.0

*) 0.1 N HCl USP II 100 rpm, 37ºC

Table 6: Stability results at 40ºC/75% RH for capsules (4 mg/capsule) prepared according to example 1 (comprising pomalidomide, microcrystalline cellulose and maltodextrin) in different packaging materials

Packaging material			**Triplex 120/Al blister**				**HDPE bottle/PP cap**			
Time (months)	0		3		6		3		6	
Water content – KF (%)	5.4		7.2		8.0		6.2		6.8	
Dissolution (%)*	Avg.	RSD	Avg.	RSD	Avg.	RSD	Avg.	RSD	Avg.	RSD
- in 5 min	52	3.2	47	3.6	39	5.1	48	4.3	41	6.8
- in 10 min	76	1.3	71	5.1	63	3.2	72	3.9	68	1.0
- in 15 min	84	1.6	79	5.3	74	2.5	81	2.9	78	0.8
- in 20 min	89	1.6	85	5.1	80	1.8	86	2.1	84	1.1
- in 30 min	94	1.6	90	4.5	87	1.5	92	1.2	90	1.0
- in 45 min	98	1.9	93	3.9	92	0.8	95	0.8	95	1.0
- Final spin 250 rpm – 10 min	101	2.3	96	3.2	95	0.9	98	0.9	97	0.7

*) 0.1 N HCl USP II 100 rpm, 37ºC

CLAIMS

1. A pharmaceutical composition comprising pomalidomide, maltodextrin and a filler, wherein the weight ratio of maltodextrin to filler ranges from 1:1 to 1:2.
2. The composition according to claim 1, wherein the maltodextrin has a dextrose equivalent (DE) of 11 to 14.
3. The composition according to claim 1 or 2, wherein the filler is selected from microcrystalline cellulose and calcium lactate.
4. The composition according to claim 3, wherein the filler is microcrystalline cellulose.
5. The composition according to any one of claims 1 to 4, wherein pomalidomide is present in an amount of more than 2% by weight based on the total weight of the composition.
6. The composition according to any one of claims 1 to 5, wherein the pomalidomide has a particle size distribution D_{90} equal to or less than 15 μm.
7. The composition according to any one of claims 1 to 6 further comprising a lubricant and optionally a disintegrant.
8. The composition according to any one of claims 1 to 7, wherein the lubricant is sodium stearyl fumarate.
9. The composition according to any one of claims 1 to 8, wherein the disintegrant is croscarmellose sodium.
10. The composition according to any one of claims 1 to 9 exhibiting a dissolution rate of at least 65% in 15 minutes and at least 90% in 45 minutes when tested in aqueous hydrochloric acid 0.1 N in a USP apparatus II at 50-100 rpm, 37ºC.
11. The composition according to any one of claims 1 to 10, wherein the composition is in the form of a capsule.

12. A process to prepare the composition according to claim 11 comprising blending pomalidomide and excipients followed by encapsulation.

13. The composition according to any one of claims 1 to 11 for use in the treatment of multiple myeloma.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2017/069242

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/48 A61K31/454
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

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 2010/135396 A2 (CELGENE CORP [US]; TUTINO ANTHONY [US]; KELLY MICHAEL T [US]) 25 November 2010 (2010-11-25) cited in the application examples 1-2	1-13
X	US 2016/039785 A1 (STAHLY G PATRICK [US] ET AL) 11 February 2016 (2016-02-11) paragraph [0267] - paragraph [0272]; example 1	1-13

☐ Further documents are listed in the continuation of Box C.

☒ 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 application or patent 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
18 October 2017	26/10/2017

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	Frelichowska, J

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2017/069242

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2010135396 A2	25-11-2010	AU 2010249615 A1	08-09-2011
		BR PI1007855 A2	23-02-2016
		CA 2752550 A1	25-11-2010
		CN 102333525 A	25-01-2012
		CN 105640918 A	08-06-2016
		CN 106176662 A	07-12-2016
		CO 6430422 A2	30-04-2012
		CR 20110435 A	06-01-2012
		CY 1118632 T1	12-07-2017
		DK 2391355 T3	27-02-2017
		EC SP11011317 A	31-10-2011
		EP 2391355 A2	07-12-2011
		EP 3199149 A1	02-08-2017
		ES 2615511 T3	07-06-2017
		HR P20170179 T1	07-04-2017
		IL 214644 A	29-10-2015
		JP 5752677 B2	22-07-2015
		JP 2012526855 A	01-11-2012
		KR 20120014114 A	16-02-2012
		LT 2391355 T	10-03-2017
		MX 342330 B	26-09-2016
		NZ 594557 A	26-07-2013
		PE 06542012 A1	31-05-2012
		PH 12015501523 A1	21-09-2015
		PL 2391355 T3	31-05-2017
		PT 2391355 T	21-02-2017
		RU 2011134499 A	27-02-2013
		SG 174137 A1	28-10-2011
		SM T201700097 B	08-03-2017
		UA 102582 C2	25-07-2013
		US 2011045064 A1	24-02-2011
		US 2014336223 A1	13-11-2014
		US 2016206607 A1	21-07-2016
		WO 2010135396 A2	25-11-2010
		ZA 201105962 B	28-11-2012
US 2016039785 A1	11-02-2016	US 2016039785 A1	11-02-2016
		US 2017258778 A1	14-09-2017
		WO 2014160690 A1	02-10-2014