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(54) Title: STABILIZED PHARMACEUTICAL FORMULATION COMPRISING EVEROLIMUS

(57) Abstract: The present invention relates to a stabilized pharmaceutical formulation comprising everolimus. Specifically, the present invention relates to a pharmaceutical formulation comprising granules comprising everolimus as an active ingredient and butylhydroxytoluene as an antioxidant. Further, the present invention relates to a method for preparing a pharmaceutical formulation comprising everolimus as an active ingredient and butylhydroxytoluene as an antioxidant, comprising the steps of: dissolving everolimus, butylhydroxytoluene and binder(s), and preparing a mixture; preparing granules from the mixture; and adding a lubricant into the granules to prepare a granule mixture.

Description

Title of Invention: STABILIZED PHARMACEUTICAL FORMULATION COMPRISING EVEROLIMUS

Technical Field

[1] The present invention relates to a stabilized pharmaceutical formulation comprising everolimus. Specifically, the present invention relates to a pharmaceutical formulation comprising granules comprising everolimus as an active ingredient and butylhydroxytoluene as an antioxidant.

Background Art

[2] Immunosuppressants are pharmaceutical compounds that reduce the activity of the immune system. They are commonly used in the therapy of autoimmune diseases. It is autoimmune diseases which are believed to involve some types of hypersensitivity of the immune system, which is, for example, known for Crohn's disease, multiple sclerosis, rheumatoid arthritis, ulcerative colitis, Addison's disease, and numerous other diseases. The immunosuppressants are also used for the prevention and treatment of organ transplant rejection due to differences in human leukocyte antigen haplotypes between the donor and recipient after an organ transplantation.

[3] The immunosuppressants that have been developed for therapeutic use may be classified according to their chemical structure and their mechanism of action. Immunosuppressive compounds comprise pimecrolimus, sirolimus, deforolimus, temsirolimus, and zotarolimus.

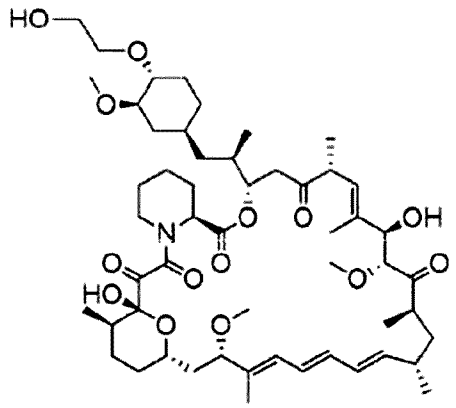
[4] Everolimus is a derivative of sirolimus wherein a hydroxyethyl group is added to the 40-O group of sirolimus, and is marketed by Novartis under the trade names of Zortress® in the US and Certican® in Republic of Korea and Europe for preventing organ transplant rejection. In addition to the use as an immunosuppressant, this drug inhibits mTOR pathway to inhibit the expression of vascular endothelial growth factor (VEGF), thereby exhibiting an anticancer activity. Thus, it is recently being marketed under the trade name of Afinitor® for the purpose of treating advanced renal cell carcinoma after failure of VEGF-targeted therapy with sunitinib or sorafenib. Many clinical trials have also been under way on breast cancer, gastric cancer, liver cancer, pancreatic cancer, and the like.

[5] Everolimus is defined as dihydroxy-12-{(2R)-1-[(1S,3R,4R)-4-(2-hydroxyethoxy)-3-methoxycyclohexyl]propan-2-yl}-19,30-dimethoxy-15,17,21,23,29,35-hexamethyl-11,36-dioxa-4-azatricyclo[30.3.1.0(4,9)]hexatriaconta-16,24,26,28-tetraene-2,3,10,14,20-pentone having Formula I below:

[6]

[7] [Formula I]

[8]



[9] A method for preparing everolimus is disclosed in US 5,665,772. US 5,665,772 specifies a rapamycin compound and derivatives derived therefrom and discloses a step and method for synthesizing everolimus.

[10] More details on the method for synthesizing everolimus and the yield as disclosed in US 5,665,772 are described in WO 2012/066502.

[11] When orally administered to human, solid sirolimus derivatives such as everolimus has very low water solubility and high molecular weight such that they have difficulties in permeating membranes of the gastrointestinal tract. Further, it is not easy that they are absorbed into the blood stream in an effective amount, since they serve as a substrate of the efflux pump such as P-glycoprotein. Sirolimus derivatives such as everolimus are thus known as having drawbacks including unpredictable dissolution rate, non-uniform bioavailability, and instability.

[12] Korean Patent No. 0695834 discloses a pharmaceutical composition having improved stability by preparing a mixture of a sirolimus derivative that is sensitive to an oxidation reaction, and an antioxidant. The Korean patent states that the stability can be improved by preparing a mixed precipitate of a sirolimus derivative with an antioxidant. However, it is disadvantageous in that complicated procedures should be involved in an actual manufacturing process.

[13] An issue of reduced stability exists in a formulation comprising everolimus as an active ingredient that is sensitive to oxidation, which should be considered in doing research on a formulation.

[14] We have thus developed a pharmaceutical formulation comprising everolimus as an active ingredient and having pharmaceutically improved properties.

Disclosure of Invention

Technical Problem

[15] The present invention is to provide a pharmaceutical formulation comprising

everolimus as an active ingredient and having pharmaceutically improved properties. Specifically, while screening an antioxidant exerting improved antioxidant effect in a pharmaceutical formulation comprising everolimus as an active ingredient, it has surprisingly been found that butylhydroxytoluene exhibits superior antioxidant effect, based on which the present invention has been achieved.

[16] Further, we found that a formulation having more improved stability can be provided when preparing granules comprising everolimus as an active ingredient and butylhydroxytoluene as an antioxidant wherein each ingredient is comprised in a specific weight ratio in the granules.

Solution to Problem

[17] The present invention provides granules comprising everolimus as an active ingredient and butylhydroxytoluene as an antioxidant. The granules may be prepared by wet granulation, dry granulation, and the like. Preferably, they are prepared by wet granulation.

[18] When preparing a formulation by using wet granulation, any known process in the art can be used for the wet granulation in view of the purpose of the present invention.

[19] The granules may comprise, based on the total weight of the granules, preferably, 0.5 to 20 wt% of everolimus, more preferably, 1 to 10 wt% of everolimus.

[20] Further, the granules may comprise, based on the total weight of the granules, preferably, 0.05 to 10 wt% of butylhydroxytoluene as an antioxidant, more preferably, 0.1 to 5 wt%.

[21] In addition, the granules may further comprise a binder, a disintegrating agent, and other excipients. Preferably, the granules may further comprise hypromellose as a binder.

[22] Moreover, the pharmaceutical formulation according to the present invention may be prepared by (i) a step of dissolving everolimus, butylhydroxytoluene and binder(s), and preparing a mixture; (ii) a step of preparing granules from the mixture; and (iii) a step of adding a lubricant into the granules to prepare a granule mixture.

[23] Further, the final granule mixture may be tableted by using a tableting machine to provide a stable tablet comprising everolimus as an active ingredient and butylhydroxytoluene as an antioxidant.

[24] The pharmaceutical formulation according to the present invention may further comprise a lubricant. The lubricant may be, but is not limited to, at least one selected from the group consisting of glyceryl behenate, magnesium stearate, sodium stearyl fumarate, and colloidal silicon dioxide. Most preferably, the lubricant of the present invention may be glyceryl behenate.

Advantageous Effects of Invention

[25] The present invention, which is directed to a pharmaceutical formulation comprising everolimus as an active ingredient, exerts superior stability and has simple manufacturing process, whereby mass production is allowed.

Mode for the Invention

[26] The present invention provides a pharmaceutical formulation comprising granules comprising everolimus as an active ingredient and butylhydroxytoluene as an antioxidant.

[27] Specifically, the granules have more improved stability when comprising 0.5 to 20 wt% of everolimus and 0.05 to 10 wt% of butylhydroxytoluene based on the total weight of the granules.

[28] More specifically, the granules have most improved stability when comprising 1 to 10 wt% of everolimus and 0.1 to 5 wt% of butylhydroxytoluene based on the total weight of the granules.

[29] The granules may be prepared by a conventional method for preparing a granule comprising dry granulation or wet granulation. Preferably, they may be prepared by wet granulation.

[30] The granules according to the present invention may further comprise a binder. The term "binder" as used herein refers to a substance to provide elasticity and adhesion so that a hardness of a formulation as formed, especially, a hardness of a tablet as formed, is increased. The binder according to the present invention may be a binder conventionally used, preferably, hypromellose.

[31] The pharmaceutical formulation according to the present invention may further comprise a lubricant. The term "lubricant" as used herein refers to a substance with which improved flowability is provided to a formulation. The lubricant may be, but is not limited to, at least one selected from the group consisting of glyceryl behenate, magnesium stearate, sodium stearyl fumarate, and colloidal silicon dioxide. Preferably, glyceryl behenate may be used as a lubricant.

[32] The pharmaceutical formulation according to the present invention may further comprise a diluent. The term "diluent" as used herein refers to an inactive substance used as a filter to provide a desired bulk, flowability, and compressibility when preparing a solid dosage form. For example, the diluent may be, but is not limited to, lactose hydrate, anhydrous lactose, sucrose, corn starch, or dibasic calcium phosphate in the form of an anhydride or a hydrate.

[33] The pharmaceutical formulation according to the present invention may further comprise a disintegrating agent. The term "disintegrating agent" as used herein refers to a substance used to accelerate the disintegration of a solid form so that an active ingredient exerting the medicinal effect is released from the form within a short time. For

example, the disintegrating agent may be, but is not limited to, carboxymethyl cellulose calcium (CMC-Ca), Crospovidone, sodium starch glycolate, croscarmellose sodium, or low-substituted hydroxypropyl cellulose.

[34] The pharmaceutical formulation of the present invention may be formulated in an oral dosage form. The oral dosage form may be, but is not limited to, a tablet.

[35] The pharmaceutical formulation of the present invention may be used for the prevention or treatment of organ transplant rejection.

[36] The present invention provides a method for preparing a pharmaceutical formulation comprising everolimus as an active ingredient and butylhydroxytoluene as an antioxidant, comprising the steps of: dissolving everolimus, butylhydroxytoluene and binder(s), and preparing a mixture; preparing first granules from the mixture; and adding a lubricant into the granules to prepare a granule mixture.

[37] Hereinafter, the present invention will be explained in more details through the working examples. However, the examples are merely provided only for a better understanding of the present invention, but are not to be construed as the limitation of the claimed scope.

[38] **A method for preparing a tablet comprising everolimus**

[39] Hypromellose, butylhydroxytoluene, and everolimus were added into an organic solvent to obtain a binding solution. The binding solution was added into a mixture of lactose hydrate, Crospovidone, and hypromellose, followed by granulating, drying, and sieving by a sieving machine. The granules after sieving were mixed with lactose hydrate, anhydrous lactose, and Crospovidone, followed by adding glyceryl behenate and finally mixing to prepare a granule mixture of everolimus. The final mixture was tableted by a tableting machine to prepare a tablet. The prepared tablet comprises 1.0 mg of everolimus.

[40]

[41] **[Examples 1 to 5]**

[42] The tablets of Examples 1 to 5 were prepared according to the preparation method above, provided that the weight percent (wt%) of everolimus and butylhydroxytoluene based on the total weight of the intra-part (granules) is different in each example in accordance with Table 1 below.

[43] [Table 1]

	Example	1	2	3	4	5
Intra-part (granules)	Everolimus (mg)	1.00	1.00	1.00	1.00	1.00
	wt% of everolimus based on the total weight of the intra-part	8.2	5.0	2.7	1.1	1.1
	Hypromellose (mg)	4.00	4.00	15.00	20.00	50.00
	Lactose hydrate (mg)	1.00	9.00	15.00	64.80	34.80
	Crospovidone (mg)	6.00	6.00	6.00	6.00	6.00
	Butylhydroxytoluene (mg)	0.20	0.20	0.20	0.20	0.20
	wt% of butylhydroxytoluene based on the total weight of the intra-part	1.6	1.0	0.5	0.2	0.2
	Total weight of the intra-part (mg)	12.2	20.2	37.2	92.0	92.0
Extra-part	Crospovidone (mg)	6.00	6.00	6.00	6.00	6.00
	Lactose hydrate (mg)	63.80	55.80	37.80	-	-
	Anhydrous lactose (mg)	112.00	112.00	113.00	96.00	96.00
	Glyceryl behenate (mg)	6.00	6.00	6.00	6.00	6.00
	Total weight of the extra-part (mg)	187.8	179.8	162.8	113.0	112.0
	Total weight of the intra- and extra-parts (mg)	200.0	200.0	200.0	200.0	200.0

[44]

[45] **[Test Example 1]**

[46] **Impurity test of Examples 1 to 5**

[47] The stability was evaluated through the impurity test on the tablets of Examples 1 to 5 using the impurity test condition below. Each formulation was stored at a stress condition (60℃ of temperature) for four weeks to evaluate the amount of impurities by liquid chromatography.

[48]

[49] <Test Method >

[50] 1) Detector: UV spectrophotometer (measurement wavelength: 276 nm)

[51] 2) Column : Zorbax SB-C18 4.6 x 250 mm, 5 ㎛

[52] 3) Injection amount: 50 μL

[53] 4) Flow rate: 2.0 mL/min

[54] 5) Column temperature: Constant temperature near 55°C

[55] 6) Sample temperature: Constant temperature near 4°C

[56] 7) Analysis time: 60 minutes

[57] 8) Mobile phase:

[58] Mobile phase A - Water, acetonitrile, and methanol (30 : 20 : 50)

[59] Mobile phase B - Acetonitrile

[60]

Time (minutes)	Mobile phase A	Mobile phase B
0	100	0
38	100	0
50	30	70
55	100	0
60	100	0

[61]

[62] The impurity test results of Examples 1 to 5 are shown in Table 2 below.

[63]

[64] [Table 2]

The impurity test results of Examples 1 to 5

Total impurities (%)	Example 1	Example 2	Example 3	Example 4	Example 5
2-weeks at a stress condition	2.05	0.56	0.45	1.76	2.20
4-weeks at a stress condition	2.16	0.87	0.93	2.48	2.71

[65] As shown in Table 2, the total amount of impurities in Examples 2 and 3 was no more than 1%, from which high stability was confirmed. It was confirmed that the total amount of impurities in Examples 1, 4, and 5 are two or three times more than in Examples 2 and 3.

[66]

[67] **[Test Example 2]**

[68] **Stability test according to the type of lubricant**

[69] A lubricant refers to a substance with which improved flowability is provided to a formulation. In this test, the stability of a formulation according to the type of lubricant was evaluated where the lubricant is glyceryl behenate, magnesium stearate, sodium stearyl fumarate, or colloidal silicon dioxide.

[70] The tablets of Examples 6 to 8 were prepared in the same manner as Examples 1 to 5,

provided that the composition is in accordance with Table 3 below.

[71]

[72] [Table 3]

	Example	3	6	7	8
Intra-part (granules)	Everolimus (mg)	1.00	1.00	1.00	1.00
	Hypromellose (mg)	15.00	15.00	15.00	15.00
	Lactose hydrate (mg)	15.00	15.00	15.00	15.00
	Crospovidone (mg)	6.00	6.00	6.00	6.00
	Butylhydroxytoluene (mg)	0.20	0.20	0.20	0.20
Extra-part	Anhydrous lactose (mg)	113.00	113.00	113.00	113.00
	Lactose hydrate (mg)	37.80	37.80	37.80	37.80
	Crospovidone (mg)	6.00	6.00	6.00	6.00
	Glyceryl behenate (mg)	6.00	-	-	-
	Magnesium stearate (mg)	-	6.00	-	-
	Sodium stearyl fumarate (mg)	-	-	6.00	-
	Colloidal silicon dioxide (mg)	-	-	-	6.00

[73] The formulations of Examples 3 and 6 to 8 were stored at a stress condition (60℃ of temperature) for four weeks to evaluate the amount of impurities by liquid chromatography using the test method below.

[74]

[75] <Test Method >

[76] 1) Detector: UV spectrophotometer (measurement wavelength: 276 nm)

[77] 2) Column : Zorbax SB-C18 4.6 x 250 mm, 5 ㎛

[78] 3) Injection amount: 50 μL

[79] 4) Flow rate: 2.0 mL/min

[80] 5) Column temperature: Constant temperature near 55℃

[81] 6) Sample temperature: Constant temperature near 4℃

[82] 7) Analysis time: 60 minutes

[83] 8) Mobile phase:

[84] Mobile phase A - Water, acetonitrile, and methanol (30 : 20 : 50)

[85] Mobile phase B - Acetonitrile

[86]

[87]

Time (minutes)	Mobile phase A	Mobile phase B
0	100	0
38	100	0
50	30	70
55	100	0
60	100	0

[88]

[89] The impurity test results of Examples 3 and 6 to 8 according to the type of lubricant are shown in Table 4 below.

[90] [Table 4]

The impurity test results of Examples 3 and 6 to 8

Total impurities (%)	Example 3	Example 6	Example 7	Example 8
2-weeks at a stress condition	0.45	3.91	1.15	1.24
4-weeks at a stress condition	0.93	7.12	3.01	3.12

[91] As shown in Table 4 above, it was confirmed that Example 3 had the most superior stability. The amount of impurities produced in Examples 7 and 8 are two times more than in Example 3, while that in Example 6 are seven times more than in Example 3.

[92] As a result, it was confirmed that the weight percent of everolimus and the antioxidant in the intra-part (granules), and the type of lubricant have an important effect on the stability of a formulation comprising everolimus.

Claims

[Claim 1] A pharmaceutical formulation comprising granules comprising everolimus as an active ingredient and butylhydroxytoluene as an antioxidant.

[Claim 2] The pharmaceutical formulation according to Claim 1, characterized in that the granules comprise 0.5 to 20 wt% of everolimus and 0.05 to 10 wt% of butylhydroxytoluene based on the total weight of the granules.

[Claim 3] The pharmaceutical formulation according to Claim 2, characterized in that the granules comprise 1 to 10 wt% of everolimus and 0.1 to 5 wt% of butylhydroxytoluene based on the total weight of the granules.

[Claim 4] The pharmaceutical formulation according to Claim 1, characterized in that the granules are prepared by wet granulation.

[Claim 5] The pharmaceutical formulation according to Claim 1, characterized in that the granules further comprise hypromellose as a binder.

[Claim 6] The pharmaceutical formulation according to Claim 1, characterized in that the formulation further comprises a lubricant.

[Claim 7] The pharmaceutical formulation according to Claim 6, characterized in that the lubricant is at least one selected from the group consisting of glyceryl behenate, magnesium stearate, sodium stearyl fumarate, and colloidal silicon dioxide.

[Claim 8] The pharmaceutical formulation according to Claim 7, characterized in that the lubricant is glyceryl behenate.

[Claim 9] The pharmaceutical formulation according to Claim 1, characterized in that the formulation is formulated in an oral dosage form.

[Claim 10] The pharmaceutical formulation according to Claim 9, characterized in that the oral dosage form is a tablet.

[Claim 11] The pharmaceutical formulation according to Claim 1, characterized in that the formulation is for the prevention or treatment of organ transplant rejection.

[Claim 12] A method for preparing a pharmaceutical formulation comprising everolimus as an active ingredient and butylhydroxytoluene as an antioxidant, comprising the steps of:
dissolving everolimus, butylhydroxytoluene and binder(s), and preparing a mixture;
preparing granules from the mixture; and
adding a lubricant into the granules to prepare a granule mixture.

[Claim 13] The method for preparing a pharmaceutical formulation according to

Claim 12, characterized in that the binder is hypromellose and the lubricant is glyceryl behenate.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR2019/000204

A. CLASSIFICATION OF SUBJECT MATTER

A61K 9/20(2006.01)i, A61K 31/436(2006.01)i, A61K 9/00(2006.01)i

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 9/20; A61K 31/436; A61K 31/4745; A61K 51/02; A61K 51/04; A61K 9/16; A61K 9/28; A61K 9/50; A61P 25/28; A61K 9/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Korean utility models and applications for utility models
Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
eKOMPASS(KIPO internal) & keywords: everolimus, butylhydroxytoluene, antioxidant, wet granulation, binder, lubricant, organ transplant rejection

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2016-0045441 A1 (DIEDERICH, A. et al.) 18 February 2016 See example 17; paragraphs [0002], [0003], [0028], [0041], [0051], [0102], [0103]; and claim 1.	1-13
X	KR 10-2014-0058670 A (NOVARTIS AG) 14 May 2014 See paragraphs [0078], [0079]; and claims 1, 10-16, 20-26, 32.	1-13
X	WO 2008-016633 A2 (ARIAD GENE THERAPEUTICS, INC.) 7 February 2008 See example 5; paragraphs [0024], [0051]; and claims 1, 5.	1-11
X	KR 10-2014-0032586 A (KOREA INSTITUTE OF RADIOLOGICAL & MEDICAL SCIENCES) 17 March 2014 See paragraphs [0006], [0024], [0030]; and claims 1, 3, 6, 7.	1-11
A	WO 2010-056754 A2 (THE BOARD REGENTS OF THE UNIVERSITY OF TEXAS SYSTEM) 20 May 2010 See the whole document.	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
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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 April 2019 (10.04.2019)	**10 April 2019 (10.04.2019)**

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/KR2019/000204

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2016-0045441 A1	18/02/2016	AR 095672 A1	04/11/2015
		AU 2014-233799 A1	10/09/2015
		BR 112015021112 A2	18/07/2017
		CA 2907500 A1	25/09/2014
		CN 105307640 A	03/02/2016
		EA 201591830 A1	29/02/2016
		EP 2976064 A1	27/01/2016
		EP 2976064 B1	19/04/2017
		ES 2633496 T3	21/09/2017
		HK 1212899 A1	24/06/2016
		IL 241254 A	30/11/2015
		JP 2016-515543 A	30/05/2016
		JP 6356215 B2	11/07/2018
		KR 10-2015-0132399 A	25/11/2015
		MA 38430 A1	31/03/2017
		MX 2015013403 A	08/01/2016
		PE 18102015 A1	04/12/2015
		PH 12015501982 A1	18/01/2016
		SG 11201506466 A	29/10/2015
		TN 2015000394 A1	03/01/2017
		TW 201503912 A	01/02/2015
		US 2018-0161280 A1	14/06/2018
		WO 2014-147567 A1	25/09/2014
KR 10-2014-0058670 A	14/05/2014	AR 088232 A1	21/05/2014
		AU 2012-320563 A1	24/04/2014
		AU 2012-320563 B2	12/05/2016
		BR 112014007902 A2	18/04/2017
		CA 2850995 A1	11/04/2013
		CL 2014000844 A1	12/09/2014
		CN 103874484 A	18/06/2014
		CN 103874484 B	21/09/2016
		CO 6930364 A2	28/04/2014
		EA 025595 B1	30/01/2017
		EA 201490743 A1	30/07/2014
		EP 2763663 A1	13/08/2014
		EP 2763663 B1	27/12/2017
		ES 2663744 T3	16/04/2018
		GT 201400062 A	02/06/2015
		IL 231648 A	28/05/2014
		JP 2014-528431 A	27/10/2014
		JP 6368242 B2	01/08/2018
		KR 10-1643219 B1	27/07/2016
		MA 35513 B1	02/10/2014
		MX 2014004166 A	15/01/2015
		PE 16492014 A1	14/11/2014
		SG 11201400730 A	27/06/2014
		TN 2014000114 A1	01/07/2015
		TW 201318625 A	16/05/2013

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/KR2019/000204

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
		TW I475993 B	11/03/2015
		US 2014-0242162 A1	28/08/2014
		US 2017-0049754 A1	23/02/2017
		US 2018-0214424 A1	02/08/2018
		WO 2013-050419 A1	11/04/2013
		ZA 201401961 B	25/11/2015
WO 2008-016633 A2	07/02/2008	EP 2054061 A2	06/05/2009
		US 2010-0266590 A1	21/10/2010
		WO 2008-016633 A3	26/06/2008
KR 10-2014-0032586 A	17/03/2014	None	
WO 2010-056754 A2	20/05/2010	AU 2014-373683 A1	30/06/2016
		CA 2743491 A1	20/05/2010
		CA 2743491 C	11/10/2016
		CA 2933908 A1	09/07/2015
		CA 2937492 A1	20/05/2010
		CA 2968049 A1	22/10/2015
		CN 102292078 A	21/12/2011
		CN 104042612 A	17/09/2014
		DK 2365802 T3	13/11/2017
		EP 2365802 A2	21/09/2011
		EP 2365802 B1	02/08/2017
		EP 3089737 A1	09/11/2016
		EP 3089737 A4	06/09/2017
		EP 3131546 A1	22/02/2017
		EP 3131546 A4	27/12/2017
		ES 2645692 T3	07/12/2017
		HK 1202076 A1	18/09/2015
		PT 2365802 T	14/11/2017
		US 2012-0064143 A1	15/03/2012
		US 2015-0202164 A1	23/07/2015
		US 2016-0324782 A1	10/11/2016
		US 2017-0079962 A1	23/03/2017
		US 9283211 B1	15/03/2016
		US 9700544 B2	11/07/2017
		WO 2010-056754 A3	19/08/2010
		WO 2015-103447 A1	09/07/2015
		WO 2015-161139 A1	22/10/2015