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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
07 December 2017 (07.12.2017)

WIPO | PCT

(10) International Publication Number
WO 2017/208105 A1

(51) International Patent Classification:
C07D 498/14 (2006.01)

(21) International Application Number:
PCT/IB2017/052926

(22) International Filing Date:
18 May 2017 (18.05.2017)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
201621018583 30 May 2016 (30.05.2016) IN

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(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, 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 2017/208105 A1

(54) Title: NOVEL CRYSTALLINE FORM OF DOLUTEGRAVIR SODIUM

(57) Abstract: The present invention provides novel crystalline form A of dolutegravir sodium with characteristic diffraction peaks at 6.3, 7.8, 9.3, 11.4, 12.4, 13.5, 12.7, 15.1, 15.8, 18.3, 19.0, 19.6, 20.7, 22.8, 23.1, 24.3 and 25.8 ± 0.2 degree two theta in an X-ray diffraction pattern. The present invention further provides process for preparation of crystalline form A of dolutegravir sodium.

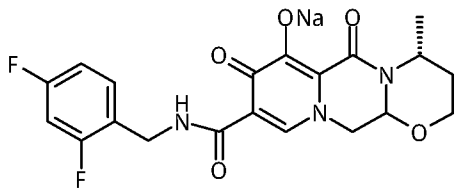
NOVEL CRYSTALLINE FORM OF DOLUTEGRAVIR SODIUM

FIELD OF INVENTION

The present invention provides novel crystalline form A of Dolutegravir sodium and process for preparation thereof.

BACKGROUND OF THE INVENTION

Dolutegravir is an integrase inhibitor. It is used against HIV infections as a single drug or fixed-dose combination with abacavir sulphate and lamivudine under the trade names Tivicay÷ and Triumeq÷ respectively. These commercial products contain dolutegravir as its sodium salt. It is chemically known as sodium (4R,12aS)-9-{[(2,4-difluorophenyl)methyl]carbamoyl}-4-methyl-6,8-dioxo-3,4,6,8,12,12a-hexahydro-2H-pyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazin-7-olate (I) having following chemical structure.



(I)

Dolutegravir sodium is disclosed in the patent US 8129385 and the patent US 9242986 mentions crystal form of a sodium salt of dolutegravir and crystal form of a hydrate of sodium salt of dolutegravir.

Another patent US 9206197 mentions amorphous form of dolutegravir sodium and process for its preparation. The applications WO 2015118460 and WO 2015139591 provide various crystalline forms of dolutegravir sodium. The applications WO 2015138933 and WO 2015092752 provide various crystalline forms of dolutegravir sodium solvates and WO 2016016279 mentions hydrates of dolutegravir sodium.

The present invention provides novel crystalline form of dolutegravir sodium, designated as Form A and process for preparation thereof.

DESCRIPTION OF DRAWING

Figure 1 ¯ X-ray powder diffraction pattern of crystalline Form A of dolutegravir sodium.
Figure 2 ¯ Infrared absorption spectrum of crystalline Form A of dolutegravir sodium.
Figure 3- DSC thermogram of crystalline Form A of dolutegravir sodium.

SUMMARY OF THE INVENTION

The present invention provides novel crystalline form A of dolutegravir sodium with characteristic diffraction peaks at 6.3é, 7.8é, 9.3é, 11.4é, 12.4é, 13.5é, 12.7é, 15.1é, 15.8é, 18.3é, 19.0é, 19.6é, 20.7é, 22.8é, 23.1é, 24.3é and 25.8é ě 0.2 degree two theta in an X-ray diffraction pattern.

The present invention further provides process for preparation of crystalline form A of dolutegravir sodium.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to novel crystalline form A of dolutegravir sodium and processes for its preparation.

In one embodiment, the present invention provides crystalline form A of dolutegravir sodium.

The crystalline form A of dolutegravir sodium having characteristic diffraction peaks at 6.3é, 7.8é, 9.3é, 11.4é, 12.4é, 13.5é, 12.7é, 15.1é, 15.8é, 18.3é, 19.0é, 19.6é, 20.7é, 22.8é, 23.1é, 24.3é and 25.8é ě 0.2 degree two theta in an X-ray diffraction pattern.

The crystalline form A of dolutegravir sodium of the present invention is characterized by X-ray powder diffraction pattern as depicted in Figure 1.

The crystalline form A of dolutegravir sodium having characteristic infrared absorption at 3431ě 2 cm^{-1}, 1643ě 2 cm^{-1}, 1538ě 2 cm^{-1}, 1504ě 2 cm^{-1}, 1424ě 2 cm^{-1}, 1320ě 2 cm^{-1}, 1278ě 2 cm^{-1}, 1096ě 2 cm^{-1}, 964 ě 2 cm^{-1}.

The crystalline form A of dolutegravir sodium is characterized by infrared absorption spectrum as depicted in Figure 2.

The crystalline form A of dolutegravir sodium is characterized by Differential Scanning Calorimetry (DSC) thermogram as depicted in Figure 3.

The present invention provides crystalline form A of dolutegravir sodium comprising:

i) X-ray powder diffraction pattern as depicted in Figure 1,
ii) Infrared absorption spectrum as depicted in Figure 2, and
iii) DSC thermogram as depicted in Figure 3.

In another embodiment, the present invention provides a process for the preparation of crystalline form A of dolutegravir sodium comprising the steps of:

a) dissolving dolutegravir sodium in a first solvent;
b) adding the solution of step (a) to a pre cooled solution of second solvent; and
c) isolating form A of dolutegravir sodium.

The first solvent and second solvent can be selected from polar solvent, non-polar solvents or mixtures thereof. Polar solvent can be selected from alcohols like methanol, ethanol, butanol, propanol; nitriles like acetonitrile, propionitrile, butyronitrile; ethers like tetrahydrofuran, dioxane, dimethoxyethane; esters like ethyl acetate, ethyl acetoacetate, butyl acetate, propyl acetate; ketones like acetone, methyl ethyl ketone, methyl isobutyl ketone; other polar solvents like dimethylformamide, dimethyl sulfoxide, water and

mixtures thereof. Non-polar solvents can be selected from hydrocarbon like hexane, cyclohexane, n-heptane, pentane, cyclopentane, toluene; chlorinated hydrocarbon solvent like methylene chloride, ethylene chloride, chloroform, carbon tetrachloride and mixtures thereof. The first solvent is preferably dimethyl sulfoxide and second solvent is preferably methanol.

In step (b) the second solvent can be pre cooled to a temperature of less than 30éC, preferably less than 20éC, more preferably less than 10éC.

In step (c) form A of dolutegravir sodium can be isolated by techniques known in art like filtration, concentration, evaporation of solvents etc.

The form A of dolutegravir sodium of the present invention was found to be stable at 40éC/ 75% RH; 25éC/ 60% RH and 5éC. The total impurity content in form A of dolutegravir sodium was found to be not more than 0.1% by HPLC, in stability.

Dolutegravir sodium which is used for preparation of form A of dolutegravir sodium can be prepared by methods as described in application WO 2010068253 or by preparations known in the literature.

The X-ray powder diffraction pattern was recorded at room temperature using PANalytical X¯Pert PRO diffractogram with Cu K radiation (≅ = 1.54060 ¡), running at 45 kV and 40 mA.

The infrared absorption spectrum was obtained using a Perkin Elmer Precisely Spectrum 400 instrument using KBr pellet method.

The present invention is further illustrated by the following representative examples and does not limit the scope of the invention.

EXAMPLES

Example 1: Preparation of crystalline form A of dolutegravir sodium:

A mixture of dolutegravir sodium (1 g) and dimethyl sulfoxide (250 ml) was heated at 130éC. The solution was cooled to 25-30éC. This solution was added dropwise to methanol (75 ml) at -10éC. Methanol (25 ml) was added to this mixture at -10éC and stirred for 6-7 hours. The mixture was then stirred for 15 minutes at 25éC. The solid filtered and dried under vacuum. Yield 0.8 g.

Example 2: Preparation of crystalline form A of dolutegravir sodium:

A mixture of dolutegravir (13 g) and dimethyl sulfoxide (104 ml) was heated to 70éC and then cooled to 25éC and filtered through micron filter. The filtrate was added dropwise to a pre-cooled solution of methanol (650 ml) and sodium hydroxide (2.65 g) at -10 to -7éC. The mixture was stirred at about -7éC for 40 minutes. The solid was filtered, washed with methanol and dried under vacuum. Yield 12.0 g.

CLAIMS

1. Crystalline form A of dolutegravir sodium having characteristic diffraction peaks at 6.3é, 7.8é, 9.3é, 11.4é, 12.4é, 13.5é, 12.7é, 15.1é, 15.8é, 18.3é, 19.0é, 19.6é, 20.7é, 22.8é, 23.1é, 24.3é and 25.8é ě 0.2 degree two theta in an X-ray diffraction pattern.

2. The crystalline form A of claim 1, having characteristic infrared absorption at 3431ě 2 cm^{-1}, 1643ě 2 cm^{-1}, 1538ě 2 cm^{-1}, 1504ě 2 cm^{-1}, 1424ě 2 cm^{-1}, 1320ě 2 cm^{-1}, 1278ě 2 cm^{-1}, 1096ě 2 cm^{-1} and 964 ě 2 cm^{-1}.

3. Crystalline form A of dolutegravir sodium comprising:

   i) X-ray powder diffraction pattern as depicted in figure 1,
   ii) Infrared absorption spectrum as depicted in figure 2, and
   iii) DSC thermogram as depicted in figure 3.

4. A process for the preparation of crystalline form A of dolutegravir sodium of claim 1, comprising:

   i) dissolving dolutegravir sodium in a first solvent;
   ii) adding the solution of step (a) to a pre cooled solution of second solvent; and
   iii) isolating form A of dolutegravir sodium.

5. The process according to claim 4, wherein the solvent is polar solvent, non-polar solvent or mixture thereof.

6. The process according to claim 5, wherein polar solvent is alcohol, ether, ester, ketone, dimethylformamide, dimethyl sulfoxide or water.

7. The process according to claim 6, wherein alcohol is methanol, ethanol, butanol or propanol; nitrile is acetonitrile, propionitrile or butyronitrile; ether is tetrahydrofuran, dioxane or dimethoxyethane; ester is ethyl acetate, ethyl acetoacetate, butyl acetate or propyl acetate; ketones is acetone, methyl ethyl ketone or methyl isobutyl ketone.

8. The process according to claim 5, wherein non-polar solvent is hydrocarbon solvent or chlorinated hydrocarbon solvent.

9. The process according to claim 8, wherein hydrocarbon solvent is hexane, cyclohexane, n-heptane, pentane, cyclopentane or toluene.

10. The process according to claim 8, wherein chlorinated hydrocarbon solvent is methylene chloride, ethylene chloride, chloroform or carbon tetrachloride.

11. The process according to claim 4, wherein in step (ii) the solution is precooled to a temperature of less than 30éC.

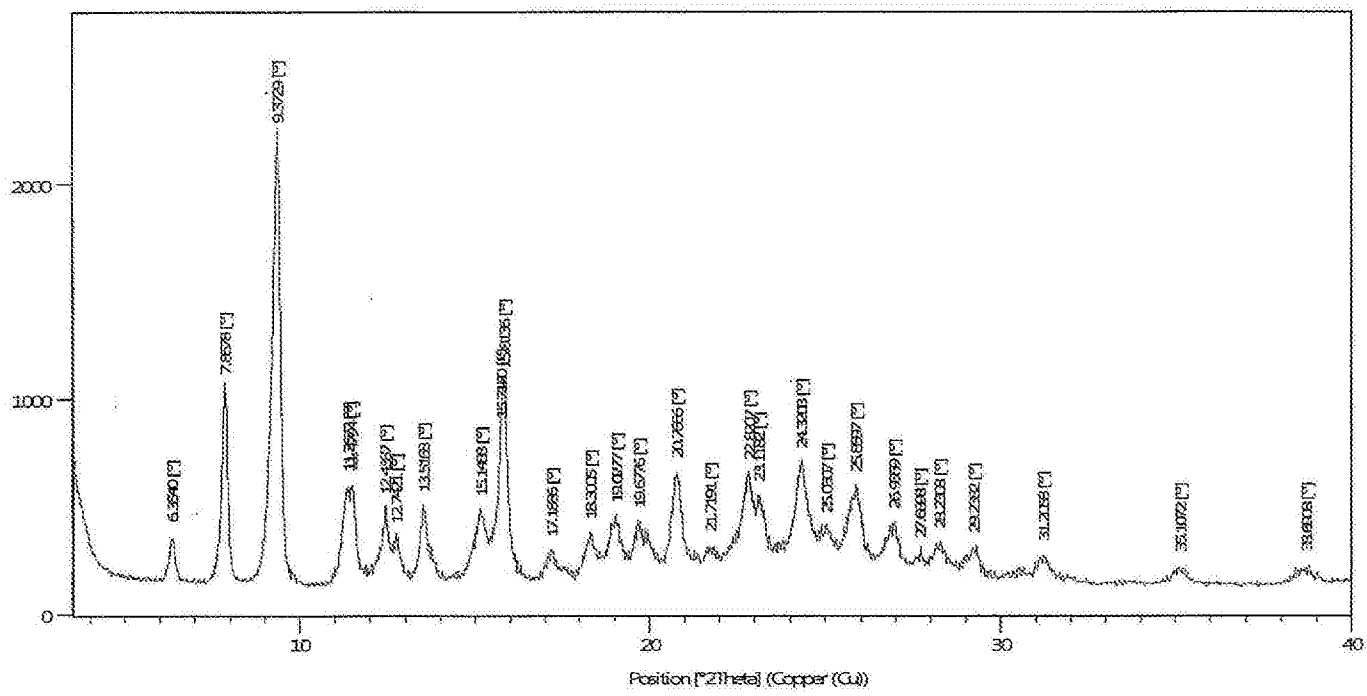
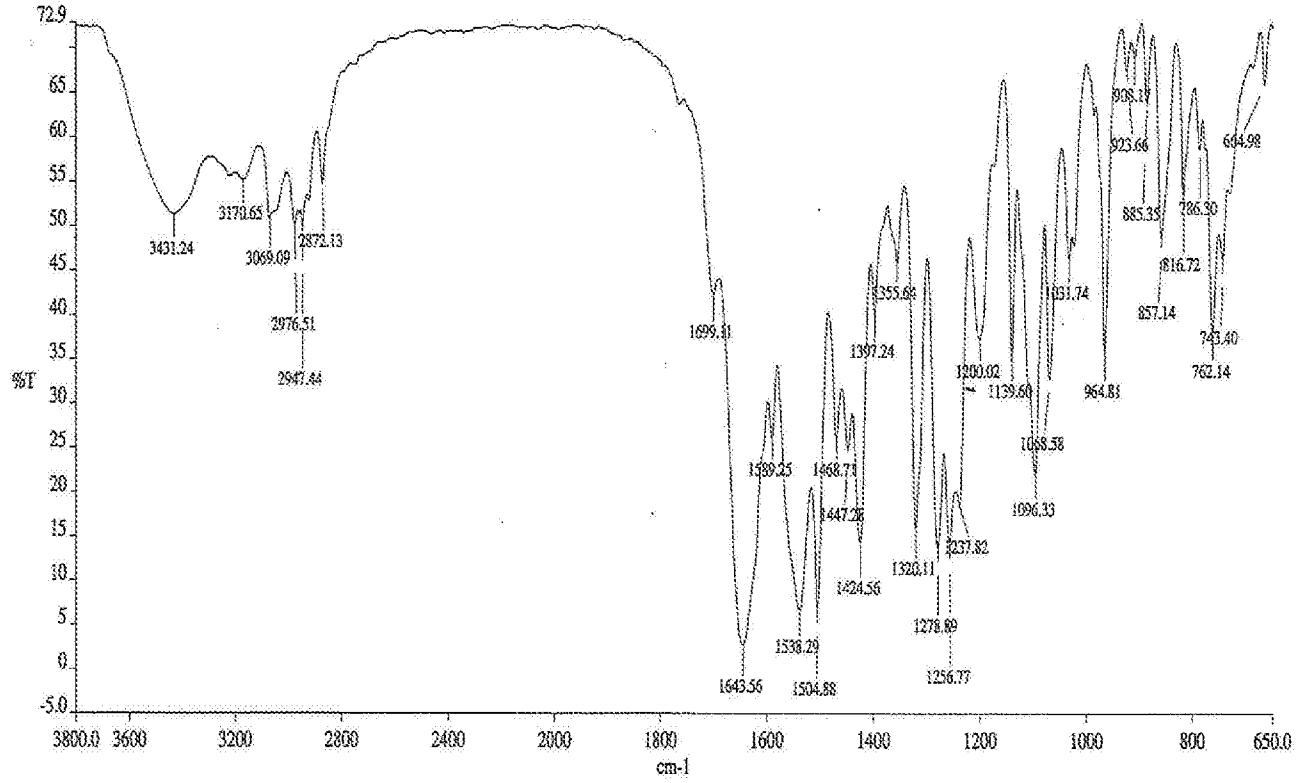


Figure 1


%T
cm-1
3431.24
3170.65
3069.09
2976.51
2947.44
2872.13
1699.11
1643.56
1589.25
1538.29
1504.88
1468.71
1447.28
1424.56
1397.24
1355.68
1320.11
1278.89
1256.77
1237.82
1200.02
1139.60
1096.33
1058.58
1031.74
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857.14
816.72
786.30
762.14
743.40
694.98

Figure 2

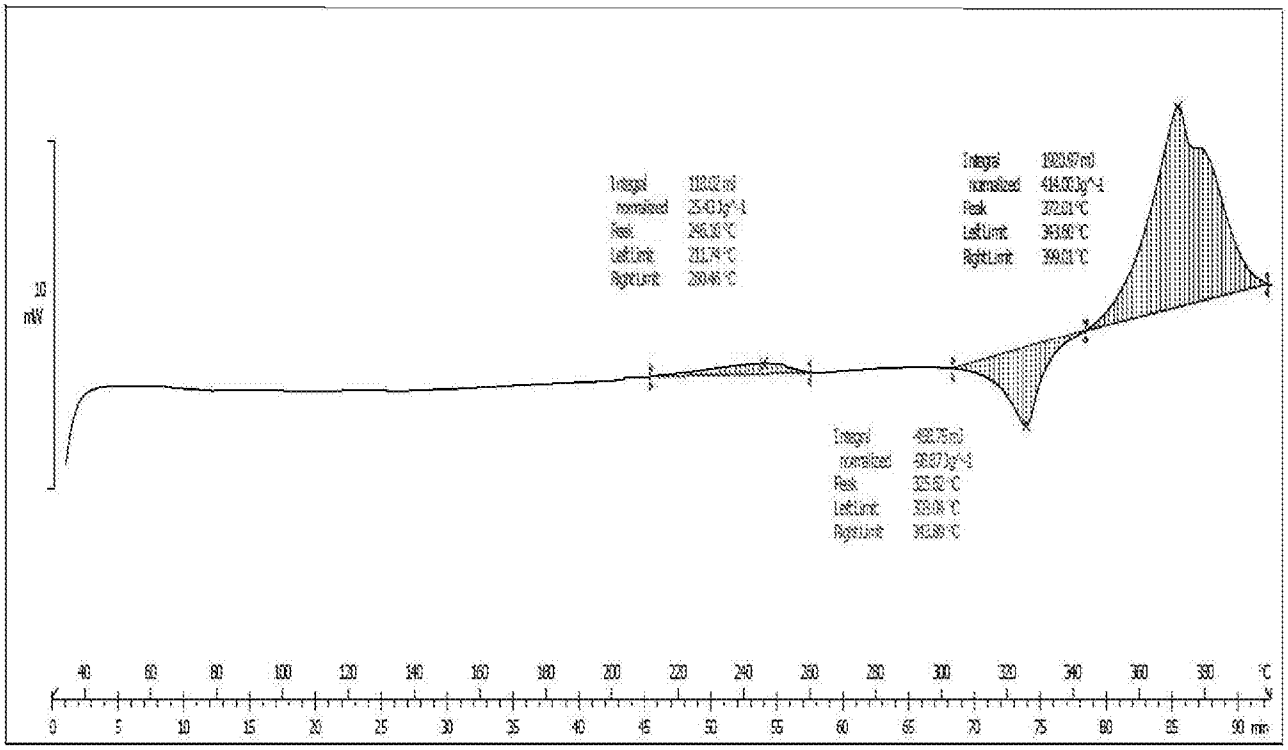

Figure 3

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2017/052926

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D498/14
ADD.

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

B. FIELDS SEARCHED

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

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

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

EPO-Internal, WPI Data, 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 2016/016279 A1 (LEK PHARMACEUTICALS [SI]; SANDOZ AG [CH]) 4 February 2016 (2016-02-04) claim 1 figure 1 -----	1-11

☐ 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
14 July 2017	09/08/2017

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2017/052926

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2016016279 A1	04-02-2016	CA 2956662 A1	04-02-2016
		EP 3177629 A1	14-06-2017
		WO 2016016279 A1	04-02-2016