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(54) Title: A COMBINATION COMPRISING ALOGLIPTIN AND METFORMIN

(57) Abstract: The present invention relates to a solid oral pharmaceutical composition comprising alogliptin and metformin fixed dose combination and to a process for preparation thereof. More particularly, it relates to a solid oral preparation of alogliptin and metformin fixed dose combination formulation which is stable and easy to manufacture.

A COMBINATION COMPRISING ALOGLIPTIN AND METFORMIN

Field of the Invention

The present invention relates to a solid oral pharmaceutical composition comprising alogliptin and metformin fixed dose combination and to a process for preparation thereof. More particularly, it relates to a solid oral preparation of alogliptin and metformin fixed dose combination formulation which is stable and easy to manufacture.

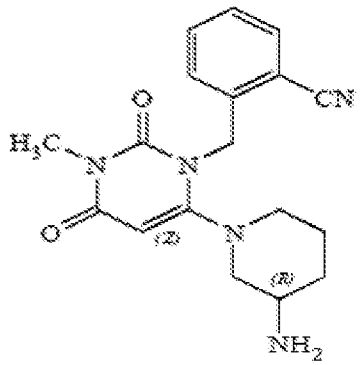
Background of the Invention

Diabetes mellitus is a group of disorders of carbohydrate metabolism in which the action of insulin is diminished or absent through altered secretion, decreased insulin activity or a combination of both factors. There are two main types of diabetes; Type 1 and Type 2:

Type 1 diabetes occurs because the insulin-producing cells of the pancreas (beta cells) are damaged. In Type 1 diabetes, the pancreas makes little or no insulin, so sugar cannot get into the body's cells for use as energy. People with Type 1 diabetes must use insulin injections to control their blood glucose.

In Type 2 diabetes, the pancreas makes insulin, but it either doesn't produce enough, or the insulin does not work properly. This diabetes occurs most often in people who are over 40 years old and overweight. Type 2 diabetes may sometimes be controlled with a combination of diet, weight management, and exercise. However, treatment also may include oral glucose-lowering medications or insulin injections.

Alogliptin, 2-[[6- [(3R)-3-aminopiperidin -1-yl]-3- methyl-2,4- dioxopyrimidin-1-yl] methyl] benzonitrile, is an orally administered anti-diabetic drug has a chemical structure which is shown in the Formula I.

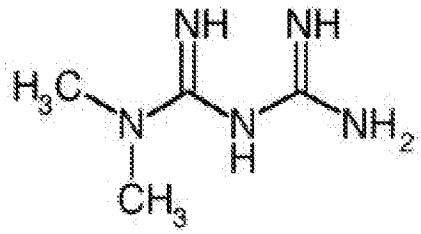


Formula I

Alogliptin disclosed in US 2005/261271, EP 1586571 and in WO 2005/095381. WO 2007/035629, disclosed alogliptin is in the form of its benzoate salt, its hydrochloride salt or its tosylate salt. Polymorphs of alogliptin benzoate are disclosed in WO 2007/035372. A process for preparing alogliptin is disclosed in WO 2007/112368 and, WO 2007/035629.

Metformin is antidiabetics having an orally-administrated biguanide structure. Metformin hydrochloride is a white to off-white crystalline compound and it is freely soluble in water and practically insoluble in acetone, ether and chloroform. Oral doses of metformin are generally recommended in the range of 500 to 2500 mg a day and a single dose may vary from 500 to 850 mg. It is used as single or in combination with sulfonylureas, alpha-glucosidase inhibitors, or insulin.

The IUPAC name of metformin is 3-(diaminomethylidene)-1,1-dimethylguanidine, has the following chemical structure of Formula II.



Formula II

It had been surprisingly observed that an unexpected therapeutic effect and especially a synergistic therapeutic effect can be obtained in the treatment of type-2 diabetes when a combination therapy comprising alogliptin and metformin are used together.

U.S. Pat. No. 8,900,638 disclose stability related concerns with the fixed dose combinations of alogliptin and metformin when alogliptin was combined with metformin.

It was observed that the fixed dose combination of alogliptin and metformin was not chemically stable as the primary and tertiary amino group of alogliptin show incompatibilities, degradation problems or extraction problems.

US2018235966 patent application discloses pharmaceutical compositions comprising alogliptin and metformin with suitable pharmaceutically acceptable excipient/s by one or more processes selected from direct compression, dry granulation and wet granulation. In this application, more process steps are used with the use of excess excipients.

In the prior art, there is the combination comprising alogliptin and metformin, the combination uses many ways to overcome the described above the problems. For example; using a bilayer tablet or multilayer tablet or adding unnecessary excipients. But the process and formulation described in the prior art are complex, time consuming and costs are high.

There is still a need for a physically and chemically stable composition.

In the present invention, physically and chemically stable pharmaceutical composition comprising alogliptin and metformin has been found surprisingly overcomes the above-mentioned problems.

Detailed Description of the Invention

The main object of the present invention is to obtain a solid oral pharmaceutical composition comprising stable and compatible combination of alogliptin and metformin with a desired dissolution and stability.

Another object of the present invention is to provide an easy and cost-effective process for the preparation of the said pharmaceutical composition.

The term "alogliptin" as used throughout the specification refers to not only alogliptin, but also its other pharmaceutically acceptable salt, pharmaceutically acceptable solvates, pharmaceutically acceptable hydrates, pharmaceutically acceptable enantiomers, pharmaceutically acceptable derivatives, pharmaceutically acceptable polymorphs and pharmaceutically acceptable prodrugs thereof.

The term "metformin" as used throughout the specification refers to not only metformin, but also its other pharmaceutically acceptable salt, pharmaceutically acceptable solvates, pharmaceutically acceptable hydrates, pharmaceutically acceptable enantiomers, pharmaceutically acceptable derivatives, pharmaceutically acceptable polymorphs and pharmaceutically acceptable prodrugs thereof.

According to one embodiment of the present invention, the solid oral pharmaceutical composition comprises;

-a first formulation comprising alogliptin free base or pharmaceutically acceptable salts thereof and at least one polymer,

-a second formulation comprising metformin free base or pharmaceutically acceptable salts thereof and at least one polymer,

wherein the formulations are present as a single granulated mass.

The term 'single granulated mass' means that the first formulation and the second formulation are granulated together.

According to one embodiment of the present invention, alogliptin is in the form of alogliptin benzoate.

According to one embodiment of the present invention, metformin is in the form of metformin free base.

Surprisingly, it has been found that the active ingredients are formulated separately with the polymers to provide the desired dissolution profile of the solid oral pharmaceutical composition.

Suitable polymers are selected from the group comprising microcrystalline cellulose, amino methacrylate copolymer, vinylpyrrolidone-vinyl acetate copolymers, polyethylene glycol and polyvinyl acetate and polyvinylcaprolactame-based graft copolymer, polyvinylpyrrolidone, hydroxypropyl cellulose, hydroxypropyl methylcellulose, copolymer of ethyl acrylate or methyl methacrylate, polyvinyl acetal diethylaminoacetate, polyoxyl 40 hydrogenated castor oil, hydrogenated castor oil, polyoxyl 15 hydroxystearate, polyoxyl castor oil, polyethylene oxide, poloxamer, polyvinyl alcohol/polyethylene glycol graft copolymer, cetearyl ethyl hexanone/isopropyl myristate, glyceryl monostearate or mixtures thereof.

According to one embodiment of the present invention, preferably polymers are microcrystalline cellulose, amino methacrylate copolymer, vinylpyrrolidone-vinyl acetate copolymers, polyethylene glycol and polyvinyl acetate and polyvinylcaprolactame-based graft copolymer, polyvinylpyrrolidone or mixtures thereof.

The fact that the formulations were formed into a single mass after being separately formed with said polymer completely eliminated the incompatibilities between the active ingredients. So, it provides desired stability.

According to one embodiment of the present invention, the weight ratio of the second formulation to the first formulation is 1.0-25.0, preferably the ratio is 5.0-20.0, more preferably 8.0–18.0. This ratio provides the desired efficacy of active agents.

The first formulation or the second formulation of the present invention can be prepared using standard techniques and manufacturing processes well known in the art, such as direct compression, wet or dry granulation, hot melt granulation, hot melt extrusion, fluidized bed granulation, extrusion/spheronization, slugging, spray drying and solvent evaporation.

Hot-melt extrusion (HME) technology is prominent in the pharmaceutical industry. HME offers the potential of shorter and more efficient times to the final product, through reduction of the processing steps involved. HME is used to disperse an active agent in a matrix at the molecular level, thus forming solid solutions.

Hot-melt extrusion is a technique for manufacturing amorphous solid dispersions in which the active agent is melted or dissolved within a dispersion carrier and mixed to produce and stabilize. Functional excipients are often added to further aid in processability or improve the dissolution rate of an active agent.

According to one embodiment of the present invention, the first formulation is obtained with hot melt extrusion method.

According to one embodiment of the present invention, the second formulation is obtained with hot melt extrusion method.

The use of this hot melt extrusion helped to achieve the desired stability of the composition. The method is easy to use and practical and most importantly it works well.

According to one embodiment of the present invention, the solid oral pharmaceutical composition further comprises at least one pharmaceutically acceptable excipient which is selected from the group comprising fillers, binders, lubricants or mixtures thereof.

Suitable fillers are selected from the group comprising mannitol, lactose monohydrate, starch, sucrose, glucose, dextrose, maltodexrin, natural and synthetic gums (e.g. acacia tree), gelatin, pregelatinized starch or mixtures thereof.

According to one embodiment of the present invention, the amount of fillers is between 3.0% and 20.0%, between 3.0% and 12.0% by weight of the total composition.

According to one embodiment of the present invention, the filler is mannitol. The amount of mannitol is between 3.0% and 20.0%, between 3.0% and 12.0%, between 4.0% and 10.0% by weight of the total composition.

Suitable binders are selected from the group comprising crospovidone, sugars, natural gums, agar, alginates, carbomers, carboxymethylcellulose sodium, cellulose acetate phthalate, magnesium aluminum silicate, maltodextrin, maltose, methylcellulose, pectin, poloxamer, polycarbophil, polydextrose, polyethylene oxide, polymethacrylates, alumina hydroxide, stearic acid, sucrose, bentonite, cetostearyl alcohol, polyoxyethilene-alkyl ethers or mixtures thereof.

According to one embodiment of the present invention, the amount of binders is between 1.0% and 10.0%, between 1.0% and 7.0% by weight of the total composition.

According to one embodiment of the present invention, the binder is crospovidone. The amount of crospovidone is 1.0% and 10.0%, between 1.0% and 7.0%, between 1.5% and 6.0% by weight of the total composition.

Suitable lubricants are selected from the group comprising magnesium stearate, calcium stearate, zinc stearate, boric acid, hydrogenated vegetable oil, sodium chlorate, magnesium lauryl sulfate, sodium oleate, sodium acetate, sodium benzoate, polyethylene glycol, stearic acid, fumaric acid, glyceryl palmito sulphate, sodium stearyl fumarate, sodium lauryl sulphate or mixtures thereof.

According to one embodiment of the present invention, the amount of lubricants is between 0.01% and 3.0%, between 0.05% and 2.0% by weight of the total composition.

According to one embodiment of the present invention, the lubricant is magnesium stearate. The amount of magnesium stearate is between 0.01% and 3.0%, between 0.05% and 2.0% by weight of the total composition.

According to one embodiment of the present invention, the solid oral pharmaceutical composition is in the form of a tablet or a capsule.

According to one embodiment of the present invention, the composition is in the form of a tablet. A tablet is selected from the group comprising mono-layer tablet, inlay tablets, orally disintegrating tablets, mini tablets, buccal tablets, sublingual tablets, effervescent tablets, immediate release tablets, modified release tablets, gastric disintegrating tablets, chewable tablets, dispersing tablets.

According to one embodiment of the present invention, the composition is in the form of a mono-layer tablet. Preferably, mono-layer tablet comprises film coating which is selected from the group comprising hydroxypropylmethylcellulose, talc, titanium dioxide, iron oxides, polyethylene glycol (PEG), polyvinyl alcohol (PVA), polyvinyl alcohol-polyethylene glycol copolymers, polyvinylprolidone, polyvinylprolidone-vinyl acetate copolymer (PVP-VA), pigments, dyes or mixtures thereof.

According to one embodiment of the present invention, the amount of film coating is between 0.01% and 5.0%, between 0.5% and 4.0% by weight of the total composition.

According to one embodiment of the present invention, the first formulation comprises 1.2% by weight of alogliptin benzoate and 1.2% by weight of polymers in the solid oral pharmaceutical composition.

According to one embodiment of the present invention, the first formulation comprises 1.5% by weight of alogliptin benzoate and 1.5% by weight of polymers in the solid oral pharmaceutical composition.

According to one embodiment of the present invention, the first formulation comprises 3.4% by weight of alogliptin benzoate and 3.4% by weight of polymers in the solid oral pharmaceutical composition.

According to one embodiment of the present invention, the second formulation comprises 76.0% by weight of metformin and 8.4% by weight of polymers in the solid oral pharmaceutical composition.

According to one embodiment of the present invention, the second formulation comprises 75.8% by weight of metformin and 8.4% by weight of polymers in the solid oral pharmaceutical composition.

According to one embodiment of the present invention, the second formulation comprises 70.3% by weight of metformin and 7.8% by weight of polymers in the solid oral pharmaceutical composition.

According to one embodiment of the present invention, the composition comprising the first formulation and the second formulation, mannitol, crospovidone, magnesium stearate.

Example 1: Film coated mono-layer tablet

	Ingredients	(%) amount (w/w)
First formulation	Alogliptin free base or pharmaceutically acceptable salts thereof	0.5 – 8.0
	Microcrystalline cellulose, amino methacrylate copolymer, vinylpyrrolidone-vinyl acetate copolymers, polyethylene glycol and polyvinyl acetate and polyvinylcaprolactame-based graft copolymer	0.5 – 15.0
Second formulation	metformin free base or pharmaceutically acceptable salts thereof	65.0 – 85.0
	Polyvinylpyrrolidone, amino methacrylate copolymer, vinylpyrrolidone-vinyl acetate copolymers, polyethylene glycol and polyvinyl acetate and polyvinylcaprolactame-based graft copolymer	0.5 – 15.0
	Fillers	3.0 – 20.0
	Binders	1.0 – 10.0
	Lubricants	0.01 – 3.0
	Film coating	0.01 – 5.0
	TOTAL	**100**

Process for example 1;

First formulation;

a. Dry mixing a polymer and alogliptin until a homogeneous mixture is obtained,
b. Heating the mixture prepared at step(a) thereby forming a melt,
c. Cooling the melt formed at step(b) thereby forming extrudates
d. Converting extrudates form to granules

Second formulation

e. Dry mixing a polymer and metformin until a homogeneous mixture is obtained,

f. Heating the mixture prepared at step(a) thereby forming a melt,
g. Cooling the melt formed at step(b) thereby forming extrudates
h. Converting extrudates form to granules,

i. Mixing the first formulation, the second formulation, binders and fillers
j. Then, adding lubricants and mixing,
k. Pressing the mixture to form tablets,
l. Coating the tablets with film-coating.

Example 2: Film coated mono-layer tablet

	Ingredients	**(%) amount (w/w)**
First formulation	Alogliptin free base or pharmaceutically acceptable salts thereof	0.5 – 8.0
	Microcrystalline cellulose, amino methacrylate copolymer, vinylpyrrolidone-vinyl acetate copolymers, polyethylene glycol and polyvinyl acetate and polyvinylcaprolactame-based graft copolymer	0.5 – 15.0
Second formulation	Metformin free base or pharmaceutically acceptable salts thereof	65.0 – 85.0
	Polyvinylpyrrolidone, amino methacrylate copolymer, vinylpyrrolidone-vinyl acetate copolymers, polyethylene glycol and polyvinyl acetate and polyvinylcaprolactame-based graft copolymer	0.5 – 15.0
	Mannitol	3.0 – 20.0
	Crospovidone	1.0 – 10.0
	Magnesium stearate	0.01 – 3.0
	Film coating	0.01 – 5.0
	TOTAL	**100**

Example 3: Film coated mono-layer tablet

	Ingredients	(%) amount (w/w)
First formulation	Alogliptin free base or pharmaceutically acceptable salts thereof	0.5 – 6.0
	Microcrystalline cellulose, amino methacrylate copolymer, vinylpyrrolidone-vinyl acetate copolymers, polyethylene glycol and polyvinyl acetate and polyvinylcaprolactame-based graft copolymer	0.5 – 8.0
Second formulation	Metformin free base or pharmaceutically acceptable salts thereof	65.0 – 85.0
	Polyvinylpyrrolidone, amino methacrylate copolymer, vinylpyrrolidone-vinyl acetate copolymers, polyethylene glycol and polyvinyl acetate and polyvinylcaprolactame-based graft copolymer	0.5 – 10.0
	Mannitol	3.0 – 12.0
	Crospovidone	1.0 – 7.0
	Magnesium stearate	0.01 – 3.0
	Film coating	0.01 – 5.0
	TOTAL	**100**

Process for example 2 or example 3;

First formulation;

a. Dry mixing a polymer and alogliptin until a homogeneous mixture is obtained,
b. Heating the mixture prepared at step (a) thereby forming a melt,
c. Cooling the melt, formed at step (b) thereby forming extrudates,
d. Converting extrudates form to granules

Second formulation

e. Dry mixing a polymer and metformin until a homogeneous mixture is obtained,

f. Heating the mixture prepared at step(a) thereby forming a melt,
g. Cooling the melt formed at step(b) thereby forming extrudates,
h. Converting extrudates form to granules,

i. Mixing the first formulation, the second formulation, mannitol and crospovidone,
j. Then, adding magnesium stearate and mixing,
k. Pressing the mixture to form tablets,
l. Coating the tablets with film-coating.

Example 4: Film coating

Ingredients
Hydroxypropylmethylcellulose
Talc
Titanium dioxide
Iron oxide yellow

CLAIMS

1. A solid oral pharmaceutical composition comprising;
   - A first formulation comprising alogliptin free base or pharmaceutically acceptable salts thereof and at least one polymer,
   - A second formulation comprising metformin free base or pharmaceutically acceptable salts thereof and at least one polymer,

   wherein the formulations are present as a single granulated mass.

2. The solid oral pharmaceutical composition according to claim 1, wherein the polymers are selected from the group comprising microcrystalline cellulose, amino methacrylate copolymer, vinylpyrrolidone-vinyl acetate copolymers, polyethylene glycol and polyvinyl acetate and polyvinylcaprolactame-based graft copolymer, polyvinylpyrrolidone, hydroxypropyl cellulose , hydroxypropyl methylcellulose , copolymer of ethyl acrylate or methyl methacrylate, polyvinyl acetal diethylaminoacetate, polyoxyl 40 hydrogenated castor oil, hydrogenated castor oil, polyoxyl 15 hydroxystearate, polyoxyl castor oil, polyethylene oxide, poloxamer , polyvinyl alcohol/polyethylene glycol graft copolymer, cetearyl ethyl hexanone/isopropyl myristate, glyceryl monostearate or mixtures thereof.

3. The solid oral pharmaceutical composition according to claim 2, wherein the polymers are microcrystalline cellulose, amino methacrylate copolymer, vinylpyrrolidone-vinyl acetate copolymers, polyethylene glycol and polyvinyl acetate and polyvinylcaprolactame-based graft copolymer, polyvinylpyrrolidone or mixtures thereof.

4. The solid oral pharmaceutical composition according to claim 1, wherein the weight ratio of the second formulation to the first formulation is 1.0-25.0, preferably the ratio is 5.0-20.0.

5. The solid oral pharmaceutical composition according to claim 1, wherein the first formulation is obtained with hot melt extrusion method.

6. The solid oral pharmaceutical composition according to claim 1, wherein the second formulation is obtained with hot melt extrusion method.

7. The solid oral pharmaceutical composition according to claim 1, further comprising at least one pharmaceutically acceptable excipient which is selected from the group comprising fillers, binders, lubricants or mixtures thereof.

8. The solid oral pharmaceutical composition according to claim 7, wherein the fillers are selected from the group comprising mannitol, lactose monohydrate, starch, sucrose, glucose, dextrose, maltodexrin, natural and synthetic gums, gelatin, pregelatinized starch or mixtures thereof.

9. The solid oral pharmaceutical composition according to claim 7, wherein the binders are selected from the group comprising crospovidone, sugars, natural gums, agar, alginates, carbomers, carboxymethylcellulose sodium, cellulose acetate phthalate, magnesium aluminum silicate, maltodextrin, maltose, methylcellulose, pectin, poloxamer, polycarbophil, polydextrose, polyethylene oxide, polymethacrylates, alumina hydroxide, stearic acid, sucrose, bentonite, cetostearyl alcohol, polyoxyethilene-alkyl ethers or mixtures thereof.

10. The solid oral pharmaceutical composition according to claim 7, wherein the lubricants are selected from the group comprising magnesium stearate, calcium stearate, zinc stearate, boric acid, hydrogenated vegetable oil, sodium chlorate, magnesium lauryl sulfate, sodium oleate, sodium acetate, sodium benzoate, polyethylene glycol, stearic acid, fumaric acid, glyceryl palmito sulphate, sodium stearyl fumarate, sodium lauryl sulphate or mixtures thereof.

11. The solid oral pharmaceutical composition according to claim 1, wherein the composition is in the form of a tablet or a capsule.

12. The solid oral pharmaceutical composition according to claim 11, wherein the composition is in the form of a tablet.

13. The solid oral pharmaceutical composition according to claim 12, wherein the composition comprising a film-coating which is selected from the group comprising hydroxypropylmethylcellulose, talc, titanium dioxide, iron oxides, polyethylene glycol, polyvinyl alcohol, polyvinyl alcohol-polyethylene glycol copolymers, polyvinylpyrrolidone, polyvinylpyrrolidone-vinyl acetate copolymer , pigments, dyes or mixtures thereof.

14. The solid oral pharmaceutical composition according to claim 1, wherein the composition comprising the first formulation and the second formulation, mannitol, crospovidone, magnesium stearate.

15. A process for preparing the solid oral pharmaceutical composition according to any preceding claim, comprising the following steps:

First formulation;

a. Dry mixing a polymer and alogliptin until a homogeneous mixture is obtained,
b. Heating the mixture prepared at step (a) thereby forming a melt,
c. Cooling the melt, formed at step (b) thereby forming extrudates,
d. Converting extrudates form to granules

Second formulation

e. Dry mixing a polymer and metformin until a homogeneous mixture is obtained,
f. Heating the mixture prepared at step(a) thereby forming a melt,
g. Cooling the melt formed at step(b) thereby forming extrudates,
h. Converting extrudates form to granules,

i. Mixing the first formulation, the second formulation, mannitol and crospovidone,
j. Then, adding magnesium stearate and mixing,
k. Pressing the mixture to form tablets,
l. Coating the tablets with film-coating.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/TR2020/050317

A. CLASSIFICATION OF SUBJECT MATTER

A61K 31/155 (2006.01)i; A61K 31/513 (2006.01)i; A61K 9/20 (2006.01)i; A61K 9/48 (2006.01)i; A61K 47/30 (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

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)

EPODOC, WPI, PubMed

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2013179307 A2 (MYLAN LAB LTD [IN]) 05 December 2013 (2013-12-05) Description page 7 lines 24-31, page 11 lines 27-30, page 14 lines 14-31, page 15 lines 1-5, examples 1-6	1-15
Y	Burke, M. D., He, X., Cook, C., Petrov, G. A., Long, S., & Coffin, M. D. (2013). Stability enhancement of drug layered pellets in a fixed dose combination tablet. Aaps Pharmscitech, 14(1), 312-320. Abstract, Table 3-4, Conclusion	1-4, 7-14
Y	US 2018289716 A1 (BOEHRINGER INGELHEIM INT [DE]) 11 October 2018 (2018-10-11) Abstract, description paragraphs [0155]-[0160]	1-4, 7-14
Y	KR 20150059166 A (CJ HEALTHCARE CORP [KR]) 29 May 2015 (2015-05-29) Abstract	1-4, 7-14

☐ 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
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Date of the actual completion of the international search	Date of mailing of the international search report
14 August 2020	**14 August 2020**

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INTERNATIONAL SEARCH REPORT
Information on patent family members

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