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(71) Applicant: **ALEMBIC PHARMACEUTICALS LIMITED** [IN/IN]; Alembic Research Center, Alembic Road, Vadodara, Gujarat 390003 (IN).

(72) Inventors: **KHAPRA, Dr. Pankaj Kumar**; Alembic Pharmaceuticals Ltd., Alembic Research Center, Alembic Road, Vadodara, Gujarat 390003 (IN). **DABRA, Dr. Rahul**; Alembic Pharmaceuticals Limited, Lab Suites 111-112 & 113-114 on Ground Floor, Lab Suites 123 & 124 on First Floor, Block –1, Building 450, MN Park, Genome Valley, Shameerpet Turkapally (V), Hyderabad 500078 (IN). **GHOSH, Soumik**; Alembic Pharmaceuticals, Lab Suites 111-112 & 114 on Ground Floor, Lab Suites 123 & 124 on First Floor, Block –1, Building 450, MN Park, Genome Valley, Shameerpet Turkapally (V), Hyderabad 500078 (IN). **ALI, Sartaj**; Alembic Pharmaceuticals Limited, Lab Suites 111-112 & 113-114 on Ground Floor, Lab Suites 123 & 124 on First Floor, Block –1, Building 450, MN Park, Genome Valley, Shameerpet Turkapally (V), Hyderabad 500078 (IN).

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(54) Title: PHARMACEUTICAL COMPOSITION OF AXITINIB

(57) Abstract: The present subject matter is directed to a stable pharmaceutical composition comprising axitinib in crystalline polymorphic form IV and one or more pharmaceutically acceptable excipients. In particular, the composition is bioequivalent to the commercially available axitinib tablets (INLYTA®).

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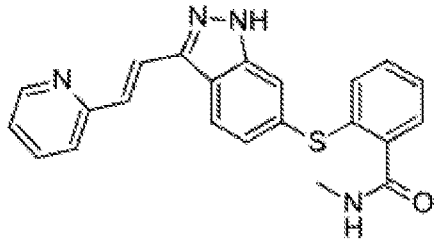
PHARMACEUTICAL COMPOSITION OF AXITINIB

FIELD OF THE SUBJECT MATTER

The present subject matter relates to a stable pharmaceutical composition comprising axitinib or a salt thereof and one or more pharmaceutically acceptable excipients.

BACKGROUND OF THE SUBJECT MATTER

Axitinib is a tyrosine kinase inhibitor indicated for the treatment of advanced renal cell carcinoma after failure of one prior systemic therapy. Axitinib is chemically described as N-methyl-2-[3-((E)2-pyridin-2-yl-vinyl)-1H-indazol-6-ylsulfanyl]-benzamide and has the following chemical structural formula:



In the United States, Axitinib is commercially available as 1 mg and 5 mg film coated tablets under the brand name INLYTA®.

Axitinib and its different polymorphs are well known in the art. E.g., U.S. Patent no 6,534,524 discloses axitinib, salt, prodrug & metabolites thereof.

U.S. Patent application publication number 20060094763 discloses crystalline polymorphic forms of axitinib viz., form I, form II, form III, form IV, form VI, form VII, and form VIII with specific powder X-ray diffraction pattern.

U.S. Patent no 8,791,140 discloses crystalline polymorphic forms of axitinib viz., form IX, XV, XXV, XVI, XLI, XII, VIII, XLI, and XV with specific powder X-ray diffraction pattern.

It is reported that axitinib is prone to photo degradation and oxidative degradation. In view of these instability issues, formulation development of axitinib poses challenge, particularly for polymorphs form XLI and form IV.

Indian patent publication number IN 3619/CHE/2015 addressed the above issues by developing formulations containing novel forms of axitinib such as form SAB-I.

The U.S. Patent application publication number 20140248347 discloses that coating containing iron oxide may help to stabilize axitinib form photo degradation.

The U.S. Patent number 8,791,140 discloses that other polymorphs such as form XLI and form XXV are more thermodynamically and photo stable, and also have better handling properties than form IV.

Therefore, there remains a need for a stable and bioequivalent pharmaceutical compositions of axitinib, particularly of form IV.

SUMMARY OF THE SUBJECT MATTER

The present subject matter relates to a solid oral composition comprising axitinib and one or more pharmaceutically acceptable excipients. In addition, it also provides a process of preparation of such composition.

In one aspect, there is provided a stable pharmaceutical composition comprising crystalline axitinib form IV and one or more pharmaceutically acceptable excipients.

In one embodiment, the stable pharmaceutical composition is devoid of other polymorphic forms of axitinib other than form IV.

In another embodiment, the pharmaceutical composition is devoid of iron oxide.

In another aspect, there is provided a stable pharmaceutical composition in the form of a tablet comprising a core and a coating, wherein the core comprises crystalline axitinib form IV.

In another embodiment, the coating part of the tablet composition is devoid of iron oxide.

In another aspect, there is provided a stable pharmaceutical composition of axitinib in the form of a tablet dosage form which is stable and bioequivalent to the commercially available axitinib tablets (INLYTA®).

In another embodiment, the stable pharmaceutical composition comprising crystalline axitinib form IV may further comprise a diluent, a disintegrating agent, a binder, a pH-modifying agent, a glidant and a lubricant.

In another aspect, there is provided a stable pharmaceutical composition comprising crystalline axitinib form IV and a pH modifying agent.

In another embodiment, the pharmaceutical composition comprises axitinib and a pH modifying agent in a ratio of from 1: 1 to 1: 25.

In another embodiment, the pharmaceutical composition comprises crystalline axitinib form IV, a diluent and a lubricant.

In another embodiment, the pharmaceutical composition of the present subject matter is used in the treatment of a patient with advanced renal cell carcinoma after failure of one prior systemic therapy.

DETAILED DESCRIPTION OF THE SUBJECT MATTER

The subject matter described herein is directed to a pharmaceutical composition comprising crystalline axitinib form IV and one or more pharmaceutically acceptable excipients.

For the purpose of the present subject matter, axitinib is a base and is present in a polymorphic form known as form IV characterized by an X-ray diffraction pattern with peaks at the following diffraction angles (2θ): 8.9, 12.0, 14.6, 15.2, 15.7, 17.8, 19.2, 20.5, 21.6, 23.2, 24.2, 24.8, 26.2, and 27.5.

The term “composition” or “pharmaceutical composition” or “solid oral composition” or “dosage form” as used herein synonymously include solid dosage forms such as tablets, capsules, granules, or pellets and the like meant for oral administration.

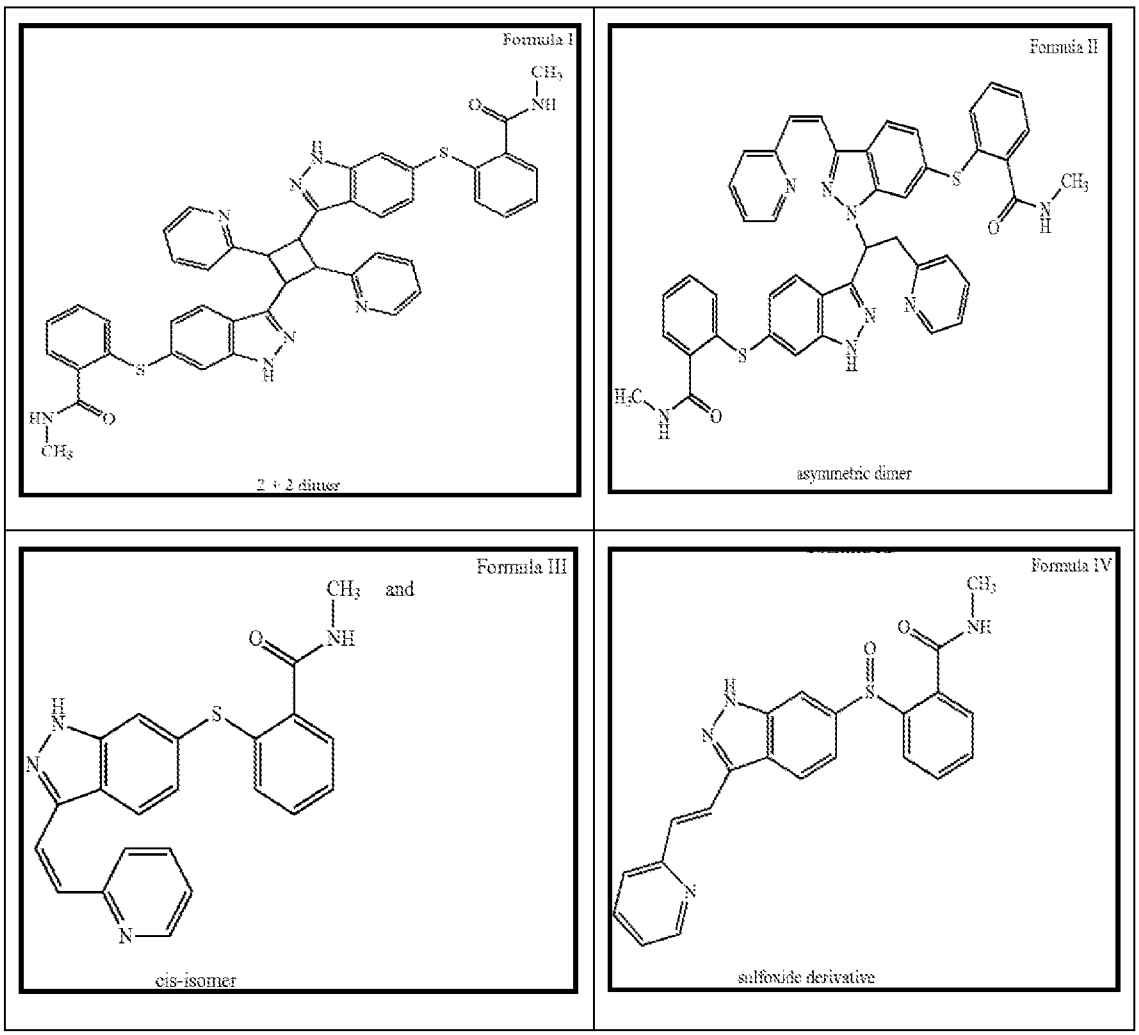
The term "subject", as used herein, may be a human or non-human mammal (e.g., rabbit, rat, mouse, horse, monkey, other lower-order primate, etc.).

Any two products are considered to be “bioequivalent” if they are pharmaceutical equivalents and if the 90% confidence interval (CI) of the relative mean Cmax, AUC(0-t) and AUC(0-∞) of the test to reference is within 80.00% to 125.00% under fasting and fed states.

The term “stable” as used herein, indicates that the composition when exposed to light or moisture should maintain the axitinib polymorphic form in the original form used i.e. form IV, on storage without getting converted to other polymorphic form/s and without substantial photo or oxidative degradation.

The phrase “photo stable” as used herein, unless otherwise indicated, specifies that the drug axitinib is not substantially degraded to photo degradants i.e. compound of formula I referred to as the 2 + 2 dimer, the compound of formula II referred to as the asymmetric dimer, and the compound of formula III be referred to as the cis-isomer throughout the prolonged storage.

Axitinib is also prone to oxidation and may yield oxidative degradant due to instability which include the compound of formula IV, which may be referred to as the sulfoxide derivative.



The term "impurity" relates to any compound having a retention time that differs from that of axitinib by at least the detection limit of the chromatography apparatus used to determine the retention time. The different retention time may be measured, for example, by HPLC. In the present context impurities can be defined as photo degradants of formula I, formula II (2 + 2 dimer impurity) & formula III, oxidative degradant of formula IV (formula IV impurity), unknown impurities and total impurities.

In one aspect, there is provided a stable pharmaceutical composition comprising crystalline axitinib form IV and one or more pharmaceutically acceptable excipients.

In one embodiment, the pharmaceutical composition is devoid of any other polymorphic forms of axitinib other than form IV.

In one embodiment, the pharmaceutical composition is devoid of iron oxide.

In another embodiment, a composition is defined to exhibit good stability when the composition retains at least 90% w/w of the initial potency for at least 2 month, atleast 3 months, for atleast 6 months, for atleast 12 months, for atleast 24 months or for atleast 36 months when stored at 40 °C/ 75% RH.

In another embodiment, a composition is defined to exhibit good stability when the composition retains at least 90% w/w of the initial potency for at least 2 month when stored at 40 °C/ 75% RH.

In another embodiment, a composition of axitinib retains at least 90% w/w, at least 95% w/w, at least 99% w/w or about 100% w/w of the initial potency. A composition retains about 90% w/w, about 91% w/w, about 92% w/w, about 93% w/w, about 94% w/w, about 95% w/w, about 96% w/w, about 97% w/w, about 98% w/w, about 99% w/w or about 100% w/w of the initial potency.

In another embodiment, a composition of axitinib retains at least 95% w/w of the initial potency when stored at 40 °C/ 75% RH for atleast 2 months.

In another aspect, there is provided a stable pharmaceutical composition in the form of a tablet comprising a core and a coating, wherein the core comprises crystalline axitinib form IV.

In another embodiment, the composition comprising crystalline axitinib form IV in an amount of from about 1%w/w to about 5%w/w based on the total weight of the

composition including coating. Crystalline axitinib form IV is present in an amount of about 1%w/w, about 2%w/w, about 3%w/w, about 4%w/w, about 5%w/w based on the total weight of the composition including coating. Crystalline axitinib form IV is present in an amount of about 2%w/w, about 2.1%w/w, about 2.2%w/w, about 2.3%w/w, about 2.4%w/w, 2.5%w/w, about 2.6%w/w, about 2.7%w/w, about 2.8%w/w, 2.9%w/w and about 3%w/w based on the total weight of the composition including coating.

In one embodiment, the coating part of the tablet composition is devoid of iron oxide.

In another embodiment, the composition of the present subject matter provides protection of axitinib from photo degradation and oxidative degradation.

In another embodiment, a composition of axitinib retains at least 90% w/w, at least 95% w/w, at least 99% w/w or about 100% w/w of axitinib in crystalline form IV when stored at 40 °C/ 75% RH for atleast 2 months. A composition retains about 90% w/w, about 91% w/w, about 92% w/w, about 93% w/w, about 94% w/w, about 95% w/w, about 96% w/w, about 97% w/w, about 98% w/w, about 99% w/w or about 100% w/w of axitinib in crystalline form IV when stored at 40 °C/ 75% RH for atleast 2 months.

In another embodiment, a composition of axitinib retains at least 95% w/w of axitinib in crystalline form IV when stored at 40 °C/ 75% RH for atleast 2 months.

In another embodiment, a composition of axitinib contains not more than 2% w/w, 1% w/w, 0.9%w/w, 0.8%w/w, 0.7%w/w, 0.6%w/w, 0.5%w/w, 0.4%w/w, 0.3%w/w, 0.2%w/w, 0.1%w/w or 0.0% w/w of total impurities when stored at 40 °C/ 75% RH for atleast 2 months, atleast 3months, atleast 6 months, atleast 9 months, atleast 12 months, atleast 24 months or atleast 36 months.

In another embodiment, a composition of axitinib contains not more than 1% w/w, 0.9%w/w, 0.8%w/w, 0.7%w/w, 0.6%w/w, 0.5%w/w, 0.4%w/w, 0.3%w/w, 0.2%w/w or 0.1%w/w of total impurities on storage at 40 °C/ 75% RH for a period of atleast 2 months.

In another embodiment, a composition of axitinib contains not more than 0.5% w/w of total impurities on storage at 40 °C/ 75% RH for a period of atleast 2 months.

In another embodiment, a composition of axitinib contains not more than 1% w/w, 0.9%w/w, 0.8%w/w, 0.7%w/w, 0.6%w/w, 0.5%w/w, 0.4%w/w, 0.3%w/w,

0.2%w/w or 0.1%w/w of formula IV impurity on storage at 40 °C/ 75% RH for a period of atleast 2 months.

In another embodiment, a composition of axitinib contains not more than 0.1% w/w of formula IV impurity on storage at 40 °C/ 75% RH for a period of atleast 2 months.

In another embodiment, a composition of axitinib lacks photo degradant impurities at initial time point.

In another embodiment, a composition of axitinib is substantially free of photo degradant impurities on storage at 40 °C/ 75% RH for a period of atleast 2 months, atleast 3 months, atleast 6 months, atleast 9 months, atleast 12 months, atleast 24 months, atleast 36 months.

In another embodiment, a composition of axitinib is substantially free of 2 + 2 dimer impurity on storage at 40 °C/ 75% RH for a period of atleast 2 months, atleast 3 months, atleast 6 months, atleast 9 months, atleast 12 months, atleast 24 months, atleast 36 months.

In another aspect, there is provided a stable pharmaceutical composition of axitinib in the form of a tablet dosage form which is stable and bioequivalent to the commercially available axitinib tablets (INLYTA®).

In another embodiment, the pharmaceutical composition comprising crystalline axitinib form IV and pharmaceutically acceptable excipients such as a diluent and a lubricant.

In another embodiment, the pharmaceutical composition comprising crystalline axitinib form IV, a diluent, a disintegrating agent, a binder, a pH-modifying agent, a glidant and a lubricant.

The term “diluent” refers to chemical compounds that are used to dilute the compound of interest prior to delivery. Suitable diluent according to the subject matter is selected from the group including but not limited to, lactose (monohydrate, spray-dried monohydrate, anhydrous and the like), cellulose and derivatives thereof like powdered cellulose, microcrystalline cellulose or silicified microcrystalline cellulose, cellulose acetate, starches and derivatives thereof such as corn starch, inorganic salts like calcium carbonate, calcium phosphate, dibasic calcium phosphate (dicalcium

phosphate), tri calcium phosphate, calcium sulphate, magnesium carbonate, magnesium oxide, sugars and derivatives such as confectioner's sugar, fructose, sucrose, dextrates, dextrin, D-sorbitol cyclodextrins, dextrose, polydextrose, trehalose, maltose, maltitol, mannitol, maltodextrin, sorbitol, inulin, xylitol, erythritol, isomalt, kaolin and lactitol or a combination thereof. The diluent is selected from the group consisting of microcrystalline cellulose, lactose monohydrate, dicalcium phosphate or a combination thereof.

In one embodiment, a pharmaceutical composition comprises axitinib and a diluent.

In one embodiment, a pharmaceutical composition comprises axitinib, lactose monohydrate and/ or dicalcium phosphate.

In another embodiment, the amount of diluent in the composition ranges from about 75%w/w to about 98%w/w, about 80% w/w to about 97% w/w or about 85% w/w to about 96% w/w based on the total weight of the core composition. Diluent may comprise in an amount of about 75% w/w, about 80% w/w, about 85% w/w, about 90% w/w, about 95%w/w or about 98%w/w based on total weight of the core composition. Diluent may comprise in an amount of about 90% w/w, about 91% w/w, about 92% w/w or about 93% w/w, about 94%w/w, about 95%w/w, about 96%w/w, about 97%w/w or about 98%w/w based on total weight of the core composition.

In another embodiment, diluent is in an amount of about 96% w/w based on total weight of the core composition.

In another embodiment, diluent is in an amount of about 95% w/w based on total weight of the core composition.

In another embodiment, diluent is in an amount of about 93% w/w based on total weight of the core composition.

In another embodiment, the amount of diluent in the composition ranges from about 75%w/w to about 95%w/w, about 80% w/w to about 95% w/w or about 85% w/w to about 95% w/w based on the total weight of the composition including coating. Diluents may comprise in an amount of about 75% w/w, about 80% w/w, about 85% w/w, about 90% w/w or about 95 % w/w based on total weight of the composition including coating. Diluent may comprise in an amount of about 90% w/w, about 91%

w/w, about 92% w/w or about 93% w/w, about 94%w/w or about 95%w/w based on total weight of the composition including coating.

In another embodiment, diluent is in an amount of about 93% w/w based on total weight of the composition including coating.

In another embodiment, diluent is in an amount of about 95% w/w based on total weight of the composition including coating.

The term "lubricant" refers to an excipient which is added to a powder blend to prevent the compacted powder mass from sticking to the equipment during the tableting or encapsulation process. It aids the ejection of the tablet form the dies, and can improve powder flow. Suitable lubricant according to the present subject matter is selected from the group including, but not limited to, magnesium stearate, calcium stearate, zinc stearate, sodium stearyl fumarate, and mixtures of magnesium stearate with sodium lauryl sulphate, or combinations thereof. The lubricant is magnesium stearate.

In another embodiment, the amount of lubricant in the composition of present subject matter ranges from about 0.5%w/w to about 3%w/w based on the total weight of the core composition.

In another embodiment, the lubricant is present in an amount of about 0.5%w/w, about 1%w/w, about 1.5%w/w about 2%w/w, about 2.5%w/w or about 3%w/w based on the total weight of the core composition.

In another embodiment, the lubricant is present in an amount of about 1%w/w, based on the total weight of the core composition.

In another embodiment, the amount of lubricant in the composition of present subject matter ranges from about 0.5%w/w to about 3%w/w based on the total weight of the composition including coating.

In another embodiment, the lubricant is present in an amount of about 0.5%w/w, about 1%w/w, about 1.5%w/w about 2%w/w, about 2.5%w/w or about 3%w/w based on the total weight of the composition including coating.

In another embodiment, the lubricant is present in an amount of about 1%w/w, based on the total weight of the composition including coating.

In another embodiment, a pharmaceutical composition comprising crystalline axitinib form IV, a diluent, a lubricant and optionally a binder.

The term "binder" refers to any chemical substance which can be used to bind together the active and inert components of the carrier together to maintain cohesive and discrete portions. Suitable binders according to the present subject matter are selected from the group including but not limited to, hydroxypropyl methylcellulose, acacia, carboxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, povidone, dextrin, gelatin, guar gum, maltodextrin, methylcellulose, pregelatinized starch and sodium alginate or a mixture of one or more of said binders.

In one embodiment, the amount of binder in the composition of present subject matter ranges from about 0%w/w to about 15%w/w based on the total weight of the composition including coating.

In another embodiment, binder is present in an amount of about 0%w/w, about 1%w/w, about 2%w/w, about 3%w/w, about 4%w/w, about 5%w/w, about 6%w/w, about 7%w/w, about 8%w/w, about 9%w/w, about 10%w/w, about 11%w/w, about 12%w/w, about 13%w/w, about 14%w/w or about 15%w/w based on the total weight of the composition including coating.

In another embodiment, binder is present in an amount of about 3%w/w based on the total weight of the composition including coating.

In another embodiment, the composition is devoid of any binder.

In another aspect, there is provided a stable pharmaceutical composition comprising crystalline axitinib form IV and a pH modifying agent.

In one embodiment, the pharmaceutical composition comprising crystalline axitinib form IV, diluent, lubricant and a pH modifying agent.

The term "pH modifying agent" refers to chemical substances that could control/ modify the local environment at the site of dissolution. Suitable pH modifying agents according to the subject matter are alkalizing agents that are selected from the group including but not limited to, ammonia, ammonium carbonate, diethanolamine, monoethanolamine, potassium hydroxide, sodium bicarbonate, sodium borate, sodium carbonate, sodium phosphate dibasic, trolamine, meglumine, magnesium

oxide, polymers & copolymers such as of acrylic acids, methacrylic acids and their esters and derivatives thereof.

In another embodiment, copolymers of methacrylic acids and esters according the subject matter are selected from amino alkyl methacrylate copolymers, methacrylic acid copolymers, methacrylic ester copolymers, ammonioalkyl methacrylate copolymers or combinations thereof, commercially available under the brand name Eudragit®.

In another embodiment, Eudragit used according to the present subject matter is selected from Eudragit® E 100, Eudragit® E 12,5, Eudragit® E PO, Eudragit® L 100-55, Eudragit® L 30 D-55, Eudragit® L 100, Eudragit® L 12,5, Eudragit® S 100, Eudragit® S 12,5 or Eudragit® FS 30 D.

In another embodiment, the amount of pH-modifying agent present in the composition ranges from about 0%w/w to about 20%w/w based on the total weight of the composition. The pH-modifying agent is present in an amount of about 0%w/w, about 1%w/w, about 2%w/w, about 3%w/w, about 4%w/w, about 5%w/w, about 6%w/w, about 7%w/w, about 8%w/w, about 9%w/w, about 10%w/w, about 11%w/w, about 12%w/w, about 13%w/w, about 14%w/w, about 15%w/w, about 16%w/w, about 17%w/w, about 18%w/w, about 19%w/w or about 20%w/w based on the total weight of the core composition.

In another embodiment, the amount of pH-modifying agent present in the composition ranges from about 0%w/w to about 20%w/w based on the total weight of the composition. The pH-modifying agent is present in an amount of about 0%w/w, about 1%w/w, about 2%w/w, about 3%w/w, about 4%w/w, about 5%w/w, about 6%w/w, about 7%w/w, about 8%w/w, about 9%w/w, about 10%w/w, about 11%w/w, about 12%w/w, about 13%w/w, about 14%w/w, about 15%w/w, about 16%w/w, about 17%w/w, about 18%w/w, about 19%w/w or about 20%w/w based on the total weight of the composition including coating.

In another embodiment, axitinib and a pH modifying agent present are in a weight ratio of from about 1:1 to about 1:25.

In another embodiment, the weight ratio of axitinib and a pH modifying agent is selected from about 1:1, about 1:2, about 1:3, about 1:4, about 1:5, about 1:6, about 1:7, about 1:8, about 1:9, about 1:10, about 1:11, about 1:12, about 1:13, about 1:14,

about 1:15, about 1:16, about 1:17, about 1:18, about 1:19, about 1:20, about 1:21, about 1:22, about 1:23, about 1:24 or about 1:25.

In one embodiment, the composition is devoid of pH modifying agent.

In another embodiment of the present subject matter provides a pharmaceutical composition comprising crystalline axitinib form IV, a diluent, a lubricant and optionally a disintegrating agent.

The term "disintegrating agent" refers to a substance which, upon addition to a solid preparation, facilitates its break-up or disintegration after administration and permits the release of an active ingredient as efficiently as possible to allow for its rapid dissolution. Suitable disintegrating agents according to the subject matter are selected from the group including, but not limited to, sodium starch glycolate, sodium carboxy methyl cellulose, calcium carboxy methyl cellulose, croscarmellose sodium, crospovidone, polyvinylpyrrolidone, methyl cellulose, microcrystalline cellulose, lower alkyl-substituted hydroxypropyl cellulose, starch, pregelatinized starch and sodium alginate, or a combination thereof.

In another embodiment, the amount of disintegrating agent in the composition of present subject matter ranges from 0%w/w to 5%w/w based on the total weight of the core composition including coating.

In another embodiment, the disintegrating agent is present in an amount of about 0%w/w, about 1%w/w, about 2%w/w, about 3%w/w, about 4%w/w or about 5%w/w based on the total weight of the composition including coating.

In another embodiment, the present subject matter provides a pharmaceutical composition that is devoid of disintegrating agent.

In another embodiment, a pharmaceutical composition comprising crystalline axitinib form IV, a diluent, a lubricant and optionally a disintegrating agent and a binder.

In another embodiment, a pharmaceutical composition comprising crystalline axitinib form IV, a diluent, a lubricant and a glidant.

The term "glidant" as used herein is intended to mean agents used in tablet and capsule formulations to improve flow-properties during tablet compression and to produce an anti-caking effect. Suitable glidants according to the present subject matter are selected from the group including but not limited to, colloidal silicon dioxide, talc,

magnesium stearate, calcium stearate, stearic acid, anhydrous colloidal silica, magnesium trisilicate, magnesium silicate or a combination thereof.

In an embodiment, the amount of glidant in the composition of present subject matter ranges from 0%w/w to 5%w/w based on the total weight of the composition including coating.

In another embodiment, the glidant is present in an amount of 0%w/w, 1%w/w, 2%w/w, 3%w/w, 4%w/w or 5%w/w based on the total weight of the composition including coating.

In another embodiment, a pharmaceutical composition comprising crystalline axitinib form IV, a diluent, a lubricant and optionally a glidant.

In another embodiment, the present subject matter provides a pharmaceutical composition that is devoid of a glidant.

In another embodiment, the pharmaceutical composition according to the present subject matter is a tablet.

In another embodiment, the pharmaceutical composition according to the present subject matter is a film coated tablet.

In another embodiment, the tablet is coated with suitable coating material.

In another embodiment, the coating is applied is an aqueous coating or a non-aqueous coating.

In another embodiment, the coating is applied as aqueous coating solution or dispersion, preferably solution.

In another embodiment, aqueous coating solution is prepared by dissolving the coating material in desired amount of water under continuous stirring.

In another embodiment, aqueous coating dispersion is prepared by dispersing the coating material in desired amount of water under continuous stirring.

In another embodiment, the tablet composition is film coated by spraying coating solution or dispersion continuously till desired coating build up is formed.

In another embodiment, the coating material comprises film forming polymer, plasticizer, filler and light protecting agent.

Suitable film forming polymer is selected from the group including but not limited to, hydroxypropyl methylcellulose, hydroxypropylcellulose, hydroxyethylcellulose, ethylhydroxyethylcellulose, methylcellulose, and sodium carboxymethylcellulose and vinyls such as polyvinyl pyrrolidone.

In one embodiment film forming polymer is present in an amount of from about 30%w/w to 50%w/w based on total weight of the coating material.

In another embodiment, film forming polymer is present in an amount of about 30%w/w, about 35%w/w or about 40%w/w, about 45%w/w or about 50%w/w based on total weight of the coating material.

In another embodiment, film forming polymer is present in an amount of 35%w/w, 36%w/w, 37%w/w, 38%w/w, 39%w/w or 40%w/w based on total weight of the coating material.

In another embodiment, film forming polymer is present in an amount of 39% based on total weight of the coating material.

In another embodiment, the film forming polymer in the coating material is hydroxypropyl methylcellulose.

Suitable plasticizer is selected from the group including but not limited to, polyhydric alcohols such as glycerol and polyethylene glycols and acetate esters such as glycerol triacetate or glyceryl triacetate, which are known as triacetin, and triethyl citrate.

In one embodiment, plasticizer is present in an amount of from about 5%w/w to 15%w/w based on total weight of the coating material.

In another embodiment, plasticizer is present in an amount of about 5%w/w, about 6%w/w, about 7%w/w, about 8%w/w, about 9%w/w or about 10%w/w based on total weight of the coating material.

In another embodiment, plasticizer is present in an amount of about 8%w/w based on total weight of the coating material.

In another embodiment, the plasticizer in the coating material is triacetin.

Suitable filler of coating material is selected from the group including but not limited lactose monohydrate, anhydrous lactose and the like, Mannitol, polyvinyl

pyrrolidone, low molecular weight hydroxypropyl cellulose, microcrystalline cellulose, silicified microcrystalline cellulose, low molecular weight hydroxypropyl methylcellulose, low molecular weight carboxymethyl cellulose, ethylcellulose, dicalcium phosphate, alginates, gelatin, polyethylene oxide, acacia, magnesium aluminum silicate, and polymethacrylates, or a combination thereof.

In one embodiment, filler is present in coating material in an amount of from about 20%w/w to 40%w/w based on total weight of the coating material.

In another embodiment, filler is present in an amount of about 20%w/w, about 25%w/w or about 30%w/w, about 35%w/w or about 40%w/w based on total weight of the coating material.

In another embodiment, filler is present in an amount of 25%w/w, 26%w/w, 27%w/w, 28%w/w, 29%w/w or 30%w/w based on total weight of the coating material.

In another embodiment, filler of coating material is present in an amount of 28%w/w based on total weight of the coating material.

In another embodiment, filler of coating material is lactose monohydrate.

In another embodiment, the film coated pharmaceutical tablet composition wherein, the coating is free of iron oxide.

Suitable light protecting material is a light blocking material selected from titanium dioxide, calcium carbonate or a light absorbing material aluminium lake selected from FD&C Red No. 40 Aluminium Lake; FD&C Red No. 4 Lake; D&C Violet No. 2 Lake; D&C Yellow No. 10 Aluminium Lake; FD&C Yellow No. 6 Aluminium Lake; FD&C Yellow No. 5 Aluminium Lake; D&C Yellow No. 7 Lake; FD&C blue No. 2 Aluminium Lake and the like or a combination thereof.

In one embodiment, the light protecting material is a light blocking material calcium carbonate.

In another embodiment, the light protecting material is a light absorbing material aluminium lake.

In another embodiment, the light protecting material is a combination of light blocking material calcium carbonate and light absorbing material aluminium lake.

In another embodiment, light blocking material is present in an amount of about 15%w/w to about 30%w/w based on total weight of the coating material.

In another embodiment, light blocking material is present in an amount of about 15%w/w, about 20%w/w, about 25%w/w or about 30%w/w based on total weight of the coating material.

In another embodiment, light blocking material is present in an amount of about 20%w/w, about 21%w/w, about 22%w/w, about 23%w/w, about 24%w/w or about 25%w/w based on total weight of the coating material.

In another embodiment, light blocking material is present in an amount of about 21%w/w based on total weight of the coating material.

In another embodiment, light absorbing material is present in an amount of from about 2%w/w to about 10%w/w based on total weight of the coating material.

In another embodiment, light absorbing material is present in an amount of about 2%w/w, about 3%w/w, about 4%w/w, about 5%w/w, about 6%w/w, about 7%w/w, about 8%w/w, about 9%w/w or about 10%w/w based on total weight of the coating material.

In another embodiment, light absorbing material comprises atleast one aluminium lake in an amount of from 2%w/w to 10%w/w.

In another embodiment, atleast one aluminium lake is present in an amount of about 2%w/w, about 3%w/w, about 4%w/w, about 5%w/w, about 6%w/w, about 7%w/w, about 8%w/w, about 9%w/w or about 10%w/w based on total weight of the coating material.

In another embodiment, light absorbing material is atleast one aluminium lake in an amount of about 4%w/w based on total weight of the coating material.

In another embodiment, the coating is a non-functional film coating.

In another embodiment, the coating material used is Opadry® II 32K165001 (Opadry II brown) as supplied by Colorcon having below composition:

Table 1: Opadry® II 32K165001 composition

Ingredient	Amount (in %w/w)
Hydroxypropyl methylcellulose	39.00
Lactose monohydrate	28.00
Calcium carbonate	21.55
Triacetin	8.00
FD&C Red No. 40/allura Red AC aluminum Lake	3.45
FD&C yellow No. 5/Tartrazine aluminum Lake	
FD&C blue No. 2/indigo carmine aluminum Lake	

In another embodiment, a pharmaceutical composition comprising:

(a) a core comprising crystalline axitinib form IV, diluent and a lubricant;

(b) a coating which is devoid of iron oxide

In another embodiment, a pharmaceutical composition comprising:

(a) a comprises about 2% to about 5% of crystalline axitinib form IV, about 80% to about 95% of a diluent and about 1% to about 3% of a lubricant by weight of the composition.

(b) a coating which is devoid of iron oxide

In another embodiment, a pharmaceutical composition comprising:

(a) a core comprising crystalline axitinib form IV, lactose anhydrous, dicalcium phosphate and magnesium stearate;

(b) a coating that is devoid of iron oxide and is comprising atleast one aluminium lake.

In another embodiment, a pharmaceutical composition comprising:

(a) a core comprising an amount of about 2%w/w to about 5%w/w of crystalline axitinib form IV, an amount of about 80%w/w to about 95%w/w of diluent which is a combination of lactose anhydrous & dicalcium phosphate and about 1%w/w to about 3%w/w of a lubricant which is magnesium stearate, wherein the amount is based on total weight of the composition including coating;

(b) a coating that is devoid of iron oxide and is comprising atleast one aluminium lake.

In another embodiment, a pharmaceutical composition comprising:

(a) a core comprising crystalline axitinib form IV, diluent, pH modifying agent and a lubricant;

(b) a coating which is devoid of iron oxide

In another embodiment, a pharmaceutical composition comprising:

(a) a core comprising an amount of about 2%w/w to about 5%w/w of crystalline axitinib form IV, about 80%w/w to about 95%w/w of diluent, about 2%w/w to 12%w/w of pH modifying agent and about 1%w/w to about 3%w/w of a lubricant, wherein the amount is based on total weight of the composition including coating;

(b) a coating which is devoid of iron oxide

In an embodiment, the manufacturing process to prepare a composition of the present subject matter is selected from direct compression, dry granulation and wet granulation or any other technique known in the art.

In another embodiment, the subject matter provides combination of unit operations selected from sifting, blending, granulation, drying, compression and optionally film coating as the steps involved in the preparation axitinib tablets.

In another embodiment, a film coated tablet composition of crystalline axitinib form IV is prepared by a process comprising the steps of:

a. sifting and blending axitinib and other desired excipients,
b. granulating the blend of step (a),
c. lubricating granules of step (b)
d. compressing lubricated blend of step (c) into tablets of desired dimensions,
e. film coating tablets of step (d) using desired coating solution.

In another embodiment, a film coated tablet composition of crystalline axitinib form IV is prepared by a process comprising the steps of:

a. sifting axitinib and other desired excipients through desired mesh followed by blending to form a blend,
b. loading blend of step (a) into a granulator and granulating it using purified water,

c. drying the wet granular mass resulted from step (b) followed by milling to get desired sized granules,
d. blending milled granules of step (c) with sifted extra granular materials,
e. lubricating granules of step (c) or (d) using sifted magnesium stearate,
f. compressing lubricated blend of step (e) into tablets of desired dimensions,
g. film coating tablets of step (f) using coating solution.

In another embodiment, a film coated tablet composition of crystalline axitinib form IV is prepared by a process comprising the steps of:

a. sifting axitinib and other desired excipients through desired mesh followed by blending to form a blend,
b. loading blend of step (a) into a granulator and granulating it using purified water,
c. drying the wet granular mass resulted from step (b) followed by milling to get desired sized granules,
d. blending milled granules of step (c) with sifted extra granular materials,
e. lubricating granules of step (c) or (d) using sifted magnesium stearate,
f. compressing lubricated blend of step (e) into tablets of desired dimensions,
g. film coating tablets of step (f) using opadry II 3K165001 coating solution which is devoid of iron oxide.

In another embodiment, a film coated tablet composition of crystalline axitinib form IV is prepared by a process comprising the steps of:

a. sifting axitinib and other desired excipients through desired mesh followed by blending to form a blend,
b. preparing a binder solution by dissolving binder in the purified water under slow stirring,
c. loading blend of step (a) into a granulator and granulating it using binder solution of step (b),
d. drying the wet granular mass resulted from step (c) followed by milling to get desired sized granules,
e. blending milled granules of step (d) with sifted extra granular materials,
f. lubricating granules of step (d) or (e) using sifted magnesium stearate,
g. compressing lubricated blend of step (f) into tablets of desired dimensions,
h. film coating tablets of step (g) using coating solution.

Another aspect of the present subject matter provides a stable pharmaceutical composition of crystalline axitinib form IV in the form of tablet dosage form which are bioequivalent to the commercially available axitinib tablets (INLYTA®).

Further embodiment of the present subject matter provides method of treating advanced renal cell carcinoma after failure of one prior systemic therapy in a patient by administering the patient the tablet composition according to the present subject matter.

Examples

The following examples further demonstrate particular embodiments of the present subject matter within the scope. These examples are solely for illustration purpose and are not to be construed as limitations as many variations are possible within the scope without deviating from it.

Example 1:

Table 2: Composition of Axitinib (form IV) film coated tablets

Ingredient	Quantity (in %w/w)	
	Example 1a	Example 1b
Granulation		
Axitinib	2.00	2.40
Lactose anhydrous	81.50	81.20
Dicalcium phosphate	12.00	11.50
Purified water	q.s.	q.s.
Lubrication		
Magnesium Stearate	1.00	0.900
Coating		
Opadry II Brown	4.00	4.00
Coated tablet weight	100.00	100.00

Example 2:

Table 3: Composition of Axitinib (form IV) film coated tablets

Ingredient	Quantity (in %w/w)
Granulation	
Axitinib	2.00
Lactose anhydrous	89.50
Croscarmellose sodium	3.50
Purified water	q.s.
Lubrication	
Magnesium Stearate	1.00
Coating	
Opadry II Brown	4.00
Coated tablet weight	100.00

Example 3:

Table 4: Composition of Axitinib (form IV) film coated tablets

Ingredient	Quantity (in %w/w)
Granulation	
Axitinib	2.00
Lactose anhydrous	89.00
Hydroxypropyl methylcellulose	4.00
Purified water	q.s.
Lubrication	
Magnesium Stearate	1.00
Coating	
Opadry II Brown	4.00
Coated tablet weight	100.00

Example 4:

Table 5: Composition of Axitinib (form IV) film coated tablets

Ingredient	Quantity (in %w/w)
Dry mix	
Axitinib	2.00
Dicalcium phosphate	89.10
Croscarmellose sodium	3.00
Binder solution	
Purified water	q.s.
Extra granular	
Colloidal silicon dioxide	0.90
Lubrication	
Magnesium Stearate	1.00
Coating	
Opadry II Brown	4.00
Coated tablet weight	100.00

Example 5:

Table 6: Composition of Axitinib (form IV) film coated tablets

Ingredient	Quantity (in %w/w)
Dry mix	
Axitinib	2.00
Lactose anhydrous	89.00
Croscarmellose sodium	3.00
Sodium lauryl sulphate	1.00
Purified water	q.s.
Extra granular	
Lubrication	
Magnesium Stearate	1.00
Coating	

Opadry II Brown	4.00
Coated tablet weight	100.00

Example 6:

Table 7: Composition of Axitinib (form IV) film coated tablets

Ingredient	Quantity (in %w/w)
Dry mix	
Axitinib	2.00
Microcrystalline cellulose	66.50
Dicalcium phosphate	10.00
Croscarmellose sodium	3.00
Sodium lauryl sulphate	1.00
Binder solution	
Hydroxypropyl methylcellulose	3.00
Purified water	q.s.
Extra granular	
Microcrystalline cellulose	10.00
Colloidal silicon dioxide	0.50
Lubrication	
Magnesium Stearate	1.00
Coating	
Opadry II Brown	3.00
Coated tablet weight	100.00

Brief manufacturing process for examples 1 to 6:

a. Axitinib and other desired excipients are sifted through desired mesh and blended,
b. binder solution is prepared by dissolving hydroxypropyl methylcellulose in purified water under slow stirring,

c. blend of step (a) is loaded into a granulator and is granulated using purified water or binder solution of step (b),
d. the resultant wet granular mass of step (c) is dried and milled to get desired sized granules,
e. optionally, milled granules of step (d) is blended with sifted extra granular materials,
f. granules of step (d) or (e) are lubricated using sifted magnesium stearate,
g. lubricated granular blend resulted from step (f) is compressed into tablets of desired dimensions,
h. tablets of step (g) are film coated using Opadry II Brown coating solution.

Example 7 to 8:

Table 8: Composition of Axitinib (form IV) film coated tablets

Name of the ingredient	Amount (in %w/w)	
	Example 7	Example 8
Granulation		
Axitinib	2.86	2.00
Microcrystalline Cellulose	88.85	85.00
Sodium bicarbonate	2.86	-
Eudragit L30 D 55	-	7.57
Croscarmellose Sodium	1.71	1.71
Binder solution		
Hydroxypropyl methylcellulose	2.86	2.86
Purified water	q.s.	q.s.
Lubrication		
Magnesium Stearate	0.86	0.86
Core Tablet Weight	100.00	100.00
Coating		
Opadry II Brown	4.50	4.50

Brief manufacturing process for examples 7 to 8:

a. Axitinib and other desired excipients are sifted through desired mesh and blended,
b. binder solution, if it is hydroxypropyl methylcellulose solution in the purified water, is prepared by dissolving hydroxypropyl methylcellulose in purified water under slow stirring,
c. blend of step (a) is loaded into a granulator and is granulated using binder solution of step (b) or purified water alone,
d. the resultant wet granular mass of step (c) is dried and milled to get desired granules,
e. granules of step (d) are lubricated using sifted magnesium stearate,
f. lubricated granular blend resulted from step (e) is compressed into tablets of desired dimensions,
g. tablets of step (f) are film coated using Opadry II Brown coating solution.

Comparative dissolution studies:

Dissolution test for 6 tablets each of example 1, example 7 and INLYTA tablets 5mg (RLD) was performed using USP apparatus II, 75 rpm in 900ml of 0.01 N HCl as medium. The Q point as per USP 29, for this test is set to be 60Q at 30 minutes.

Table 9: Dissolution studies

Time (in minutes)	Mean dissolution (in % w/w)			
	INLYTA® tablets 5 mg	Example 1a	Example 1b	Example 7
15	74	38	33	53
30	90	75	69	69
45	96	85	82	77
60	99	89	87	82

Stability studies:

The tablets obtained in example 1b and example 7 were filled in a HDPE container along with silica canister and is subjected to a stability evaluation at 40° C and 75% relative humidity. The samples from stability were evaluated at different time intervals for assay, impurity levels and dissolution and results are presented as below:

Table 10: Stability studies for example 1b

Assay	Amount (in %w/w)			
	Initial	1 month	2 months	3 months
	97.7	98.7	97.3	98.2
Impurities				
2 + 2 dimer Impurity	0.00	0.00	0.00	0.00
formula IV Impurity	0.019	0.022	0.027	0.027
Total impurities	0.264	0.261	0.300	0.262
Dissolution test				
Time point (Min)	**Mean dissolution (in % w/w)**			
15	33	43	40	42
30	69	75	75	73
45	82	84	84	85
60	87	88	88	89

Table 11: Stability studies for example 7

Assay	Amount (in %w/w)		
	Initial	1 month	2 months
	100.7	105.7	100.7
Impurities			
2 + 2 dimer Impurity	0.00	0.00	0.00
formula IV Impurity	0.023	0.012	0.034
Total impurities	0.042	0.154	0.174
Dissolution test			
Time point (Min)	**Mean dissolution (in % w/w)**		
15	53	57	50
30	69	74	66
45	77	83	75
60	82	88	81

We Claim:

1. A stable pharmaceutical composition comprising:
   (a) a core comprising crystalline axitinib form IV and one or more pharmaceutically acceptable excipient,
   (b) a coating over said core, wherein coating is devoid of iron oxide.

2. The composition of claim 1, wherein the composition is devoid of any crystalline forms of axitinib other than form IV.

3. The composition of claim 1, wherein one or more pharmaceutically acceptable excipient comprises: a diluent; a disintegrating agent; a pH-modifying agent; a binder; a glidant; a lubricant; or mixtures thereof.

4. The composition of claim 1, wherein one or more pharmaceutically acceptable excipient comprises a pH-modifying agent.

5. The composition of claim 4, wherein crystalline axitinib form IV and a pH modifying agent are present in a weight ratio of about 1:1 to about 1:25.

6. The composition of claim 3, wherein the core comprises about 2% to about 5% of crystalline axitinib form IV, about 80% to about 95% of a diluent and about 1% to about 3% of a lubricant by weight of the composition.

7. The composition of claim 1 to 6, wherein the coating comprises a film forming polymer, a filler, a plasticizer and a light protecting agent.

8. The composition of claim 1 to 7, wherein the coating comprises hydroxypropyl methyl cellulose, lactose monohydrate, triacetin, calcium carbonate and atleast one aluminium lake.

9. The composition of claim 1, wherein the composition exhibits less than 0.10% w/w of 2+2 dimer impurity and less than 0.5% w/w of total impurities when stored at 40°C/ 75% RH for at least 2 months.

10. The composition of claim 1, wherein the composition is bioequivalent to commercially available axitinib tablets (INLYTA®).

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2019/055454

A. CLASSIFICATION OF SUBJECT MATTER
A61K31/4439,A61K9/20,A61K9/00,C07D401/06 Version=2019.01

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, 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)

TotalPatent One, IPO Internal Database, Reprints Desk

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2014/0248347 A1 (PFIZER INC.) 04 SEPTEMBER 2014 (04.09.2014) *paras 130-134,176-180,183-186,188; Tables 17,19; examples 2-4*	1-10
X	US 2006/0094763 A1 (AGOURON PHARMACEUTICALS, INC.) 04 MAY 2006 (04.05.2006) *claim 1; paras 131,137; example 8*	1-3,7,9-10

☐ 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
"D" document cited by the applicant in the international application
"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
09-09-2019	09-09-2019
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INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IB2019/055454

Citation	Pub.Date	Family	Pub.Date
US 2014/0248347 A1	04-09-2014	EP 2760434 A1	06-08-2014
		WO 2013046133 A1	04-04-2013
US 2006/0094763 A1	04-05-2006	EP 1819696 A1	22-08-2007
		WO 2006048751 A1	11-05-2006