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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
6 August 2015 (06.08.2015)

WIPO | PCT

(10) International Publication Number
WO 2015/114314 A1

(51) International Patent Classification:
A61K 31/573 (2006.01) *A61K 9/20* (2006.01)
A61K 31/58 (2006.01) *A61P 35/00* (2006.01)
A61K 9/00 (2006.01)

(21) International Application Number:
PCT/GB2015/050175

(22) International Filing Date:
27 January 2015 (27.01.2015)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
303/MUM/2014 28 January 2014 (28.01.2014) IN

(71) Applicant: **CIPLA LIMITED** [IN/IN]; Cipla House, Peninsula Business Park, Ganpatrao Kadam Marg, Lower Parel, Mumbai 400 013 (IN).

(71) Applicant *(for MW only)*: **KING, Lawrence** [GB/GB]; 10 Old Bailey, London EC4M 7NG (GB).

(72) Inventors: **MALHOTRA, Geena**; 4 Anderson House, Opposite Mazgaon Post Office, Mazgaon, Maharashtra, Mumbai 400 010 (IN). **RAUT, Preeti**; A - 502, Anant Tejpal Scheme Road No.5, Ville Parle (East), Maharashtra, Mumbai 400 057 (IN).

(74) Agent: **A.A. THORNTON & CO.**; 10 Old Bailey, London EC4M 7NG (GB).

(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, 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, KN, KP, KR, 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).

Published:

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

WO 2015/114314 A1

(54) Title: PHARMACEUTICAL COMPOSITION COMPRISING ABIRATERONE

(57) Abstract: The present invention relates to relates to a pharmaceutical composition comprising abiraterone and one or more pharmaceutically acceptable excipients, to a process for preparing such pharmaceutical composition and to the use of the said pharmaceutical composition for the treatment of prostate cancer.

PHARMACEUTICAL COMPOSITION COMPRISING ABIRATERONE

FIELD OF INVENTION:

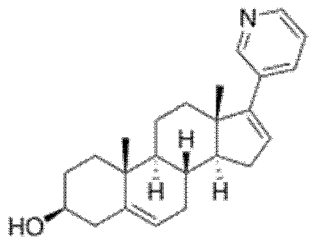
The present invention relates to a pharmaceutical composition comprising a 17"-hydroxylase/C 17,20-lyase enzyme (CYP17) inhibitor, to a process for preparing such pharmaceutical composition and to the use of the said pharmaceutical composition for the treatment of prostate cancer.

BACKGROUND AND PRIOR ART:

Prostate cancer is one of the most commonly diagnosed solid organ malignancies in the United States (US) and remains the second leading cause of cancer deaths among American males. Approximately 240,000 new diagnoses of prostate cancer and over 28,000 deaths were estimated in the US in 2012. Prostate cancer deaths are typically the result of metastatic castration-resistant prostate cancer (mCRPC), and historically the median survival for males with mCRPC has been less than two years.

Abiraterone acetate is an irreversible inhibitor of CYP 17, an androgen biosynthesis inhibitor. This enzyme is expressed in testicular, adrenal and prostatic tumor tissues. Inhibition of this enzyme results in further reduction of testosterone synthesis in patients already undergoing androgen deprivation therapy.

Abiraterone acetate in combination with prednisone is indicated for the treatment of patients with mCRPC who have received prior chemotherapy of docetaxel. Abiraterone is structurally represented as:



WO2013012959 discloses a composition comprising a solid dispersion of abiraterone and a solid matrix, wherein abiraterone is dispersed in the solid matrix.

US2013251804 discloses a dosage form of abiraterone in the form of a rounded pill with a water-soluble polymer coating having a thickness between 10 and 500 micrometers.

WO2013164473 discloses abiraterone acetate dissolved or dispersed in a carrier, wherein the carrier comprises one or more lipid excipients.

WO2014145813 discloses a method of producing a composition comprising nanoparticles of abiraterone acetate. The method comprises dry milling a composition comprising abiraterone acetate, a millable grinding compound, a facilitating agent and one or both of an antioxidant and a sequestering agent, in a mill comprising a plurality of milling bodies, for a time period sufficient to produce a composition comprising fine particles of the abiraterone acetate.

WO2014009436 discloses a nanosuspension comprising particles of abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof having an average particle size, d(0.5), of less than 1000 nm.

The recommended dose of abiraterone acetate is 1000 mg per day (QD), in combination with prednisone 5 mg twice a day (bid). Tablets comprising 250 mg abiraterone acetate are sold under the trade name Zytiga®. Thus, the required dosage is comprised in four Zytiga® tablets that have to be administered orally once a day.

One of the issues with abiraterone is that its pharmacokinetic properties are affected by the prandial status of a patient receiving the treatment, i.e. it exhibits a "food effect". In particular, the bioavailability of abiraterone increases with food, more specifically 10 times in a fed state as compared to a fasted state. Also, after a low fat meal, maximum or peak serum concentration (C_{max}) and area under the curve (AUC) are elevated 5 to 7 times when compared with the fasted state, whereas the C_{max} and AUC are elevated 10 to 17 times after a high fat meal. This leads to erratic and unpredictable bioavailability. As such, abiraterone is recommended to be administered in a fasted state in an attempt to minimize the food effect. Patients receive specific instructions to administer Zytiga® on an empty stomach, that is, no food intake during a period of 2 hours before dosing, and for a period one hour after dosing.

Zytiga® is administered in a fasted state in an attempt to minimize the food effect. However, Zytiga® has poor bioavailability in fasted subjects and must therefore be administered at a very

high daily dose of 1000 mg. Administration of an abiraterone composition with food may change its bioavailability by affecting either the drug substance or the composition in which the drug substance is formulated.

This situation is unsatisfactory and inconvenient to the patients especially cancer patients since their medications usually consist of multiple drug regimen demanding the administration of large numbers of tablets or capsules often along with intravenous therapy.

Further, these cancer patients often suffer from nausea and lesions of the oral mucosa. Therefore the oral administration of abiraterone may be hampered by factors such as emesis and ingestion and would ultimately lead to decreased bioavailability of abiraterone.

Hence, it would be desirable to reduce the dosing regimen as well as nullify the food effect of abiraterone. Further, the resulting composition of abiraterone should be stable as well as exhibit optimal dissolution properties.

However, these characteristics are often difficult to achieve with high concentrations of abiraterone.

Accordingly, there have been no prior arts disclosing the dosage and ease of administration of abiraterone thereby facilitating patient compliance. Hence, the currently commercialized dosage form and the recommended dose still do not address the unsolved tribulations of the abiraterone therapy and the economic factor of manufacturing.

In particular, the dry milling process disclosed in WO2014145813 may generally lead to particle agglomeration of small primary particles to larger secondary particles which could be a major hindrance in the milling process.

Attempts to address the prior art problems have lead the inventors of the present invention to develop a patient compliant pharmaceutical composition with technical advancement and economic significance.

OBJECTS OF THE INVENTION:

The object of the present invention is to provide a pharmaceutical composition comprising abiraterone optionally with one or more pharmaceutically acceptable excipients.

Another object of the present invention is to provide a rapid release pharmaceutical composition comprising abiraterone.

Another object of the present invention is to provide a pharmaceutical composition comprising abiraterone which ensure patient compliance.

Another object of the present invention is to provide a pharmaceutical composition comprising abiraterone having improved surface area and solubility.

Another object of the present invention is to provide a pharmaceutical composition comprising abiraterone, wherein the total daily dose is less than 1000 mg.

Another object of the present invention is to provide a pharmaceutical composition comprising abiraterone devoid of any food effect.

Another object of the present invention is to provide a pharmaceutical composition comprising abiraterone for once a day administration.

Another object of the present invention is to provide a process for preparing a pharmaceutical composition comprising abiraterone optionally with one or more pharmaceutically acceptable excipients.

Another object of the present invention is to provide a method of treating prostate cancer by administering a pharmaceutical composition comprising abiraterone.

Another object of the present invention is to provide the use of pharmaceutical composition comprising abiraterone for the treatment of prostate cancer.

SUMMARY OF THE INVENTION:

According to one aspect of the present invention, there is provided a pharmaceutical composition comprising abiraterone and one or more pharmaceutically acceptable excipients.

According to another aspect of the present invention, there is provided a process for preparing a pharmaceutical composition, comprising admixing one or more pharmaceutically acceptable excipients with abiraterone.

According to yet another aspect of the present invention there is provided a pharmaceutical composition comprising abiraterone for use in the treatment of prostate cancer.

According to a further aspect of the present invention there is provided a method of treatment of prostate cancer which comprises administering a pharmaceutical composition comprising abiraterone.

DETAILED DESCRIPTION OF THE INVENTION:

Abiraterone is commercially available as a conventional tablet formulation for the treatment of prostate cancer. The required dosage is comprised in four abiraterone tablets that have to be administered orally once a day. Further, cancer patients are usually on a multiple drug regimen demanding the administration of large numbers of tablets or capsules often along with intravenous therapy.

Patient compliance in such a regimen can be addressed by decreasing the number of tablets or capsules administered as well as the type of dosage forms that are administered, with due consideration to the bioavailability of the administered drug. The bioavailability of the drug cannot be compromised to meet patient compliance.

Hence, abiraterone as an active pharmaceutical agent used for treating prostate cancer, would be, preferred in a low dose oral composition provided in such a dosage form which exhibit desired therapeutic effect and at the same time would ensure patient compliance. A low dose orally dispersible composition of abiraterone when designed was considered as the best approach, as these compositions could be dispersed in water and then easily administered by the patient and thus are advantageous for use in elder and noncompliant cancer patients.

The present invention provides a pharmaceutical composition comprising abiraterone and one or more pharmaceutically acceptable excipients, which is intended to ensure patient compliance due to simplification of therapy.

The term “abiraterone” is used in broad sense to include not only “abiraterone” *per se* but also its pharmaceutically acceptable derivatives thereof. Suitable derivatives include pharmaceutically acceptable salts, pharmaceutically acceptable solvates, pharmaceutically acceptable hydrates, pharmaceutically acceptable isomers, pharmaceutically acceptable esters, pharmaceutically acceptable anhydrates, pharmaceutically acceptable enantiomers, pharmaceutically acceptable polymorphs, pharmaceutically acceptable prodrugs, pharmaceutically acceptable tautomers and/or pharmaceutically acceptable complexes thereof.

Preferably, the pharmaceutical composition of the present invention comprises abiraterone in the form of abiraterone acetate.

The term “low dose” as used herein refers to a therapeutically effective dose of abiraterone, which dose is less than the usual or the conventional dose required to produce equal or higher therapeutic effect. Preferably, the term “low dose” means a total daily dose of abiraterone of less than 1000 mg per day.

The term "pharmaceutical composition" includes oral dosage forms, such as but not limited to, tablets, soft gelatin capsule, capsules (filled with powders, powders for reconstitution, pellets, beads, mini-tablets, pills, micro-pellets, small tablet units, multiple unit pellet system (MUPS), disintegrating tablets, dispersible tablets, granules, sprinkles microspheres and multiparticulates), sachets (filled with powders, pellets, beads, mini-tablets, pills, micro-pellets, small tablet units, MUPS, disintegrating tablets, dispersible tablets, granules, sprinkles microspheres and multiparticulates) and sprinkles.

However, other dosage forms such as oral liquid dosage forms (liquids, liquid dispersions, suspensions, solutions, emulsions, syrups, elixirs) may also be envisaged under the ambit of the invention.

Preferably, the pharmaceutical composition is a single unit dosage form. More preferably, the pharmaceutical composition is a single unit dosage form adapted for once daily administration.

Preferably, the pharmaceutical composition of the present invention comprising abiraterone is in the form of a tablet. More preferably, the pharmaceutical composition of the present invention

comprising abiraterone is in the form of an oral disintegrating tablet, disintegrating tablet or dispersing tablet, for example a tablet that dissolves in water.

The pharmaceutical composition of the present invention preferably comprises less than 1000 mg of abiraterone, more preferably from about 125 mg to about 800 mg of abiraterone.

There is also provided a pharmaceutical composition comprising abiraterone with one or more pharmaceutically acceptable excipients wherein composition is formulated to provide a total daily dose of abiraterone of less than 1000 mg, preferably from about 125 mg to about 800 mg.

The pharmaceutical composition, according to the present invention may be administered at least once a day. Preferably, the pharmaceutical composition is administered once a day. The daily dose is preferably less than the conventionally administered dose, more preferably from about 300 mg to about 800 mg of abiraterone, still more preferably from about 175 mg to about 800 mg, and most preferably from about 125 mg to about 800 mg of abiraterone. Preferably, the composition is formulated to be administered as a single daily dose.

Preferably, the pharmaceutical composition of the present invention may be administered with or without food. More preferably, the composition does not exhibit a food effect.

The inventors of the present invention have also further observed that the solubility properties of abiraterone are improved by nanosizing, thus leading to better bioavailability of the drug.

Nanonization of hydrophobic or poorly water-soluble drugs generally involves the production of drug nanocrystals through either chemical precipitation (bottom-up technology) or disintegration (top-down technology). Different methods may be utilized to reduce the particle size of the hydrophobic or poorly water soluble drugs. [Huabing Chen *et al.*, discusses the various methods to develop nanoformulations in "Nanonization strategies for poorly water-soluble drugs," Drug Discovery Today, Volume 00, Number 00, March 2010].

The present invention thus provides a pharmaceutical composition comprising abiraterone wherein abiraterone is in the nanosize range.

The term "nanosize" as used herein refers to abiraterone particles having an average particle size of less than or equal to about 2000 nm, preferably less than or equal to about 1000 nm.

Mostly all of the particles have a particle size of less than or equal to about 2000 nm, preferably less than or equal to about 1000 nm. Preferably, the particle size of abiraterone varies with D_{90} not less than or equal to 700 nm, more preferably less than or equal to 300 nm.

The term "particles" as used herein refers to individual particles of abiraterone, or particles of abiraterone granules and/or mixtures thereof.

The nanosize particles of the present invention can be obtained by any of the process such as but not limited to milling, precipitation, homogenization, high pressure homogenization, spray-freeze drying, supercritical fluid technology, double emulsion/solvent evaporation, PRINT (Particle replication in non-wetting templates), thermal condensation, ultrasonication, spray drying or the like. Such nanoparticles obtained by any of these processes may further be formulated into desired dosage forms.

The nanoparticles of the abiraterone are preferably prepared by:

(1) homogenizing abiraterone and at least one excipient to produce a homogenized dispersion; and

(2) milling the said homogenized dispersion to produce a slurry comprising abiraterone and/or abiraterone particles having an average particle size of less than or equal to about 2000 nm

(3) processing the slurry to obtain the desired dosage form.

Preferably, the process comprises a wet milling step. Alternatively, the process does not include a dry milling step.

The present invention provides a process for preparing a pharmaceutical composition, which process comprises which process comprises admixing one or more pharmaceutically acceptable excipients with abiraterone.

Preferably, the pharmaceutical composition of the present invention in the form of an orally disintegrating tablet that can be prepared by any of the processes such as freeze drying/lyophilization, moulding, sublimation, spray drying, mass extrusion and direct compression or the like.

Suitable excipients may be used for formulating the tablet dosage form according to the present invention such as, but not limited to, disintegrants, diluents, plasticizers, binders, glidants, lubricants, sweeteners, flavoring agents, antioxidants , texture enhancers , viscosity modifying agents , polymers , channeling agents , anti-caking agents, anti-microbial agents, antifoaming agents, emulsifiers, surfactants, buffering agents and coloring agents and combinations thereof.

Suitable disintegrants or super disintegrants include, but are not limited to, agar-agar, calcium carbonate, microcrystalline cellulose, crospovidone, povidone, polacrilin potassium, sodium starch glycolate, potato or tapioca starch, other starches, pre-gelatinized starch, clays, alginic acid, alginates such as sodium alginate other algins, other celluloses, gums, ion-exchange resins, magnesium aluminum silicate, sodium dodecyl sulfate, sodium carboxymethyl cellulose, croscarmellose sodium, polyvinylpyrollidone, cross-linked PVP, carboxymethyl cellulose calcium, crosslinked sodium carboxymethyl cellulose, docusate sodium, guar gum, low-substituted HPC, polacrilin potassium, poloxamer, povidone, sodium glycine carbonate and sodium lauryl sulfate or mixtures thereof.

The amount of disintegrant in the pharmaceutical compositions may range from about 5% w/w to about 30% w/w of the total weight of the composition.

Suitable binders may also present in the in the pharmaceutical compositions of the present invention, which may comprise one or more, but not limited to polyvinyl pyrrolidone (also known as povidone), polyethylene glycol(s), acacia, alginic acid, agar, calcium carragenan, cellulose derivatives such as ethyl cellulose, methyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, sodium carboxymethylcellulose, dextrin, gelatin, gum arabic, guar gum, tragacanth, sodium alginate, or mixtures thereof or any other suitable binder.

The amount of binder in the pharmaceutical compositions may range from about 5% w/w to about 20% w/w of the total weight of the composition.

Suitable carriers, diluents or fillers for use, in the pharmaceutical composition of the present invention may comprise one or more, but not limited to lactose (for example, spray-dried lactose, α-lactose, β-lactose) lactose available under the trade mark Tablettose, various grades of lactose available under the trade mark Pharmatose or other commercially available forms of lactose, lactitol, saccharose, sorbitol, mannitol, dextrates, dextrins, dextrose, maltodextrin,

croscarmellose sodium, microcrystalline cellulose (for example, microcrystalline cellulose available under the trade mark Avicel), hydroxypropylcellulose, L-hydroxypropylcellulose (low substituted), hydroxypropyl methylcellulose (HPMC), methylcellulose polymers (such as, for example, Methocel A, Methocel A4C, Methocel A15C, Methocel A4M), hydroxyethylcellulose, sodium carboxymethylcellulose, carboxymethylene, carboxymethyl hydroxyethylcellulose and other cellulose derivatives, starches or modified starches (including potato starch, corn starch, maize starch and rice starch) or mixtures thereof.

The amount of carriers, diluents or fillers in the pharmaceutical compositions may range from about 15% w/w to about 60 % w/w of the total weight of the composition.

Glidants, anti-adherents and lubricants may also be incorporated in the pharmaceutical composition of the present invention, which may comprise one or more, but not limited to stearic acid and pharmaceutically acceptable salts or esters thereof (for example, magnesium stearate, calcium stearate, zinc stearate, sodium stearyl fumarate or other metallic stearate), talc, waxes (for example, microcrystalline waxes) and glycerides, mineral oil, light mineral oil, PEG, silica acid or a derivative or salt thereof (for example, silicates, silicon dioxide, colloidal silicon dioxide and polymers thereof, crospovidone, magnesium aluminosilicate and/ or magnesium alumino metasilicate), sucrose ester of fatty acids, hydrogenated vegetable oils (for example, hydrogenated castor oil, peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil and soybean oil), glycerin, sorbitol, mannitol, other glycols, sodium lauryl sulfate, talc, long chain fatty acids and their salts, ethyl oleate, ethyl laurate, agar, syloid silica gel (a coagulated aerosol of synthetic silica (Evonik Degussa Co., Plano, Tex. USA), a pyrogenic silicon dioxide (CAB-O-SIL, Cabot Co., Boston, Mass. USA), or mixtures thereof.

The amount of glidants, anti-adherents and lubricants in the pharmaceutical compositions may range from about 0.1% w/w to about 5 % w/w of the total weight of the composition.

Anti-caking agents may also be incorporated in the pharmaceutical composition of the present invention. Suitable anti-caking additives include, but are not limited to, calcium silicate, magnesium silicate, silicon dioxide, colloidal silicon dioxide, talc, or mixtures thereof.

Anti-microbial agents and/or preservatives may also be incorporated in the pharmaceutical composition of the present invention. Suitable anti-microbial agents and/or preservatives include,

but are not limited to, benzalkonium chloride, benzethonium chloride, benzoic acid, benzyl alcohol, butyl paraben, cetylpyridinium chloride, cresol, chlorobutanol, dehydroacetic acid, ethylparaben, methylparaben, phenol, phenylethyl alcohol, phenoxyethanol, phenylmercuric acetate, phenylmercuric nitrate, potassium sorbate, propylparaben, sodium benzoate, sodium dehydroacetate, sodium propionate, sorbic acid, citric acid, tartaric acid, lactic acid, malic acid, acetic acid, benzoic acid, thimersol, thymo, or mixtures thereof.

Sweetening agents may also be incorporated in the pharmaceutical composition of the present invention. Suitable sweetening agent or taste-masking agents include, but are not limited to, essential oils, water soluble extracts, sugar (natural or synthetic), monosaccharides, oligosaccharides, aldose, ketose, dextrose, maltose, lactose, glucose, fructose, sucrose, mannitol xylitol, D-sorbitol, erythritol, pentitol, hexitol, malitol, acesulfame potassium, talin, glycyrrhizin, sucralose, aspartame, saccharin, sodium saccharin, acesulfame, thaumatin, dihydrochalcone, alitame, miraculin, monellin, stevside sodium cyclamate, eugenyl formate aldehyde flavorings or mixtures thereof.

Suitable flavors/flavouring agents which may be used in the pharmaceutical composition of the present invention include, but are not limited to, essential oils including distillations, solvent extractions, or cold expressions of chopped flowers, leaves, peel or pulped whole fruit containing mixtures of alcohols, esters, aldehydes and lactones; essences including either diluted solutions of essential oils, or mixtures of synthetic chemicals blended to match the natural flavor of the fruit (e.g., strawberry, raspberry and black currant); artificial and natural flavors of brews and liquors, e.g., cognac, whisky, rum, gin, sherry, port, and wine; tobacco, coffee, tea, cocoa, and mint; fruit juices including expelled juice from washed, scrubbed fruits such as lemon, orange, and lime; spear mint, pepper mint, wintergreen, cinnamon, cacoe/cocoa, vanilla, liquorice, menthol, eucalyptus, aniseeds nuts (e.g., peanuts, coconuts, hazelnuts, chestnuts, walnuts, colanuts), almonds, raisins; and powder, flour, or vegetable material parts including tobacco plant parts, e.g., genus Nicotiana and ginger or mixtures thereof.

Suitable antioxidants which may be used in the pharmaceutical composition of the present invention include, but are not limited to, tocopherols, ascorbic acid, sodium pyrosulfite, butylhydroxytoluene, butylated hydroxyanisole, edetic acid, and edetate salts, or mixtures thereof.

Suitable texture enhancers which may be used in the pharmaceutical composition of the present invention include, but are not limited to, pectin, polyethylene oxide, and carrageenan, or mixtures thereof.

Surface stabilizers are surfactants that are capable of stabilizing the increased surfaced charge drug. Suitable amphoteric, non-ionic, cationic or anionic surfactants may be included in the pharmaceutical composition of the present invention.

Suitable surfactants which may be used in the pharmaceutical composition of the present invention may comprise of one or more, but not limited to Polysorbates, Sodium dodecyl sulfate (sodium lauryl sulfate), Lauryl dimethyl amine oxide, Docusate sodium, Cetyl trimethyl ammonium bromide (CTAB) Polyethoxylated alcohols, Polyoxyethylene sorbitan, Octoxynol, N, N–dimethyldodecylamine–N–oxide, Hexadecyltrimethylammonium bromide, Polyoxyl 10 lauryl ether, Brij, Bile salts (sodium deoxycholate, sodium cholate), Polyoxyl castor oil, Nonylphenol ethoxylate Cyclodextrins, Lecithin, Methylbenzethonium chloride. Carboxylates, Sulphonates, Petroleum sulphonates, alkylbenzenesulphonates, Naphthalenesulphonates, Olefin sulphonates, Alkyl sulphates, Sulphates, Sulphated natural oils & fats, Sulphated esters, Sulphated alkanolamides, Alkylphenols, ethoxylated & sulphated, Ethoxylated aliphatic alcohol, polyoxyethylene surfactants, carboxylic esters Polyethylene glycol esters, Anhydrosorbitol ester and its ethoxylated derivatives, Glycol esters of fatty acids, Carboxylic amides, Monoalkanolamine condensates, Polyoxyethylene fatty acid amides, Quaternary ammonium salts, Amines with amide linkages, Polyoxyethylene alkyl & alicyclic amines, N,N,N,N tetrakis substituted ethylenediamines 2- alkyl 1- hydroxyethyl 2-imidazolines, N -coco 3-aminopropionic acid/ sodium salt, N-tallow 3 -iminodipropionate disodium salt, N-carboxymethyl n dimethyl n-9 octadecenyl ammonium hydroxide, n-cocoamidethyl n-hydroxyethylglycine sodium salt or mixtures thereof. A preferred surfactant is docusate sodium and/or sodium lauryl sulfate.

The amount of surfactant in the pharmaceutical compositions may range from about 2% w/w to about 10% w/w of the total weight of the composition.

Viscosity modifying agents are excipients that are capable of stabilizing the formulation by increasing the viscosity of the formulation and thus preventing physical interaction of nanoparticles under the operating conditions employed.

The amount of viscosity modifying agents in the pharmaceutical compositions may range from about 4% w/w to about 20% w/w of the total weight of the composition.

Viscosity modifying agents which may be used in the pharmaceutical composition of the present invention may comprise one or more, but not limited to derivatives of sugars, such as lactose, sucrose, saccharose, hydrolyzed starch (maltodextrin) or mixtures thereof. A preferred viscosity modifying agent is lactose.

Polymers or polymers blends, which may be used in the pharmaceutical composition of the present invention, may comprise one or more hydrophilic polymers, but not limited to cellulose derivates like hydroxypropylcellulose, hydroxymethylcellulose, hydroxypropylmethylcellulose, methylcellulose polymers hydroxyethylcellulose, sodium carboxymethylcellulose, carboxymethylene and carboxymethyl hydroxyethylcellulose; acrylics like acrylic acid, acrylamide, and maleic anhydride polymers, acacia, gum tragacanth, locust bean gum, guar gum, or karaya gum, agar, pectin, carrageenan, gelatin, casein, zein and alginates, carboxypolymethylene, bentonite, magnesium aluminum silicate, polysaccharides, modified starch derivatives and copolymers or mixtures thereof.

The amount of polymers or polymers blends in the pharmaceutical compositions range from about 2% w/w to about 15% w/w, of the total weight of the composition.

Suitable channeling agents for use in compositions of the invention, may comprise one or more, but are not limited to sodium chloride, sugars, polyols and the like or mixtures thereof.

Preferably, the channeling agents may be present in an amount ranging from about 0.5% to about 10% by weight of the composition.

The pharmaceutical composition of the present invention, may further comprise at least one additional active pharmaceutical ingredient such as, but not limited to, prednisone and dutasteride, or a pharmaceutically acceptable derivatives thereof.

The present invention also provides a method of treating prostate cancer by administering a pharmaceutical composition of abiraterone.

The present invention also provides a method of treating prostate cancer by administering a pharmaceutical composition of abiraterone in combination with prednisone.

The present invention also provides abiraterone for use in the treatment of prostate cancer, wherein the total daily dose of the abiraterone is less than 1000 mg, preferably from about 125 mg to about 800 mg, and wherein abiraterone is administered as a single daily dose.

Further, the present invention also provides a method of treating prostate cancer by administering a pharmaceutical composition of abiraterone in combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer who have received prior chemotherapy containing docetaxel.

The present invention also provides the use of the pharmaceutical composition comprising abiraterone for treating prostate cancer.

In an embodiment, the present invention also provides the use of the pharmaceutical composition comprising abiraterone for treating prostate cancer in combination with prednisone.

Further, the present invention also provides the use of the pharmaceutical composition comprising abiraterone for treating prostate cancer in combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer who have received prior chemotherapy containing docetaxel.

The following examples are for the purpose of illustration only and are not intended in any way to limit the scope of the present invention.

Example 1:

Sr. No.	Ingredients	Quantity (mg/tab)
Binder Slurry		
1.	Abiraterone Acetate	125.0 - 700.0
2.	Sodium Lauryl Sulphate	6.9 - 38.6
3.	Hydroxypropylmethylcellulose	25.0 - 140.0
4.	Docusate Sodium	2.5 - 14.0
5.	Lactose Monohydrate	25.0 - 140.0
6.	Purified water	q.s
Dry Mix		
7.	Lactose Monohydrate	62.5 - 350.0
8.	Crospovidone	25.0 - 140.0
Blending & Lubrication		
9.	Sodium Chloride	15.0 - 84.0
10.	Crospovidone	10.0 - 56.0
11.	Silicified Microcrystalline Cellulose	59.2 - 331.5
12.	Magnesium Stearate	0.9 - 5.0
Total Weight		**357.0 - 1999.1**

Process:

A) Drug Slurry Preparation:

1) Docusate sodium, hydroxypropylmethylcellulose, Lactose and Sodium Lauryl Sulphate were dissolved in water.

2) Abiraterone Acetate was dispersed in the solution obtained in step (1) and then milled to form a slurry.

B) Granulation:

3) Lactose and crospovidone were sprayed onto the slurry in step (2) and granulated.

C) Blending & Lubrication:

4) The granules obtained in step (3) were blended and lubricated with crospovidone, silicified microcrystalline cellulose, sodium Chloride and magnesium stearate.

D) Compression:

5) The lubricated granules obtained in step (4) were compressed to form dispersible tablets

Example 2:

Sr. No.	Ingredients	Quantity (mg/tab)
Binder Slurry		
1.	Abiraterone Acetate	125.0 - 700.0
2.	Sodium Lauryl Sulphate	8.0 - 44.8
3.	Hydroxypropylmethylcellulose	25.0 - 140.0
4.	Docusate Sodium	2.8 - 15.4
5.	Sucrose	25.0 - 140.0
6.	Purified water IP	q.s
Dry Mix		
7.	Lactose Monohydrate	50.0 - 280.0
8.	Crospovidone	25.0 - 140.0
9.	Sucrose	25.0 - 140.0
Blending & Lubrication		
10.	Crospovidone	12.5 - 70.0
11.	Silicified Microcrystalline Cellulose	57.9 - 324.0
12.	Magnesium Stearate	0.9 - 5.0

Total Weight	**357.1 - 1999.2**

Process:

A) Drug Slurry Preparation:

1) Docusate sodium, hydroxypropylmethylcellulose, sucrose and Sodium Lauryl Sulphate were dissolved in water.

2) Abiraterone Acetate was dispersed in the solution obtained in step (1) and then milled to form a slurry.

B) Granulation:

3) Lactose and crospovidone were sprayed onto the slurry in step (2) and granulated.

C) Blending & Lubrication:

4) The granules obtained in step (3) were blended and lubricated with crospovidone, silicified microcrystalline cellulose, sodium Chloride and magnesium stearate.

D) Compression:

5) The lubricated granules obtained in step (4) were compressed to form dispersible tablets

Example 3:

Sr. No.	Ingredients	Quantity (mg/tab)
Binder Slurry		
1.	Abiraterone Acetate	125.0
2.	Sodium Lauryl Sulphate	6.9
3.	Hydroxypropylmethylcellulose	25.0
4.	Docusate Sodium	2.5
5.	Lactose Monohydrate	25.0
6.	Purified water	q.s

Dry Mix		
7.	Lactose Monohydrate	62.5
8.	Crospovidone	25.0
Blending & Lubrication		
9.	Sodium Chloride	15.0
10.	Crospovidone	10.0
11.	Silicified Microcrystalline Cellulose	59.2
12.	Magnesium Stearate	0.9
Total Weight		**357.0**

Process:

A) Drug Slurry Preparation:

1) Docusate sodium, hydroxypropylmethylcellulose, lactose and Sodium Lauryl Sulphate were dissolved in water.

2) Abiraterone Acetate was dispersed in the solution obtained in step (1) and then milled to form a slurry.

B) Granulation:

3) Lactose and crospovidone were sprayed onto the slurry in step (2) and granulated.

C) Blending & Lubrication:

4) The granules obtained in step (3) were blended and lubricated with crospovidone, silicified microcrystalline cellulose, sodium Chloride and magnesium stearate.

D) Compression:

5) The lubricated granules obtained in step (4) were compressed to form dispersible tablets

Example 4:

Sr. No.	Ingredients	Quantity (mg/tab)
Binder Slurry		
1.	Abiraterone Acetate	125.0
2.	Sodium Lauryl Sulphate	8.0
3.	Hydroxypropylmethylcellulose	25.0
4.	Docusate Sodium	2.8
5.	Sucrose	25.0
6.	Purified water IP	q.s
Dry Mix		
7.	Lactose Monohydrate	50.0
8.	Crospovidone	25.0
9.	Sucrose	25.0
Blending & Lubrication		
10.	Crospovidone	12.5
11.	Silicified Microcrystalline Cellulose	57.9
12.	Magnesium Stearate	0.9
Total Weight		**357.1**

Process:

A) Drug Slurry Preparation:

1) Docusate sodium, hydroxypropylmethylcellulose, sucrose and Sodium Lauryl Sulphate were dissolved in water.

2) Abiraterone Acetate was dispersed in the solution obtained in step (1) and then milled to form a slurry.

B) Granulation:

3) Lactose and crospovidone were sprayed onto the slurry in step (2) and granulated.

C) Blending & Lubrication:

4) The granules obtained in step (3) were blended and lubricated with crospovidone, silicified microcrystalline cellulose, sodium Chloride and magnesium stearate.

D) Compression:

5) The lubricated granules obtained in step (4) were compressed to form dispersible tablets

Example 5:

Sr. No.	Ingredients	Quantity (mg/tab)
Binder Slurry		
1.	Abiraterone Acetate	500.0
2.	Sodium Lauryl Sulphate	32.0
3.	Hydroxypropylmethylcellulose	100.0
4.	Docusate Sodium	11.0
6.	Purified water IP	q.s
Dry Mix		
7.	Lactose Monohydrate	200.0
8.	Crospovidone	100.0
Blending & Lubrication		
10.	Crospovidone	50.0
11.	Silicified Microcrystalline Cellulose	231.4
12.	Magnesium Stearate	3.60
Total Weight		**1228.0**

Process:

A) Drug Slurry Preparation:

1) Docusate sodium, hydroxypropylmethylcellulose, and Sodium Lauryl Sulphate were dissolved in water.

2) Abiraterone Acetate was dispersed in the solution obtained in step (1) and then milled to form a slurry.

B) Granulation:

3) Lactose and crospovidone were sprayed onto the slurry in step (2) and granulated.

C) Blending & Lubrication:

4) The granules obtained in step (3) were blended and lubricated with crospovidone, silicified microcrystalline cellulose, sodium Chloride and magnesium stearate.

D) Compression:

5) The lubricated granules obtained in step (4) were compressed to form dispersible tablets

Example 6:

Sr. No.	Ingredients	Quantity (mg/tab)
Binder Slurry		
1.	Abiraterone Acetate	750.0
2.	Sodium Lauryl Sulphate	48.0
3.	Hydroxypropylmethylcellulose	150.0
4.	Docusate Sodium	16.5
6.	Purified water IP	q.s
Dry Mix		
7.	Lactose Monohydrate	300.0
8.	Crospovidone	150.0

Blending & Lubrication		
10.	Crospovidone	75.0
11.	Silicified Microcrystalline Cellulose	347.1
12.	Magnesium Stearate	5.4
Total Weight		**1842.0**

Process:

A) Drug Slurry Preparation:

1) Docusate sodium, hydroxypropylmethylcellulose, and Sodium Lauryl Sulphate were dissolved in water.

2) Abiraterone Acetate was dispersed in the solution obtained in step (1) and then milled to form a slurry.

B) Granulation:

3) Lactose and crospovidone were sprayed onto the slurry in step (2) and granulated.

C) Blending & Lubrication:

4) The granules obtained in step (3) were blended and lubricated with crospovidone, silicified microcrystalline cellulose, sodium Chloride and magnesium stearate.

D) Compression:

5) The lubricated granules obtained in step (4) were compressed to form dispersible tablets.

Example 7:

Sr. No.	Ingredients	Quantity (mg/tab)
Dry Mix		
1.	Abiraterone Acetate	1000.0
2.	Sodium Lauryl Sulphate	30.0
3.	Microcrystalline Cellulose	396.0
4.	Lactose Monohydrate	396.0
5.	Croscarmellose sodium	50.0
Binder Solution		
7.	Polyvinylpyrollidone	50.0
8.	Purified Water	q.s.
Blending & Lubrication		
10.	Croscarmellose Sodium	50.0
11.	Colloidal Silicon Dioxide	12.0
12.	Magnesium Stearate	16.0
Total Weight		**2000.0**

Process:

A) Dry Mix:

1) Abiraterone Acetate, Sodium Lauryl Sulphate, Microcrystalline Cellulose, Lactose Monohydrate and Croscarmellose sodium were mixed in a granulator.

B) Preparation of Binder solution:

2) Polyvinylpyrollidone was dissolved in water to form the binder solution.

C) Granulation:

3) The mixture obtained in step (1) was granulated with the binder solution obtained in step (2).

D) Blending & Lubrication:

4) The granules obtained in step (3) were dried, blended and lubricated with croscarmellose sodium, colloidal silicon dioxide and magnesium stearate.

E) Compression:

5) The lubricated granules obtained in step (4) were compressed to form dispersible tablets.It will be readily apparent to one skilled in the art that varying substitutions and modifications may be made to the invention disclosed herein without departing from the spirit of the invention. Thus, it should be understood that although the present invention has been specifically disclosed by the preferred embodiments and optional features, modification and variation of the concepts herein disclosed may be resorted to by those skilled in the art, and such modifications and variations are considered to be falling within the scope of the invention.

It is to be understood that the phraseology and terminology used herein is for the purpose of description and should not be regarded as limiting. The use of “including,” “comprising,” or “having” and variations thereof herein is meant to encompass the items listed thereafter and equivalents thereof as well as additional items.

It must be noted that, as used in this specification and the appended claims, the singular forms "a," "an" and "the" include plural references unless the context clearly dictates otherwise.

Claims

1. A pharmaceutical composition comprising abiraterone and one or more pharmaceutically acceptable excipients.

2. The pharmaceutical composition according to claim 1, comprising abiraterone in the form of a pharmaceutically acceptable derivative thereof.

3. The pharmaceutical composition according to claim 2, wherein the pharmaceutically acceptable derivative is a salt, solvate, complex, hydrate, ester, tautomer, anhydrate, enantiomer, polymorph, derivative or prodrug.

4. The pharmaceutical composition according to claim 3, wherein abiraterone is in the form of abiraterone acetate.

5. The pharmaceutical composition according to any preceding claim, wherein the composition comprises less than 1000 mg of abiraterone.

6. The pharmaceutical composition according to any preceding claim, wherein the composition comprises from about 125 mg to about 800 mg of abiraterone.

7. The pharmaceutical composition according to any preceding claim, wherein the composition is formulated to provide a total daily dose of less than 1000 mg of abiraterone.

8. The pharmaceutical composition according to any preceding claim, wherein the composition is formulated to provide a total daily dose of from about 125 mg to about 800 mg of abiraterone.

9. The pharmaceutical composition according to any preceding claim, for once daily administration.

10. The pharmaceutical composition according to any preceding claim, wherein the composition is in an oral dosage form.

11. The pharmaceutical composition according to claim 10, wherein the oral dosage form is a single unit dosage form.

12. The pharmaceutical composition according to claim 11, wherein the single unit dosage form is for adapted once daily administration.

13. The pharmaceutical composition according to any one of claims 10 to 12, wherein the composition is a solid oral dosage form.

14. The pharmaceutical composition according to claim 13, wherein the solid oral dosage form is a tablet, coated tablet, powder, powder for reconstitution, pellets, beads, mini-tablet, multilayer tablet, bilayered tablet, tablet-in-tablet, pill, micro-pellet, small tablet unit, MUPS (multiple unit pellet system), disintegrating tablet, dispersible tablet, granules, microspheres, multiparticulates, capsule (filled with powder, powder for reconstitution, pellets, beads, mini-tablets, pills, micro-pellets, small tablet units, MUPS, orally disintegrating MUPS, disintegrating tablets, dispersible tablets, granules, sprinkles, microspheres and multiparticulates), sachet (filled with powders, powders for reconstitution, pellets, beads, mini-tablets, pills, micro-pellets, small tablet units, MUPS, disintegrating tablets, dispersible tablets, modified release tablets or capsules, effervescent granules, granules, sprinkles microspheres and multiparticulates), or sprinkles.

15. The pharmaceutical composition according to any one of claims 10 to 12, wherein the composition is a liquid oral dosage form.

16. The pharmaceutical composition according to claim 15, wherein the liquid oral dosage form is an emulsion, solution, suspension, syrup or elixir.

17. The pharmaceutical composition according to any preceding claim, wherein the abiraterone particles are nano-sized.

18. The pharmaceutical composition according to any preceding claim, wherein the abiraterone particles have an average particle size of less than about 2000 nanometers.

19. The pharmaceutical composition according to any preceding claim, wherein the abiraterone particles have an average particle size of less than about 1000 nanometers.

20. The pharmaceutical composition according to any preceding claim, wherein the one or more pharmaceutically acceptable excipients is selected from one or more disintegrants, diluents, plasticizers, binders, glidants, lubricants, sweeteners, flavoring agents, antioxidants, texture enhancers, viscosity modifying agents, polymers, channeling agents, anti-caking agents, anti-microbial agents, antifoaming agents, emulsifiers, surfactants, buffering agents, coloring agents and combinations thereof.

21. The pharmaceutical composition according to claim 20, wherein the one or more pharmaceutically acceptable excipients comprises a disintegrant present in an amount of from about 5% w/w to about 30% w/w of the total weight of the composition.

22. The pharmaceutical composition according to any preceding claim, formulated to be administered with or without food.

23. The pharmaceutical composition according to any preceding claim, formulated to be administered as a single daily dose.

24. The pharmaceutical composition according to any preceding claim, further comprising one or more active pharmaceutical ingredients selected from prednisone, dutasteride or their pharmaceutically acceptable derivatives thereof.

25. The pharmaceutical composition according to claim 24, wherein the active pharmaceutical ingredient is prednisone.

26. A process for preparing a pharmaceutical composition according to any one of claims 1 to 23, which process comprises admixing one or more pharmaceutically acceptable excipients with abiraterone.

27. A process for preparing a pharmaceutical composition according to claim 24 or 25, which process comprises admixing one or more pharmaceutically acceptable excipients with abiraterone and prednisone, dutasteride or their pharmaceutically acceptable derivatives thereof.

28. The pharmaceutical composition according to any one of claims 1 to 25 for use in the treatment of prostate cancer.

29. The pharmaceutical composition for use according to claim 28, wherein the use comprises administering a total daily dose of the abiraterone of less than 1000 mg, preferably from about 125 mg to about 800 mg.

30. Use of a pharmaceutical composition according to any one of claims 1 to 25 in the manufacture of a medicament for the treatment of prostate cancer.

31. Use of a pharmaceutical composition according to claim 30, wherein the use comprises administering a total daily dose of the abiraterone of less than 1000 mg, preferably from about 125 mg to about 800 mg.

32. Abiraterone for use in the treatment of prostate cancer, wherein the total daily dose of the abiraterone is less than 1000 mg, preferably from about 125 mg to about 800 mg, and wherein abiraterone is administered as a single daily dose.

33. A method of treatment of prostate cancer comprising administering a therapeutically effective amount of a composition according to any one of claims 1 to 25 to a patient in need thereof.

34. A method of treatment according to claim 33, wherein the method comprises administering a total daily dose of the abiraterone of less than 1000 mg, preferably from about 125 mg to about 800 mg.

35. A pharmaceutical composition substantially as herein described with reference to the examples.

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2015/050175

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/573 A61K31/58 A61K9/00 A61K9/20 A61P35/00
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A61P

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, BIOSIS, EMBASE, SCISEARCH, WPI 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 2014/009436 A1 (SANDOZ AG [CH]; GRAHEK ROK [SI]; KOCEVAR KLEMEN [SI]; NOVAK STAGOJ MAT) 16 January 2014 (2014-01-16) cited in the application	1-23,26, 35
Y	claims; examples	1-35

X	WO 2013/164473 A1 (JAGOTEC AG [CH]) 7 November 2013 (2013-11-07) cited in the application	1-5,7, 10,11, 13,14, 17-22, 26,28-35
Y	claims; examples	1-35

X,P	WO 2014/145813 A1 (ICEUTICA INC [US]) 18 September 2014 (2014-09-18) cited in the application claims; examples	1-8, 10-14, 17-35

	-/--	

[X] Further documents are listed in the continuation of Box C.

[X] 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
9 March 2015	23/03/2015

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Venturini, Francesca

2

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2015/050175

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2012/042224 A2 (CIPLA LTD [IN]; MALHOTRA GEENA [IN]; PURANDARE DR SHRINIVAS MADHUKAR [) 5 April 2012 (2012-04-05) examples 3-6	1-35
A	HUABING CHEN ET AL: "Nanonization strategies for poorly water-soluble drugs", DRUG DISCOVERY TODAY, vol. 16, no. 7, April 2011 (2011-04), pages 354-360, XP028187050, ISSN: 1359-6446, DOI: 10.1016/J.DRUDIS.2010.02.009 [retrieved on 2010-03-03] table 2	1-35

2

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/GB2015/050175

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2014009436 A1	16-01-2014	NONE	
WO 2013164473 A1	07-11-2013	EP 2844294 A1	11-03-2015
		WO 2013164473 A1	07-11-2013
WO 2014145813 A1	18-09-2014	US 2014287039 A1	25-09-2014
		WO 2014145813 A1	18-09-2014
WO 2012042224 A2	05-04-2012	AU 2011309872 A1	11-04-2013
		CA 2812505 A1	05-04-2012
		CN 103209687 A	17-07-2013
		EP 2621471 A2	07-08-2013
		JP 2013538845 A	17-10-2013
		KR 20140011300 A	28-01-2014
		NZ 608380 A	31-10-2014
		PE 01662014 A1	17-02-2014
		US 2014147503 A1	29-05-2014
		WO 2012042224 A2	05-04-2012