International Patent Classification:
A61K 9/20 (2006.01)  A61K 9/16 (2006.01)
A61K 31/50 (2006.01)

International Application Number:
PCT/EP20 15/064811

International Filing Date:
30 June 2015 (30.06.2015)

Filing Language: English
Publication Language: English

Priority Data:
14174996.0  30 June 2014 (30.06.2014)  EP
15151083.1  14 January 2015 (14.01.2015)  EP

Applicant: GALENICUM HEALTH S.L. [ES/ES];
Avenida Diagonal 123, 11th Floor, 08005 Barcelona (ES).

Inventor: ARROYO HIDALGO, Sergio; Avenida Diagonal
123, 11th Floor, E-08005 Barcelona (ES).

Agents: MAR JANET ARTIGAS, Georgina et al; Aven-
da Diagonal 123, 11th Floor, 08005 Barcelona (ES).

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, LS, LU, LY, MA, MD, ME, MG, MK, MN,
MW, MX, MY, N, 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.

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))

Title: STABLE PHARMACEUTICAL COMPOSITIONS IN THE FORM OF IMMEDIATE RELEASE TABLETS

FIG. 1

Abstract: The present invention relates to stable pharmaceutical compositions of abiraterone acetate or a pharmaceutically ac-
ceptable salt thereof, in the form of immediate release tablets, to a process for the manufacture of said stable pharmaceutical compos-
itons and to the use thereof in the treatment of cancer.
Stable pharmaceutical compositions in the form of immediate release tablets

The present invention relates to stable pharmaceutical compositions of abiraterone acetate or a pharmaceutically acceptable salt thereof, in the form of immediate release tablets, to a process for the manufacture of said stable pharmaceutical compositions and to the use thereof in the treatment of cancer.

STATE OF THE ART

Abiraterone is a selective inhibitor of 17a-hydroxylase/C17,20 lyase (CYP17A1), an enzyme which is known to be essential for the biosynthesis of androgens and oestrogens. CYP17 is expressed in testicular, adrenal, and prostatic tumor tissues.

Said enzyme complex catalyzes the conversion of pregnenolone and progesterone to their 17a-hydroxy derivatives by its 17a-hydroxylase activity, and the subsequent formation of the androgens dehydroepiandrosterone (DHEA) and androstenedione, by its C17,20 lyase activity. The androgens DHEA and androstenedione are precursors of testosterone. As a consequence, inhibition of CYP17 activity by abiraterone decreases circulating levels of testosterone and other androgens in cancer patients.

Abiraterone is poorly bioavailable. Therefore, the prodrug abiraterone acetate which is rapidly deacetylated to abiraterone in vivo is used.

Abiraterone acetate (INN, CB7630; JNJ-212082; Zytiga®) is a pregnenolone analog used in castration-resistant prostate cancer (CRPC). Abiraterone acetate (i.e 3β-17-(3-pyridinyl)androsta-5,16-dien-3-yl acetate) is absorbed through the gut when administered orally and then deacetylated in the liver to the active drug abiraterone.

Abiraterone acetate was first approved by the FDA in April 2011 for the treatment of patients with metastatic CRPC, who have received prior chemotherapy containing docetaxel. Abiraterone acetate was launched in USA and Europe by Johnson & Johnson under the tradename Zytiga®. The chemical structure of abiraterone acetate, as commercially available, is shown in formula (1):
Abiraterone acetate is a white to off-white, non-hygroscopic, crystalline powder. Its molecular formula is \(\text{C}_{25}\text{H}_{33}\text{NO}_2\) and it has a molecular weight of 391.55 g/mol. Abiraterone acetate is practically insoluble in water.

Different routes of synthesis for abiraterone acetate are known in the art, e.g. from WO 93/20097, WO 95/09178 and WO 2006/021777.

Abiraterone acetate (Zytiga®) is being marketed as an immediate-release tablet containing 250 mg of abiraterone acetate. A daily dose of 1000 mg abiraterone acetate is administered once daily in combination with 5 mg prednisone twice daily for the treatment of patients with metastatic castration-resistant prostate cancer.

A problem exists with abiraterone acetate in that its pharmacokinetic properties are affected by the prandial status of a patient receiving treatment, i.e. it exhibits a ‘food effect’. In particular, the bioavailability of abiraterone acetate increases with food.

ZYTIGA® is administered in a fasted state in an attempt to minimise the erratic and unpredictable bioavailability demonstrated in the fed state. However, ZYTIGA® has poor bioavailability in fasted subjects and must therefore be administered at a very high daily dose.

Administration of a drug composition with food may change its bioavailability by affecting either the drug substance or the composition in which the drug substance is formulated. In practice, it is difficult to determine the exact mechanism by which food changes the bioavailability of a drug substance or composition. Food can alter the bioavailability of a drug by different mechanisms, including: delayed gastric emptying; stimulation of bile flow;
changed gastrointestinal pH; increased visceral blood flow; changed luminal metabolism; and physical or chemical interactions of food components with the drug compound or one or more excipients contained in the composition. Still further, food induced changes in gut physiology can contribute to these effects, or there may be instability of the drug substance.

Accordingly, whereas it is not uncommon for the pharmacokinetic properties of a drug substance to be affected by the presence or absence of food in the stomach when administered to a patient, or before the drug substance has passed from the stomach, the presence of a food effect, its direction (positive or negative) and its magnitude is unpredictable. A particular formulation strategy that reduces or eliminates a food effect with respect to one particular drug substance or composition might not necessarily have a similar effect with other drug substances or compositions.

Abiraterone acetate is classified by the manufacturer of Zytiga® as BCS class IV drug. In BCS (Biopharmaceutics Classification System) drugs are classified on the basis of the parameters solubility, permeability and dissolution. BCS class IV compounds exhibit low permeability and low solubility. Those compounds have a poor bioavailability. That is, their bioavailability is limited by both solvation rate and permeability. Usually they are not well absorbed over the intestinal mucosa and a high variability is expected, which makes them particularly difficult to administer orally. These factors alone or in combination may contribute to the observed large food effect and intra-subject and inter-subject variability of this drug substance in its current commercial presentation. However, abiraterone acetate poses particular formulation problems, not only because of its erratic bioavailability, but also because of its poor bioavailability in fasted subjects, it must be administered at such a high daily dose (1000 mg/day).

There remains a need to develop formulations, which can improve the bioavailability of abiraterone acetate in fasting conditions, reduce the food effect in the fed state as well as the high intra- and inter-subject variability.

Accordingly, it would be desirable to improve solubility of abiraterone acetate in order to have good bioavailability of the drug and be able to reduce intra- and inter-subject variability during abiraterone acetate administration. At the same time, being manufactured by a simple and robust process with high reproducibility. Furthermore, the stability of the tablet is maintained and the dissolution profiles are good. The invention also provides better tolerated and safer dosage forms that achieve more predictable and consistent plasma exposure.
The above issues have been addressed in the present invention and specific embodiments thereof.

5 DESCRIPTION OF THE INVENTION

The present invention provides stable pharmaceutical compositions of abiraterone acetate or a pharmaceutically acceptable salt thereof in the form of immediate release tablets.

Furthermore, the present invention provides a pharmaceutical composition in the form of an immediate release tablet comprising abiraterone acetate, which has an improved solubility of the drug resulting in good bioavailability and efficacy of the pharmaceutical composition. Said pharmaceutical compositions are able to reduce the intra- and inter-subject variability when abiraterone acetate is administered due to its low solubility and low permeability.

The compositions of the present invention offer the additional benefit of a simple, robust and reproducible process that helps to reduce the intra- and inter-subject variability of abiraterone acetate.

It has been found that a specific particle size together with a specific amount of surfactant can be used to stabilize pharmaceutical compositions of abiraterone acetate or a pharmaceutically acceptable salt thereof, especially immediate release tablets manufactured by wet granulation.

The stable immediate release tablets as disclosed herein are uniform in content. Moreover, the batches show good flowability.

In a first aspect, the present invention relates to a pharmaceutical composition in the form of immediate release tablets comprising abiraterone acetate or a pharmaceutically acceptable salt thereof, wherein the pharmaceutical composition comprises between 2 and 8 % w/w of surfactant in respect of the total amount of the pharmaceutical composition and/or the D50 of abiraterone acetate is between 3 to 10 microns as measured by laser diffraction spectroscopy and/or the D90 of abiraterone acetate is less than 20 microns as measured by laser diffraction spectroscopy.

The particle size distribution of the abiraterone acetate was analysed by laser diffraction spectroscopy using a Malvern Mastersizer 2000 hydro2000-SM particle size analyzer with
water and polysorbate 80 as dispersant, stir speed of 2500 rpm, cyclomixture during one minute, sonication during 30 sec, sample concentration 100 mg/20 ml and measurement time 12 seconds.

Pharmaceutical compositions of the prior art comprising abiraterone acetate use low quantities of surfactant, i.e. CN102743393 discloses the use of 0.1 % of SDS (sodium lauryl sulfate).

The term "pharmaceutical composition" as used herein refers to a finished dosage formulation, which contains the active agent abiraterone acetate and which is in the form in which it can be marketed for use.

An immediate release tablet as herein disclosed has to be understood as a tablet having a dissolution performance such as 60 % or more of the active agent contained in said pharmaceutical composition dissolves within 60 minutes (min). In a preferred embodiment, the immediate release composition as herein disclosed releases at least 80 % of the active agent in 60 minutes. In another embodiment, the pharmaceutical composition as herein disclosed releases at least 80 % of the active agent in 45 min, preferably in 35 min and more preferably in 30 min. In a preferred embodiment, the pharmaceutical composition as herein disclosed releases at least 80 % of the active agent in 30 min and at least a 95 % of the active agent in 60 min. The dissolution test for an immediate release pharmaceutical composition comprising the active agent as herein disclosed is performed in the following conditions: USP Apparatus: II (Paddles). Speed: 50 rpm. Medium: 0.25% SLS in 56.5 mM phosphate buffer, pH 4.5. Wavelength 237 nm.

In a preferred embodiment of the first aspect, the pharmaceutical composition comprises between 2 and 8 % w/w of surfactant in respect of the total amount of the pharmaceutical composition and the D50 of abiraterone acetate is between 3 to 10 microns as measured by laser diffraction spectroscopy and the D90 of abiraterone acetate is less than 20 microns as measured by laser diffraction spectroscopy.

In a preferred embodiment of the first aspect, the pharmaceutical composition comprises between 3 and 6 % w/w of surfactant in respect of the total amount of the pharmaceutical composition, preferably between 3.5 and 5 % w/w of surfactant in respect of the total amount of the pharmaceutical composition, more preferably 4 % w/w of surfactant in respect of the total amount of the pharmaceutical.
The poor water solubility and low permeability of the BCS class IV compounds entails a further challenge in formulating abiraterone acetate in a tablet with good bioavailability. One method of formulating such compounds is by the addition of a surfactant which enhances the solubility of the drug.

The term "surfactant" refers to a pharmaceutically acceptable excipient having hydrophobic and hydrophilic units which are capable of solubilizing a non-water soluble drug in water. Any of a variety of surfactants selected from a group consisting of anionic, amphoteric, nonionic, cationic surfactants, and combinations of two or more thereof may be used in accord with the present invention.

As used herein, the term "nonionic surfactant" refers to an ionic surfactant in which the hydrophilic portion of the surfactant carries no charge. One class of nonionic surfactants useful in the present invention are polyoxyethylene derivatives of polyol esters, long chain alkyl glucosides or polyglucosides, PEG-80 sorbitan laurate, polysorbates (e.g., polysorbate 80, polysorbate 40, polysorbate 20), and the like.

The use of an ionic surfactant not only can act as an aid to drug solubilisation, it may also generate an environment around the drug substance that mimics the environment created by the release of endogenous or natural surfactants such as ionic surfactants as part of the process of digestion after the intake of food. It is believed that ionic surfactants may interact with the drug substance to form micelles that in turn interact with the unstirred water layer (UWL)- a bicarbonate-rich layer of mucus that maintains pH levels at around 7 at the vill surface - and the intestinal mucosa, to enhance absorption therethrough.

In a preferred embodiment of the first aspect, the surfactant is selected from nonionic, ionic and mixtures thereof; preferably is an ionic surfactant.

In a preferred embodiment of the first aspect, the surfactant is an ionic surfactant selected from cationic, anionic, zwitterionic and mixtures thereof. Preferably, the surfactant is an anionic surfactant.

Suitable anionic surfactants includes sodium lauryl sulphate, sodium palmate, sodium stearate and triethanolamine lauryl sulphate.

In a more preferred embodiment of the first aspect, the anionic surfactant is sodium lauryl sulphate. The sodium lauryl sulphate functions as a wetting agent and helps solubilisation.
In a further embodiment of the first aspect, the pharmaceutical composition comprises between 3.5 and 5 % w/w of sodium lauryl sulfate in respect of the total amount of the pharmaceutical composition, preferably about 4 % w/w of sodium lauryl sulfate in respect of the total amount of the pharmaceutical composition.

In a preferred embodiment, the pharmaceutical composition of the present invention is stable. The term "stable" as used herein refers to a pharmaceutical composition comprising abiraterone acetate wherein the total content of impurities originating from the decomposition of abiraterone acetate does not exceed 5 % area, preferably 3 % area, more preferably 2 % area and most preferably 1 % area determined by liquid chromatography (HPLC) at 237 nm if such a composition is stored for 2 months at 40°C and 75 % relative humidity (RH).

When the pharmaceutical composition as herein disclosed comprises excipients such as a filler, a lubricant, a disintegrant, a binder or glidant, these excipients are pharmaceutically acceptable. The term "pharmaceutically acceptable" indicates that the substance or composition must be compatible chemically and/or toxicologically, with the other ingredients comprising a formulation, and/or the mammal being treated therewith.

The term "filler" as used herein refers to pharmaceutically acceptable excipients which are added to the bulk volume of the active agent making up the solid composition. As a result, the size of the solid composition increases, which makes its size suitable for handling. Fillers are convenient when the dose of drug per solid composition is low and the solid composition would otherwise be too small. In a preferred embodiment of the pharmaceutical composition as herein disclosed, said pharmaceutical composition comprises at least a filler. Preferably, the total amount of filler or fillers present in the pharmaceutical composition ranges from 30 to 65 % w/w in respect of the total amount of the pharmaceutical composition. More preferably, the total amount of filler or fillers present in the pharmaceutical composition ranges from 25 to 55 % by weight in respect of the total amount of the pharmaceutical composition.

In a preferred embodiment of the pharmaceutical composition as herein disclosed, said pharmaceutical composition further comprises a filler selected from dicalcium phosphate, cellulose, compressible sugars, dibasic calcium phosphate dihydrate, lactose, mannitol, microcrystalline cellulose, starch, tribasic calcium phosphate, and mixtures thereof. Preferably, the pharmaceutical composition comprises microcrystalline cellulose, lactose or
mixtures thereof.

As used herein, "disintegrant" means a substance or a mixture of substances added to a tablet to facilitate its breakup or disintegration after administration. In a preferred embodiment of the pharmaceutical composition as herein disclosed, said pharmaceutical composition comprises at least a disintegrant. Preferably, the total amount of disintegrant or disintegrants present in the pharmaceutical composition ranges from 1 to 15 % w/w in respect of the total amount of the pharmaceutical composition. More preferably, the total amount of disintegrant or disintegrants present in the pharmaceutical composition ranges from 5 to 10 % by weight in respect of the total amount of the pharmaceutical composition.

In a preferred embodiment of the pharmaceutical composition as herein disclosed, said pharmaceutical composition comprises at least a disintegrant selected from water-soluble disintegrants, disintegrant selected from starch, pregelatinized starch, sodium starch glycolate, povidone, croscarmellose sodium, crospovidone, microcrystalline cellulose, and mixtures thereof. Preferably the pharmaceutical composition comprises croscarmellose sodium.

The term "binder" as used herein is defined as an agent able to bind particles which cannot be bound only by a simple compression force. The binder may be present in the pharmaceutical composition in the form of a single compound or in the form of a mixture of compounds. In a preferred embodiment of the pharmaceutical composition as herein disclosed, said pharmaceutical composition comprises at least a binder. Preferably, the total amount of binder or binders present in the pharmaceutical composition ranges from 1 to 10 % w/w in respect of the total amount of the pharmaceutical composition. More preferably, the total amount of binder or binders present in the pharmaceutical composition ranges from 2 to 8 % by weight in respect of the total amount of the pharmaceutical composition.

In a preferred embodiment of the pharmaceutical composition as herein disclosed, said pharmaceutical composition further comprises a binder selected from starch, maltodextrin, gelatin, natural and synthetic gums, cellulose and its derivatives, polyvinyl alcohol, polyvinylpyrrolidone and mixtures thereof. Preferably the pharmaceutical composition comprises polyvinylpyrrolidone.

As used herein, "lubricant" means a substance that reduces friction between the composition of the present invention and the surfaces of the apparatus used to compact the composition into a compressed form. The function of a lubricant in the product formulation is
to prevent powder from sticking to the punches, dies, and other metal components of the tablet press. In a preferred embodiment of the pharmaceutical composition as herein disclosed, said pharmaceutical composition comprises at least a lubricant. Preferably, the total amount of lubricant or lubricants present in the pharmaceutical composition ranges from 0.5 to 5 % w/w in respect of the total amount of the pharmaceutical composition. More preferably, the total amount of lubricant or lubricants present in the pharmaceutical composition ranges from 1.2 to 2 % by weight in respect of the total amount of the pharmaceutical composition.

The inventors have surprisingly found that the such quantities of lubricant help to avoid the tablet sticking during the process.

In a preferred embodiment of the pharmaceutical composition as herein disclosed, said pharmaceutical composition comprises at least a lubricant selected calcium stearate, magnesium stearate, polyethylene glycol, sodium stearyl fumarate, stearic acid, talc, or mixtures thereof. Preferably, the pharmaceutical composition comprises magnesium stearate.

As used herein, "glidant" means a substance which improves the flow characteristics of powder mixtures in the dry state. In a preferred embodiment of the pharmaceutical composition as herein disclosed, said pharmaceutical composition comprises at least a glidant. Preferably, the total amount of glidant or glidants present in the pharmaceutical composition ranges from 0.08 to 3 % w/w in respect of the total amount of the pharmaceutical composition. More preferably, the total amount of glidant or glidants present in the pharmaceutical composition ranges from 0.05 to 1.5 % w/w in respect of the total amount of the pharmaceutical composition.

In a preferred embodiment of the pharmaceutical composition as herein disclosed, said pharmaceutical composition comprises at least a glidant selected from the group consisting of colloidal silicon dioxide, talc, starch, starch derivatives, and mixtures thereof. Preferably, the pharmaceutical composition comprises colloidal silicon dioxide.

In a preferred embodiment, the pharmaceutical composition comprises from 100 to 400 mg of active agent per unit dose. Preferably, the pharmaceutical composition comprises about 250 mg of active agent per unit dose. As used herein, the term "unit dose" or "unit dosage" refers to a physically discrete unit that contains a predetermined quantity of active ingredient calculated to produce a desired therapeutic effect. The unit dose or unit dosage
may be in the form of a tablet, capsule, sachet, etc. referred to herein as a "unit dosage form".

In a further embodiment of the pharmaceutical composition as herein disclosed, the pharmaceutical compositions are manufactured by wet granulation techniques.

The term "pharmaceutical granulate" or "granulate" or "granular component" as used herein refers to the part of the pharmaceutical composition that has been obtained by granulating a powder into larger particles herein called granules. As used herein, the term "granulation" refers to the process of agglomerating powder particles into larger agglomerates (i.e. granules) that contain the active pharmaceutical ingredient. The term "granulation" includes wet granulation techniques. The term "wet granulation" refers to any process comprising the steps of addition of a liquid to powder starting materials, preferably kneading, and drying to yield a solid dosage form.

In a further embodiment of the pharmaceutical composition in the form of tablet of the first aspect, comprises:

i) an intragranular portion comprising abiraterone acetate and at least a surfactant, at least a binder, at least a filler, at least a disintegrant, and;

ii) an extragranular portion comprising at least a lubricant and at least a glidant.

The disintegrant can be incorporated either intragranular, extragranular or it can be distributed both intra and extragranular. According to the literature and the state of the art, in general the extragranular incorporation seemed to favour the dissolution (Gordon MS, Chowhan ZT. Effect of mode of croscarmellose sodium incorporation on tablet dissolution and friability. J Pharm Sci 1990; 79(1): 43-7). So, it would be expected that using disintegrant in extragranular incorporation gave faster disintegration times than either intragranular or mix of intra- and extra- granular disintegrant. However, the inventors have found that incorporating the disintegrant in the pharmaceutical composition of abiraterone, faster disintegration times were obtained and the release of the drug was at least 80 % of the active agent in 30 min and at least a 95 % of the active agent in 60 min.

In a preferred embodiment of the pharmaceutical composition in the form of tablet of the first aspect, comprises:

i) an intragranular portion comprising abiraterone acetate, sodium lauryl sulfate, polyvinylpyrrolidone, lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, and;
ii) an extragranular portion comprising colloidal silicon dioxide and magnesium stearate.

It has been found that hardness can affect dissolution profiles of pharmaceutical compositions of abiraterone acetate or a pharmaceutically acceptable salt thereof, especially in immediate release tablets manufactured by wet granulation.

In a further embodiment of the pharmaceutical composition as herein disclosed, the pharmaceutical composition has an average hardness between 100 and 200 N, preferably between 120 and 180 N, more preferably between 130 and 160 N, and even more preferably between 135 and 145 N.

The inventors found that the critical steps in the manufacturing process were wet granulation, drying and compression. The inventors have surprisingly found that simple, robust and reproducible process is obtained adding a portion of the binder in the solution and another portion in the comprising intragranular mixture.

In a second aspect, the present invention relates to a process for the manufacture of the pharmaceutical composition as defined in any of the preceding claims, comprising the following steps:

(i) providing a solution of at least a surfactant and at least a portion of the amount of the binder;

(ii) providing an intragranular mixture of abiraterone acetate or a pharmaceutically acceptable salt thereof and at least one disintegrant, at least one filler and the rest of amount of the binder;

(iii) granulating the mixture obtained in step (ii) with the solution of step (i) by a wet granulation process to produce a granulate;

(iv) drying the granulate of the previous step (iii);

(v) optionally, performing a sieving of the granulate obtained in step (iv);

(vi) blending the granulate of step (iv) with at least one extragranular excipient;

(vii) adding at least one lubricant to the blended composition of step (vi);

(viii) compressing the blended composition of step (vii) to obtain a tablet composition.

In a further embodiment of the process of the second aspect, the intragranular composition comprises abiraterone acetate or a pharmaceutically acceptable salt thereof, a first intragranular filler, optionally a second intragranular filler, an intragranular disintegrant, an intragranular surfactant and an intragranular binder; and the extragranular composition comprises an extragranular glidant and an extragranular lubricant.
In a preferred embodiment of the process of the second aspect, the process comprises the following steps:
i) providing a solution of sodium lauryl sulfate and at least a portion of the amount of polyvinylpyrrolidone;
ii) providing an intragranular mixture of abiraterone acetate or a pharmaceutically acceptable salt thereof and at least one disintegrant, at least one filler and the rest of amount of polyvinylpyrrolidone;
iii) granulating the mixture obtained in step (ii) with the solution of step (i) by a wet granulation process to produce a granulate;
iv) drying the granulate of the previous step (iii);
v) optionally, performing a sieving of the granulate obtained in step (iv);
vi) blending the granulate of step (iv) with at least one extragranular excipient;
vii) adding at least one lubricant to the blended composition of step (vi);
viii) compressing the blended composition of step (vii) to obtain a tablet composition.

In a preferred embodiment of the process of the second aspect, the step (iv) is performed to an endpoint up to 2.5 % w/w of water content in respect of the total amount of the granulate.

In another preferred embodiment of the process of the second aspect, the drying is carried out in a fluid bed at an input temperature between 30 and 50 °C.

In another preferred embodiment of the process of the second aspect, in the step (viii) the tablets are compressed in order to have an average hardness between 100 and 200 N, preferably between 120 and 180 N, more preferably between 130 and 160 N, and even more preferably between 135 and 145 N.

In a third aspect, the present invention relates to the pharmaceutical composition obtained by the process of the second aspect.

In a fourth aspect, the present invention relates to a pharmaceutical batch comprising at least 20,000 units of the pharmaceutical composition of the first or third aspect. In a preferred embodiment of the fourth aspect, the pharmaceutical batch comprises at least 50,000 units.

In a preferred embodiment of the pharmaceutical batch as herein disclosed, the content of abiraterone acetate or the pharmaceutically acceptable salt thereof is uniform.
In a further embodiment of the pharmaceutical batch as herein disclosed, the tablets are packaged in a blister pack of aluminium/PVC or aluminium/aluminium or in a high density polyethylene (HDPE) bottle. In a preferred embodiment of the pharmaceutical batch as herein disclosed, the pharmaceutical composition as herein disclosed are packaged in a high density polyethylene (HDPE) bottle. Preferably, the HDPE bottle as herein disclosed, has a polypropylene child-resistant closure.

The term "blister" or bubble pack refers to a sheet in a package construction with recesses designed to hold dosage forms. The blisters are then hermetically sealed using flat strips of appropriate thermomoldable materials (plastics, aluminum, paper), which represent the frangible element through which it is then possible to remove the product. An aluminium/PVC blister refers to a blister the thermomoldable material is from PVC and the backing is a lidding seal of aluminium foil. Blister packs are commonly used as unit-dose packaging for pharmaceutical tablets, capsules or lozenges. Blister packs can provide barrier protection for shelf life requirements, and a degree of tamper resistance.

The term "batch" as used herein refers to a specific quantity of a drug or other material that is intended to have uniform character and quality, within specified limits, and is produced according to a single manufacturing order during the same cycle of manufacture. A batch, in the case of a drug product produced by continuous process, is a specific identified amount produced in a unit of time or quantity in a manner that assures its having uniform character and quality within specified limits (Code of Federal Regulations Title 21, Food and Drug Administration department of Health and Human Services, Subchapter C, Section 210.3 (b) (2) and (10)).

The term "pharmaceutical batch" as used herein refers to a batch as defined above of a pharmaceutical composition manufactured in accordance with the principles and guidelines of Good Manufacturing Practice (GMP) at an industrial scale and which is intended for commercialization (Directive 91/356/EEC).

The pharmaceutical composition may be manufactured at laboratory scale, not necessarily following GMP and not intended for commercialization. The pharmaceutical composition may also be manufactured for validation, following GMP. A batch of a pharmaceutical composition which is manufactured for validation is called "pilot batch".

Each pharmaceutical batch of finished product must fulfil the regulatory requirements of the
corresponding Medicine Agency before being released for sale or supply, such as impurities thresholds and stability data.

The term "uniform" as used herein refers to the content of the active ingredient in the tablets of a pharmaceutical batch has to be homogeneous. According to the FDA criteria, uniformity is considered as achieving 90-110 % potency of the theoretical strength with a relative standard deviation (RSD) of less than 5 % for all samples (Guidance for Industry ANDA's: Blend Uniformity Analysis, published August 1999).

The term "active ingredient" refers to a therapeutically active compound, as well as any prodrugs thereof and pharmaceutically acceptable salts, hydrates and solvates of the compound and the prodrugs.

For the release of a pharmaceutical batch the distribution of the active ingredient in the tablets has to be homogeneous, that is, content uniformity is required. All batches are expected to be uniform within normal process variation. Process validation studies are conducted prior to the marketing of a drug product to assure that production processes are controlled. The test batch is manufactured prior to validation, yet it is the basis on which an application is approved (MANUAL OF POLICIES AND PROCEDURES, MAPP 5225.1). It is essential, therefore, to assure that the test batch is uniform. In-process tests for uniformity should be conducted throughout the entire production process, e.g., at commencement or completion of significant phases (21 CFR 211.110). These tests should be designed to detect potential in-process anomalies (MAPP 5225.1).

A fifth aspect of the present invention relates to the pharmaceutical composition of the first or third aspect or the pharmaceutical batch of the fourth aspect, for use in the treatment of cancer, preferably metastatic prostate cancer.

A sixth aspect of the present invention relates to a cardboard box with a patient information leaflet comprising at least one unit of the pharmaceutical composition of the first or third aspect.

A seventh aspect of the present invention relates to a method for preparing a pharmaceutical dossier to obtain the marketing authorization of pharmaceutical composition of the first or third aspect comprising the following steps:

i) manufacturing at least one pharmaceutical batch of the fourth aspect;
ii) performing stability tests of the batches of step (i);
iii) compiling the results obtained in steps (i) to (iii); and
iv) providing the compiled results of step (iii) in a data carrier.

The term "pharmaceutical dossier" to obtain the marketing authorization refers to a dossier with data proving that the drug has quality, efficacy and safety properties suitable for the intended use, additional administrative documents, samples of finished product or related substances and reagents necessary to perform analyzes of finished product as described in that dossier.

In an eighth aspect, the present invention relates to a data carrier comprising the compiled results of a pharmaceutical dossier obtained by the method of the seventh aspect. In a preferred embodiment of the eighth aspect, said data carrier is selected from the group consisting of a digital data carrier such as CD, DVD, USB, hard drive; and paper. The term "data carrier" refers to a device for recording (storing) information (data). The recording can be done using virtually any form of energy. A storage device may hold information, process information, or both. Most often the term is used with computers. Data carrier can permanently hold data, like files.

All percentages, parts, and ratios herein are by weight unless specifically noted otherwise. As used herein, the term "about" refers preferably to a range that is ±10 %, preferably ±5 %, or more preferably ±1 % of a value with which the term is associated. Unless otherwise indicated, all the analysis methods are carried out according to the European Pharmacopoeia 7th edition.

Unless otherwise indicated, all the analysis methods are carried out according to the European Pharmacopoeia 7th edition.

**DESCRIPTION OF THE FIGURES**

FIG. 1: immediate release dissolution profile. Percentage of the active agent dissolved over time in minutes for example 1 of the present invention, at 0.25% SLS in 56.5 mM phosphate buffer, pH 4.5.

FIG. 2: immediate release dissolution profile of abiraterone acetate tablets of batch example 5a and 5b at t=0; % dissolved vs time (min).
EXAMPLES

Example 1: Abiraterone acetate tablet composition

<table>
<thead>
<tr>
<th>Examples</th>
<th>% w/w</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intragranular</strong></td>
<td></td>
</tr>
<tr>
<td>Abiraterone acetate (mg)</td>
<td>250.00 mg</td>
</tr>
<tr>
<td>Lactose monohydrate</td>
<td>26-32 %</td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
<td>17-21 %</td>
</tr>
<tr>
<td>Croscarmellose sodium</td>
<td>5.5-7.5 %</td>
</tr>
<tr>
<td>Povidone (K29/K32)</td>
<td>4-6 %</td>
</tr>
<tr>
<td>Sodium lauryl sulfate</td>
<td>2-4.5 %</td>
</tr>
<tr>
<td><strong>Extragranular</strong></td>
<td></td>
</tr>
<tr>
<td>Colloidal Silicon dioxide (mg)</td>
<td>0.5-2 %</td>
</tr>
<tr>
<td>Magnesium stearate (mg)</td>
<td>1.2-2 %</td>
</tr>
</tbody>
</table>

Example 2: Manufacture of abiraterone acetate tablets of example 1 by wet granulation

(1) A portion of povidone (K29/K32) and sodium lauryl sulfate was dissolved in purified water using a magnetic agitator.

(2) Abiraterone acetate, lactose monohydrate, microcrystalline cellulose, croscarmellose and the rest of povidone (K29/23) were added to the high shear mixer and mixed the blend for 15 minutes.

(3) The granulation solution prepared in step (1) was added to the blend of step (2) and kneaded for 10 minutes.

(4) The granulate of step (3) was dried in a fluid bed at 37 °C.

(5) The granulate obtained was sieved through a 1.0 mm mesh.

(6) The colloidal silicon dioxide was sieved and blended it with the granulate obtained in step (5) for 10 minutes in a blender.

(7) The magnesium stearate was sieved and blended it with the granulate from step (6) for 5 minutes in a blender.

(8) The final blend was compressed into tablets using a tablet press to obtain tablets comprising about 250 mg of abiraterone acetate.
Examples 3: Particle size volume distribution

The particle size distribution of the abiraterone acetate was analysed by laser diffraction spectroscopy using a Malvern Mastersizer 2000 hydro2000-SM particle size analyser.

The particle size distribution was D50 of 4.53 microns and D90 of 10.60 microns.

Example 4: Water content

The amount of water of the pharmaceutical compositions as herein disclosed was measured by loss on drying (LOD) using a Halogen Moisture Analyzer. The water content of the granulate in the step (4) of the process described above was less than 2.5%.

Example 5: Abiraterone acetate tablet compositions. Comparative example having disintegrant intragranular with disintegrant extragranular.

<table>
<thead>
<tr>
<th>Examples</th>
<th>Ex 5a (% w/w)</th>
<th>Ex 5b (% w/w)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intragranular</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abiraterone acetate (mg)</td>
<td>250.00 mg</td>
<td>250.00 mg</td>
</tr>
<tr>
<td>Lactose monohydrate</td>
<td>26-32 %</td>
<td>26-32 %</td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
<td>17-21 %</td>
<td>17-21 %</td>
</tr>
<tr>
<td>Croscarmellose sodium</td>
<td>5.5-7.5 %</td>
<td>-</td>
</tr>
<tr>
<td>Povidone (K29/K32)</td>
<td>4-6 %</td>
<td>4-6 %</td>
</tr>
<tr>
<td>Sodium lauryl sulfate</td>
<td>2-4.5 %</td>
<td>2-4.5 %</td>
</tr>
<tr>
<td><strong>Extragranular</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Croscarmellose sodium</td>
<td>-</td>
<td>5.5-7.5 %</td>
</tr>
<tr>
<td>Colloidal Silicon dioxide (mg)</td>
<td>0.5-2 %</td>
<td>0.5-2 %</td>
</tr>
<tr>
<td>Magnesium stearate (mg)</td>
<td>1.2-2 %</td>
<td>1.2-2 %</td>
</tr>
</tbody>
</table>

Example 5a was manufactured following the process described in Example 2.

Example 5b - Manufacture of abiraterone acetate tablets of example 5b with disintegrant added extragranular.
(1) A portion of povidone (K29/K32) and sodium iauryi sulfate was dissolved in purified water using a magnetic agitator.

(2) Abiraterone acetate, lactose monohydrate, microcrystalline cellulose and the rest of povidone (K29/23) were added to the high shear mixer and mixed the blend for 15 minutes.

(3) The granulation solution prepared in step (1) was added to the blend of step (2) and kneaded for 10 minutes.

(4) The granulate of step (3) was dried in a fluid bed at 37 °C.

(5) The granulate obtained was sieved through a 1.0 mm mesh.

(6) The colloidal silicon dioxide and croscarmellose sodium was sieved and blended it with the granulate obtained in step (5) for 10 minutes in a blender.

(7) The magnesium stearate was sieved and blended it with the granulate from step (6) for 5 minutes in a blender.

(8) The final blend was compressed into tablets using a tablet press to obtain tablets comprising about 250 mg of abiraterone acetate.

Example 6: Dissolution profiles

Dissolution profile were performed from the 2 batches obtained in example 5a and 5b following the method USP Apparatus: 11 (Paddles), speed: 50 r.p.m. medium: 0.25 % sodium lauryl sulfate in 56.5 mM phosphate buffer, pH 4.5 and wavelength 237 nm during 60 minutes (sample at 5, 10, 20, 30, 45 and 60 minutes) for abiraterone acetate tablets at t=0.

Figure 2 show the results of dissolution tests performed with abiraterone acetate tablets according to example 5 (2 batches: 5a and 5b) at t=0.

Table 1:

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>% dissolved</th>
<th>% dissolved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Batch</td>
<td>Ex 5a</td>
<td>Ex 5b</td>
</tr>
<tr>
<td>Time</td>
<td>T0</td>
<td>T0</td>
</tr>
<tr>
<td>0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>5</td>
<td>12.9</td>
<td>3.4</td>
</tr>
<tr>
<td>10</td>
<td>32.5</td>
<td>7.6</td>
</tr>
</tbody>
</table>
Example 7: Hardness

The average hardness of the pharmaceutical compositions as herein disclosed was measured using a tablet hardness tester Pharma Test PTB 111E-500. The average hardness of the tablet is between 130 and 160 N. This hardness has shown the best immediate release dissolution profiles, namely at least 80% of the active agent is released in 45 min.

Example 8: Stability data

All the stability tests were performed with the tablets packaged in HDPE bottles sealed with an aluminium foil and child-resistant closure. Dissolution test of abiraterone (% abiraterone) was determined at 60 min using method USP Apparatus: II (Paddles), speed: 50 r.p.m. medium: 0.25 % sodium lauryl sulfate in 56.5 mM phosphate buffer, pH 4.5 and wavelength 237 nm.

<table>
<thead>
<tr>
<th>Batch Nº</th>
<th>Example 1</th>
<th>t=0</th>
<th>25 ºC / 60% RH- 6 month</th>
<th>30 ºC / 65% RH - 6 month</th>
<th>40 ºC / 75% RH- 6 month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dissolution (% abiraterone acetate)</td>
<td>98.2</td>
<td>98.2</td>
<td>96.4</td>
<td>96.0</td>
<td></td>
</tr>
<tr>
<td>Assay (%)</td>
<td>103.65</td>
<td>99.06</td>
<td>98.38</td>
<td>100.59</td>
<td></td>
</tr>
<tr>
<td>RELATED SUBSTANCES Unknown individual impurities (%)</td>
<td>0.06</td>
<td>0.08</td>
<td>0.1</td>
<td>0.16</td>
<td></td>
</tr>
<tr>
<td>Total impurities (%)</td>
<td>0.13</td>
<td>0.14</td>
<td>0.24</td>
<td>0.54</td>
<td></td>
</tr>
</tbody>
</table>
1. A pharmaceutical composition in the form of immediate release tablets comprising abiraterone acetate or a pharmaceutically acceptable salt thereof, wherein the pharmaceutical composition comprises between 2 and 8 % w/w of surfactant in respect of the total amount of the pharmaceutical composition and/or the D50 of abiraterone acetate is between 3 to 10 microns as measured by laser diffraction spectroscopy and/or the D90 of abiraterone acetate is less than 20 microns as measured by laser diffraction spectroscopy.

2. The pharmaceutical composition according to the preceding claim, wherein the pharmaceutical composition comprises between 2 and 8 % w/w of surfactant in respect of the total amount of the pharmaceutical composition and the D50 of abiraterone acetate is between 3 to 10 microns as measured by laser diffraction spectroscopy and the D90 of abiraterone acetate is less than 20 microns as measured by laser diffraction spectroscopy.

3. The pharmaceutical composition according to any one of the preceding claims, wherein the pharmaceutical composition comprises between 3 and 6 % w/w of surfactant in respect of the total amount of the pharmaceutical composition, preferably between 3.5 and 5 % w/w of surfactant in respect of the total amount of the pharmaceutical composition, more preferably 4 % w/w of surfactant in respect of the total amount of the pharmaceutical.

4. The pharmaceutical composition according to any one of the preceding claims, wherein the surfactant is selected from nonionic, ionic and mixtures thereof; preferably is an ionic surfactant.

5. The pharmaceutical composition according to any one of the preceding claims, wherein the surfactant is an ionic surfactant selected from cationic, anionic, zwitterionic and mixtures thereof; preferably is an anionic surfactant.

6. The pharmaceutical composition according to any one of the preceding claims, wherein the pharmaceutical composition comprises an intragranular component comprising abiraterone acetate or a pharmaceutically acceptable salt thereof, and at least one anionic surfactant.
7.- The pharmaceutical composition according to any one of the preceding claims, wherein the anionic surfactant is sodium lauryl sulphate.

8.- The pharmaceutical composition according to any one of the preceding claims, wherein the pharmaceutical composition comprises between 3.5 and 5 % w/w of sodium lauryl sulfate in respect of the total amount of the pharmaceutical composition, preferably about 4 % w/w of sodium lauryl sulfate in respect of the total amount of the pharmaceutical composition.

9.- The pharmaceutical composition according to any one of the preceding claims, wherein the pharmaceutical composition comprises at least a filler, preferably the total amount of filler or fillers present in the pharmaceutical composition ranges from 30 to 65 % w/w in respect of the total amount of the pharmaceutical composition and wherein the filler is microcrystalline cellulose, lactose or mixtures thereof.

10.- The pharmaceutical composition according to any one of the preceding claims, wherein the pharmaceutical composition comprises at least a disintegartant, preferably the total amount of disintegartant or disintegartants present in the pharmaceutical composition ranges from 1 to 15 % w/w in respect of the total amount of the pharmaceutical composition and wherein the disintegartant is croscarmellose sodium.

11.- The pharmaceutical composition according to any one of the preceding claims, wherein the pharmaceutical composition comprises at least a binder, preferably the total amount of binder or binders present in the pharmaceutical composition ranges from 1 to 10 % w/w in respect of the total amount of the pharmaceutical composition and wherein the binder is polyvinylpyrrolidone.

12.- The pharmaceutical composition according to any one of the preceding claims, wherein the pharmaceutical composition comprises at least a lubricant, preferably the total amount of lubricant or lubricants present in the pharmaceutical composition ranges from 0.5 to 5 % w/w in respect of the total amount of the pharmaceutical composition and wherein the lubricant is magnesium stearate.

13.- The pharmaceutical composition according to any one of the preceding claims, wherein the pharmaceutical composition comprises at least a glidant, preferably the total amount of glidant or glidants present in the pharmaceutical composition ranges from 0.08 to 3 % w/w in respect of the total amount of the pharmaceutical composition and
wherein the glidant is colloidal silicon dioxide.

14.- The pharmaceutical composition according to any one of the preceding claims, wherein the pharmaceutical composition comprises from 100 to 400 mg of active agent per unit dose, preferably about 250 mg of active agent per unit dose.

15.- The pharmaceutical composition according to any one of the preceding claims, wherein the pharmaceutical compositions are manufactured by wet granulation.

16.- The pharmaceutical composition in the form of tablet according to any one of the preceding claims comprises:
   i) an intragranular portion comprising abiraterone acetate and at least a surfactant, at least a binder, at least a filler, at least a disintegrant, and;
   ii) an extragranular portion comprising at least a lubricant and at least a glidant.

17.- The pharmaceutical composition in the form of tablet according to the preceding claim comprises:
   i) an intragranular portion comprising abiraterone acetate, sodium lauryl sulfate, polyvinylpyrrolidone, lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, and;
   ii) an extragranular portion comprising colloidal silicon dioxide and magnesium stearate.

18.- The pharmaceutical composition according to any one of the preceding claims, wherein the pharmaceutical composition has an average hardness between 130 and 160 N, preferably between 135 and 145 N.

19.- A process for the manufacture of the pharmaceutical composition as defined in any of the preceding claims, comprising the following steps:
   i) providing a solution of at least a surfactant and at least a portion of the amount of the binder;
   ii) providing an intragranular mixture of abiraterone acetate or a pharmaceutically acceptable salt thereof and at least one disintegrant, at least one filler and the rest of amount of the binder;
   iii) granulating the mixture obtained in step (ii) with the solution of step (i) by a wet granulation process to produce a granulate;
   iv) drying the granulate of the previous step (iii);
   v) optionally, performing a sieving of the granulate obtained in step (iv);
vi) blending the granulate of step (iv) with at least one extragranular excipient;
vii) adding at least one lubricant to the blended composition of step (vi);
viii) compressing the blended composition of step (vii) to obtain a tablet composition.

20.- The process according to the preceding claim, wherein the intragranular composition comprises abiraterone acetate or a pharmaceutically acceptable salt thereof, a first intragranular filler, optionally a second intragranular filler, an intragranular disintegrant, an intragranular surfactant and an intragranular binder; and the extragranular composition comprises an extragranular glidant and an extragranular lubricant.

21.- The process according to the any one of the preceding process claims, comprising the following steps:
i) providing a solution of sodium lauryl sulfate and at least a portion of the amount of polyvinylpyrrolidone;
ii) providing an intragranular mixture of abiraterone acetate or a pharmaceutically acceptable salt thereof and at least one disintegrant, at least one filler and the rest of amount of polyvinylpyrrolidone;
iii) granulating the mixture obtained in step (ii) with the solution of step (i) by a wet granulation process to produce a granulate;
iv) drying the granulate of the previous step (iii);
v) optionally, performing a sieving of the granulate obtained in step (iv);
vi) blending the granulate of step (iv) with at least one extragranular excipient;
vii) adding at least one lubricant to the blended composition of step (vi);
viii) compressing the blended composition of step (vii) to obtain a tablet composition.

22.- The process according to any of the preceding process claims, wherein the step (iv) is performed to an endpoint up to 2.5 % w/w of water content in respect of the total amount of the granulate.

23.- The process according to any of the preceding process claims, wherein the drying is carried out in a fluid bed at an input temperature between 30 and 50 °C.

24.- The process according to any of the preceding process claims, wherein in the step (viii) the tablets are compressed in order to have an average hardness between 130 and 160 N, preferably between 135 and 145 N.

25.- The pharmaceutical composition obtained by the process of the preceding claims.
26.- A pharmaceutical batch comprising at least 20,000 units of the pharmaceutical composition as defined in any one of claims 1 to 18 or 25.

27.- The pharmaceutical batch according to the preceding claim, comprising at least 50,000 units.

28.- The pharmaceutical batch according to any one of the two preceding claims wherein the tablets are packaged in a high density polyethylene (HDPE) bottle.

29.- The HDPE bottle according to the preceding claim, wherein the HDPE bottle has a polypropylene child-resistant closure.

30.- The pharmaceutical composition according to any one of claims 1 to 18 or 25 or the pharmaceutical batch according to any one of claims 26 to 28, for use in the treatment of cancer, preferably metastatic prostate cancer.

31.- A cardboard box with a patient information leaflet comprising at least one unit of the pharmaceutical composition as defined in any one of claims 1 to 18 or 25.

32.- A method for preparing a pharmaceutical dossier to obtain the marketing authorization of pharmaceutical composition as defined in any one of claims 1 to 18 or claim 25 comprising the following steps:
   i) manufacturing at least one pharmaceutical batch as defined in any one of claims 26 to 28;
   ii) performing stability tests of the batches of step (i);
   iii) compiling the results obtained in steps (i) to (iii); and
   iv) providing the compiled results of step (iii) in a data carrier.

33.- A data carrier comprising the compiled results of a pharmaceutical dossier obtained by the method of the preceding claim.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

A61K9/20 A61K31/58
A61K9/16

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

B. FIELDS SEARCHED

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

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

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

EPO-Internal, WPI Data, CHEM ABS Data, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>CN 103 446 069 A (CHONGQING PHARM RES INST CO) 18 December 2013 (2013-12-18) page 1; example 7 examples</td>
<td>1-33</td>
</tr>
<tr>
<td>Y</td>
<td></td>
<td>19-25</td>
</tr>
</tbody>
</table>

[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 because it 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

"I" document member of the same patent family

Date of the actual completion of the international search
31 July 2015

Date of mailing of the international search report
12/08/2015

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

Authorized officer
Palma, Vera

Form PCT/ISA/210 (second sheet) (April 2005)
<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>wo 2013/164473 AI (JAGOTEC AG [CH]) 7 November 2013 (2013-11-07) page 1; examples</td>
<td>1-18, 26-33</td>
</tr>
<tr>
<td>X,P</td>
<td>wo 2015/032873 AI (SYNTHON BV [NL]) 12 March 2015 (2015-03-12) page 1 page 9, line 9 - line 10 examples</td>
<td>1-3, 7, 9-16, 18, 25, 30</td>
</tr>
<tr>
<td>Patent document cited in search report</td>
<td>Publication date</td>
<td>Patent family member(s)</td>
</tr>
<tr>
<td>---------------------------------------</td>
<td>-----------------</td>
<td>-------------------------</td>
</tr>
<tr>
<td>CN 103446069 A</td>
<td>18-12-2013</td>
<td>NONE</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 2015515970 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>WO 2013164473 A1</td>
</tr>
<tr>
<td>WO 2015032873 A1</td>
<td>12-03-2015</td>
<td>NONE</td>
</tr>
</tbody>
</table>