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Title: OXIDATION STABILITY OF ABIRATERONE ACETATE

Abstract: The present invention relates to a pharmaceutical composition comprising abiraterone acetate or a pharmacetically acceptable salt, hydrate or solvate thereof, characterized in that the abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof is stabilized against oxidative degradation.
Oxidation stability of abiraterone acetate

Description

The present invention relates to a process for the preparation of a pharmaceutical composition in which pharmaceutical composition the abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof is stabilized against oxidative degradation. The present invention further relates to a pharmaceutical composition comprising abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof, wherein the abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof is stabilized against oxidative degradation.

Abiraterone is a selective inhibitor of 17 α-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 17α-hydroxy derivatives by its 17α-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-21 2082; Zytiga®) is a pregnenolone analog used in castration-resistant prostate cancer (CRPC). Abiraterone acetate (i.e. 17-(pyridin-3-yl)androsta-5,16-dien-3β-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 (I):

![Chemical structure](image)

(I)

Abiraterone acetate is a white to off-white, non-hygroscopic, crystalline powder which is practically insoluble in water. Its molecular formula is C_{26}H_{33}NO_{2} and it has a molecular weight of 391.55 g/mol. The compound abiraterone acetate in dry crystalline form is quite stable. No significant degradation is observed after exposure to different stress tests such as simulated sunlight, elevated temperature, humid conditions and oxygen from air.

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.

Pharmaceutically active salts are known in the art from WO 2006/021777 and WO 09/009132.

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.
Abiraterone acetate is classified 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. Usually they are not well absorbed over the intestinal mucosa and a high variability is expected.

The low solubility of abiraterone acetate in water is one of the factors leading to a low bioavailability of abiraterone acetate as used within Zytiga®. At a daily dose of 1000 mg in patients with metastatic CRPC, steady-state values (mean ± SD) of Cmax were 226 ± 178 ng/mL and of AUC were 1173 ± 690 ng.hr/ml. The absolute bioavailability of abiraterone acetate with Zytiga® is reported to be no more than 10%, as the drug is mainly metabolized to abiraterone and then excreted by feces (-88%) and urine (-5%) with a terminal half life of 12 ± 5 hours. (Zytiga® prescribing information). This means in consequence that, from the 4 Zytiga® tablets of 250 mg each, adding up to 1 g, which the patient has to take each day at once, only 10% of the drug can develop a therapeutical effect.

Accordingly, different dosage forms comprising abiraterone acetate were prepared in order to improve the bioavailability of abiraterone acetate and to reduce the necessary daily dose of abiraterone acetate.

During preparation of dosage forms having an improved solubility and dissolution rate of abiraterone acetate, such as solid dispersions, nanosuspensions, liquid formulations and adsorbates, it was surprisingly found that formulating abiraterone acetate has a negative influence on the chemical stability of the compound. In particular, oxidative degradation of formulated abiraterone acetate has been observed.

Degradation of abiraterone acetate is adversely affecting the stability of the pharmaceutical preparation.
The observed oxidative degradation of formulated abiraterone acetate was unexpected as the compound abiraterone acetate in dry crystalline form is known to be very stable, e.g. with regard to oxygen from air.

Moreover, the commercially available product Zytiga®, wherein abiraterone acetate is present in dry crystalline form, is stable at room temperature.

Unexpectedly, degradation, in particular oxidative degradation, was observed in Zytiga® tablets after stress and accelerated stability testing. In particular, at accelerated conditions of 40°C/75% relative humidity (RH) decomposition of abiraterone acetate is detected over time. According to this finding, Zytiga® tablets may not be suitable for regions with high relative humidity or elevated temperatures.

Accordingly, it would be desirable to provide a pharmaceutical composition of abiraterone acetate that is less prone to degradation, in particular to oxidative degradation.

Therefore it was an object of the present invention to provide a pharmaceutical composition comprising abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof which exhibits an increased stability against degradation, in particular against oxidative degradation.

It is further desirable, to provide a pharmaceutical composition that can be stored and used at room temperature for a specific time of more than 18 months and can be stored without temperature limitations.

It is further desirable to provide a pharmaceutical composition that can be used and stored under the conditions of climate zones with high temperature or high temperature and high humidity.

According to the present invention this object is achieved by a process for the preparation of a pharmaceutical composition comprising abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof, in which pharmaceutical
composition the abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof is stabilized against oxidative degradation, wherein said abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof is mixed with one or more excipients and processed to provide a pharmaceutical composition, and characterized in that means are employed which stabilize the abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof against oxidative degradation.

In one embodiment the process for the preparation of a pharmaceutical composition comprising abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof, wherein the abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof is stabilized against oxidative degradation comprises a further step, wherein the pharmaceutical composition is packaged to provide a packaged pharmaceutical composition.

The invention further relates to a pharmaceutical composition comprising abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof, characterized in that the abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof is stabilized against oxidative degradation.

In the inventive pharmaceutical composition oxidative degradation of abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof is significantly reduced or is substantially not observed compared to abiraterone acetate in the form of the commercially available product Zytiga® and compared to abiraterone acetate formulated without means which stabilize the compound against oxidative degradation.

One aspect of the invention is a pharmaceutical composition comprising abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof, wherein at least 95 wt% of abiraterone acetate, based on the total weight of abiraterone acetate is not affected by oxidative degradation, preferably at least 96 wt%, more preferably at least 97 wt%, more preferably at least 98 wt%, even more preferably at least 99
wt%, most preferably at least 99.5 wt% of abiraterone acetate, based on the total weight of abiraterone acetate is not affected by oxidative degradation.

As a consequence, the inventive pharmaceutical composition, wherein abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof is stabilized against oxidative degradation has superior storage stability. In particular, no significant increase of oxidation degradation products has been observed during storage, such that the products could be used in different climate zones.

Thus, in one embodiment, the present invention is directed to a pharmaceutical composition comprising abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof, characterized in that, when exposed to a temperature of 40°C and 75% relative humidity (RH) for 6 months, preferably 12 months, more preferably 18 months, even more preferably 24 months under air atmosphere, the total amount of oxidation degradation products does not increase by more than 1.5%, more preferably not more than 1.0%, even more preferably not more than 0.5%.

In another embodiment, the present invention is directed to a pharmaceutical composition comprising abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof packaged in any type of packaging or container closure system, characterized in that, when exposed to a temperature of 40°C and 75% RH for 6 months, preferably 12 months, more preferably 18 months, even more preferably 24 months the total amount of oxidation degradation products does not increase by more than 1.5%, more preferably not more than 1.0%, even more preferably not more than 0.5%.

In still another embodiment, the present invention is directed to a pharmaceutical composition comprising abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof, characterized in that, when exposed to a temperature of 60°C for 7 days, preferably for 14 days, more preferably for 21 days, even more preferably for 28 days under air atmosphere, the total amount of oxidation degradation products does not increase by more than 0.5%, more preferably not more than 0.2%.
In yet another embodiment, the present invention is directed to a pharmaceutical composition comprising abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof packaged in any type of packaging or container closure system, characterized in that, when exposed to a temperature of 60°C for 7 days, preferably for 14 days, more preferably for 21 days, even more preferably for 28 days the total amount of oxidation degradation products does not increase by more than 0.5%, more preferably not more than 0.2%.

As used herein, the term "oxidation degradation product" refers to an impurity resulting from chemical reaction of abiraterone acetate with oxygen during manufacture and/or storage of the active pharmaceutical ingredient and/or the pharmaceutical composition. Abiraterone, which can be formed from abiraterone acetate via ester bond cleavage it is a hydrolytic degradation product and is not regarded as an oxidation degradation product.

As used herein, the amount of individual and total oxidation degradation products are defined by ultra high pressure liquid chromatography (UPLC) according to the following method:

The chromatographic separation is performed on Waters ACQUITY UPLC System and BEH C18, 1.7µm, 100 x 2.1 mm column at a column temperature of 60 °C using gradient elution of mobile phase A (70 : 30 v/v of 5 mM NaH2P04 adjusted to pH=7.5 and acetonitrile) and mobile phase B (90 : 10 v/v of acetonitrile and water) at a flow rate of 0.9 mL/min and the following gradient run program:

<table>
<thead>
<tr>
<th>Time (minutes)</th>
<th>% A</th>
<th>% B</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>70</td>
<td>30</td>
</tr>
<tr>
<td>12.2</td>
<td>70</td>
<td>30</td>
</tr>
<tr>
<td>17.1</td>
<td>40</td>
<td>60</td>
</tr>
<tr>
<td>19.6</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>23.0</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>23.1</td>
<td>70</td>
<td>30</td>
</tr>
</tbody>
</table>
Ultraviolet detection is performed at 255 nm.

A sample solution is prepared by diluting a quantity of sample equivalent to 10 mg of abiraterone acetate in 10 ml volumetric flask to volume with 60 % acetonitrile in water. A sample injection volume of 10 µl is being used.

The amounts of oxidation degradation products are measured in area % of the resulting ultra high pressure liquid chromatography (UPLC) spectrum - not including the abiraterone acetate and abiraterone peak area %.

According to the invention, the term "stabilized against oxidative degradation" means that the oxidative degradation of abiraterone acetate is significantly reduced or is substantially not observed compared to abiraterone acetate in the form of the commercially available product Zytiga® and compared to abiraterone acetate formulated without means which stabilize the compound against oxidative degradation.

One aspect of the invention is a pharmaceutical composition comprising abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof, wherein the total amount of oxidation degradation products does not exceed 5 wt%, based on the weight of the composition, preferably the total amount of oxidation degradation products does not exceed 3 wt%, more preferably 2 wt%, more preferably 1.5 wt%, even more preferably 1 wt%, even more preferably 0.5 wt%, most preferably 0.2 wt%, based on the weight of the composition.

According to the invention abiraterone acetate may be used in the form of the free base or in the form of pharmaceutically acceptable salts, hydrates or solvates of abiraterone acetate. Examples for pharmaceutically acceptable salts are acetates, sulfates, pyrosulfates, bisulfates, sulfites, bisulfites, phosphates, monohydrogen-phosphates, dihydrogenphosphates, metaphosphates, pyrophosphates, chlorides, bromides, iodides, propionates, decanoates, caprylates, acrylates, formates, isobutyrates, caproates, heptanoates, propiolates, oxalates, malonates, succinates, suberates, sebacates, fumarates, maleates, butyne-1,4-dioates, hexyne-1,6-dioates, benzoates, chlorobenzoates, methylbenzoates, dinitrobenzoates, hydroxybenzoates,
methoxybenzoates, phthalates, sulfonates, xylenesulfonates, phylacetates, phenylpropionates, phenylbutyrates, citrates, lactates, gammahydroxy-butyrates, glycolates, tartrates, alkanesulfonates (e.g. methane-sulfonate or mesylate), propanesulfonates, naphthalene-1-sulfonates, naphthalene-2-sulfonates, and mandelates.

In a preferred embodiment abiraterone acetate is used in the form of the free base or as the hydrochloric, sulfuric or toluoyltartaric acid salt or, in particular, the methanesulfonic acid salt (i.e. the mesylate). More preferably, abiraterone acetate is in the form of the free base or the mesylate salt.

Herein, the term "abiraterone acetate" is used indifferently for the free base or any pharmaceutically acceptable salt thereof and will be understood as relating also to solvates and hydrates thereof.

According to the invention abiraterone acetate is used in crystalline form, in amorphous form or in dissolved form.

In the following, means for stabilizing the abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof in a pharmaceutical preparation against oxidative degradation are described. Said means are equally employed in the inventive process for the preparation of a pharmaceutical composition comprising abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof, in which pharmaceutical composition the abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof is stabilized against oxidative degradation.

In order to prevent oxidative degradation the abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof in the pharmaceutical composition of the present invention may be stabilized by the addition of at least one antioxidant.

Therefore, in one embodiment, the present invention relates to a pharmaceutical composition, wherein the abiraterone acetate or a pharmaceutically acceptable salt,
hydrate or solvate thereof is stabilized against oxidative degradation by the addition of at least one antioxidant.

Suitable antioxidants for use according to the invention include butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), ascorbyl palmitate (AP), propyl gallate, alpha tocopherol or any mixtures thereof.

In the pharmaceutical composition of the invention the antioxidant is present in an amount of 0.0001 to 5% by weight, preferably 0.001 to 0.5% by weight, more preferably 0.01 to 0.1% by weight, even more preferably 0.05% by weight, based on the weight of the pharmaceutical composition.

According to the present invention it has surprisingly been found that also adjustment of the pH exerts a stabilizing effect resulting in an improved stability against oxidative degradation and therefore in an improved storage stability.

Thus, in another embodiment the invention relates to a pharmaceutical composition, wherein the abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof is stabilized against oxidative degradation by means of pH adjustment. In particular, the pH of the pharmaceutical composition is adjusted to be within a range of 1 to 9, preferably to be within a range of 1.5 to 8.5, more preferably to be within a range of 2 to 8, even more preferably the pH of the pharmaceutical composition is adjusted to be about 3.

The pharmaceutical composition according to the present invention may comprise an external coating. Said external coating may be functional such as moisture protective coating, enteric coating or oxidation protective coating. Suitable enteric coatings are known in the art. For the purpose of oxygen protection, i.e. in order to prevent oxidative degradation, oxygen scavengers may be used in the coating. Alternatively, said external coating may be non-functional such as color coating.
A coating is also useful in order to improve handling, i.e. no protective gloves are required by medical staff administering the inventive pharmaceutical composition to a patient.

In one embodiment, the present invention relates to a pharmaceutical composition, wherein the abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof is stabilized against oxidative degradation by means of a functional coating, preferably a moisture protective coating, an oxidation protective coating or a gastro protective coating, more preferably an oxygen impermeable coating.

In particular, the oxygen impermeable coating is selected from the group consisting of polyvinyl alcohol, and cellulose derivatives.

In another embodiment, the present invention relates to a pharmaceutical composition, wherein the abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof is stabilized against oxidative degradation by means of a non-functional coating.

In yet another embodiment, the present invention relates to a pharmaceutical composition, wherein the abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof is stabilized against oxidative degradation by means of preparation under inert atmosphere.

As used herein, the term "inert atmosphere" relates to a substantially oxygen free environment, e.g. nitrogen atmosphere.

According to the invention the inert atmosphere comprises less than 5% oxygen, preferably less than 3% oxygen, more preferably less than 1% oxygen, even more preferably less than 0.5% oxygen, most preferably the inert atmosphere comprises less than 0.2% oxygen.
In one embodiment the inert atmosphere is a nitrogen atmosphere. According to the invention the nitrogen atmosphere contains at least 95% of nitrogen, preferably at least 98% of nitrogen, more preferably at least 99.5% of nitrogen.

In a further embodiment, the present invention relates to a pharmaceutical composition, wherein the abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof is stabilized against oxidative degradation by means of special packaging and/or storage.

The special packaging and/or storage may be achieved by packaging and/or storage under vacuum.

As used herein, the term "vacuum" is defined as a region with a gaseous pressure much less than atmospheric pressure. According to the invention "vacuum" also relates to pressures below and often considerably below atmospheric pressure.

Alternatively, the special packaging and/or storage may be achieved by packaging and/or storage under inert atmosphere, packaging with at least one oxygen scavenger/absorber and/or oxygen barrier packaging.

In one embodiment the invention relates to a pharmaceutical composition that is packaged and/or stored under inert atmosphere.

In another embodiment the invention relates to a pharmaceutical composition that is packaged with at least one oxygen scavenger/absorber. According to the invention the oxygen absorption capacity of the at least one scavenger/absorber is more than 5 ml of oxygen per 1 g of scavenger/absorber, preferably more than 10 ml, preferably more than 30 ml, even more preferably the oxygen absorption capacity of the at least one oxygen scavenger/absorber is more than 50 ml of oxygen per 1 g of scavenger/absorber.

As used herein, the term "oxygen scavengers" relates to packaging materials, films or devices that chemically react with oxygen to remove it from the packaging
environment - oxidizable inorganic and/or organic compounds, enzymatic oxygen absorber and multi-component systems like unsaturated organic polymers.

The terms "oxygen scavengers" and "oxygen absorbers" are used interchangeably herein.

In still another embodiment the invention relates to a pharmaceutical composition that is packaged using oxygen barrier packaging material.

Suitable examples of oxygen barrier packaging materials are glass (i.e. bottles, vials), metal (i.e. multilayer systems containing aluminum layer) and packaging materials containing ethylene vinyl alcohol copolymers, polyvinylidene chloride copolymers, polyvinyl alcohol films or polyethylene terephthalate polyester.

Thus, in one embodiment the pharmaceutical composition of the present invention is packaged in glass bottles or metal blister, preferably aluminum blister.

The pharmaceutical composition of the present invention can be stored and transported without temperature limitations, e.g. it can be stored and transported at up to 40 °C, more preferably up to 50 °C.

The inventive pharmaceutical composition may optionally further comprise one or more pharmaceutically acceptable excipients generally used in the art. Such excipients may include one or more fillers, diluents, lubricants, binders, granulating aids, disintegrating agents, colorants, flavoring agents, sweeteners, glidants, preservatives, stabilizers, solubilizers, antioxidants or buffers and other excipients depending on the route of administration and the dosage form used.

The pharmaceutical composition of the present invention may be in the form of a solid dispersion, a nanosuspension, an adsorbate, a liquid lipidic formulation, e.g. a self-microemulsifying drug delivery system, or a pharmaceutical preparation comprising or derived from a solid dispersion, a nanosuspension, an adsorbate, a liquid lipidic formulation, e.g. a self-microemulsifying drug delivery system.
According to the present invention the pharmaceutical composition preferably is an oral dosage form. Said oral dosage form may be selected from the group consisting of a tablet, a capsule, a sachet, a powder, a syrup or a liquid.

In a further embodiment of the invention the pharmaceutical composition as described hereinabove is for use in the treatment of cancer, preferably metastatic prostate cancer.

It should be understood that the abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof in the pharmaceutical composition of the present invention is stabilized against oxidative degradation by one or more of the means described hereinabove, including any combination of the means that may be used to confer stability against oxidative degradation.

Figures

Figure 1: Chromatograms of Zytiga® samples stored at 60°C after 7 days under different atmosphere conditions. Sensitivity of Zytiga® tablets to oxygen is observed. No increase of hydrolytic degradation product is detected (free abiraterone impurity is eluted at Rt-2.347).

Figure 2: Stability trend for total impurities in Zytiga® tablets at accelerated stability condition

Figure 3: Increase in total impurities of abiraterone acetate in samples of solid dispersions, tablets prepared from solid dispersions, the reference product Zytiga® and the starting API after storage at 60°C for 7 days under air, nitrogen and oxygen atmosphere.

Figure 4: Increase in total impurities of abiraterone acetate in samples of solid dispersions, tablets prepared from solid dispersions, the reference product Zytiga® and the starting API after storage at 40°C for 1 month under air.
Figure 5: Increase in total impurities of abiraterone acetate in samples of nanosuspensions, tablets prepared from nanosuspensions, the reference product Zytiga® and the starting API after storage at 60°C for 1 month under air.

Figure 6: Increase in total impurities of abiraterone acetate after storage at 60°C for 7 days under air and nitrogen in mixtures with abiraterone acetate (with and without butylated hydroxytoluene (BHT)).

Figure 7: Increase in total impurities of abiraterone acetate after storage at 40°C for 1 month under air and nitrogen in mixtures with abiraterone acetate (with and without butylated hydroxytoluene (BHT)).

Figure 8: Increase in total impurities in abiraterone acetate adsorbate and starting active pharmaceutical ingredient (API) after storage at 60°C for 7 days under oxygen, air and nitrogen.

Specific embodiments of the present invention will further be demonstrated by the following examples. It should be understood that these examples are disclosed only by way of illustration and should not be construed as limiting the scope of the present invention.

Examples

Stability evaluation of Zytiga® tablets

The shelf-life of Zytiga® is 12 months at 20°C to 25°C (68 °F to 77°F) with excursions permitted to 15°C to 30°C (59°F to 86°F) [USP Controlled Room temperature].

To evaluate the chemical stability the commercially available product Zytiga® tablets were put on stress and accelerated stability conditions. Sensitivity of Zytiga® to different environmental factors was tested. Level of free abiraterone and total impurities were measured.

Influence of temperature and oxygen
Abiraterone acetate formulated in Zytiga™ tablets is prone to degradation at elevated temperature. Decomposition was mainly due to oxidation degradation, practically no increase of hydrolytic degradation product abiraterone was detected. The results shown in Table 1 and Figure 1 demonstrate that degradation at higher temperature could be prevented by storage under inert atmosphere (nitrogen).

**Table 1**

<table>
<thead>
<tr>
<th>Storage condition &amp; time points</th>
<th>60 °C</th>
<th>50 °C</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>initial analysis</td>
<td>nitrogen - 7 days</td>
</tr>
<tr>
<td>Abiraterone (%)</td>
<td>0.08</td>
<td>0.11</td>
</tr>
<tr>
<td>Total (%)</td>
<td>0.15</td>
<td>0.23</td>
</tr>
</tbody>
</table>

Accelerated stability

Results of accelerated stability (Table 2) show increase in total impurities up to 2% after 6 months of testing.

**Table 2**

<table>
<thead>
<tr>
<th>Storage condition &amp; time points</th>
<th>40 °C</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>initial analysis</td>
</tr>
<tr>
<td>Abiraterone (%)</td>
<td>0.08</td>
</tr>
<tr>
<td>Total (%)</td>
<td>0.15</td>
</tr>
</tbody>
</table>

The stability trend for total impurities in Zytiga™ tablets at accelerated stability condition is shown in Figure 2.

Preparation of solid dispersions and pharmaceutical compositions with solid dispersions

**Example 1 (101X1, 101X2, 101X3)**

Polymethacrylate (Eudragit L100) was dissolved in ethanol. Abiraterone acetate was added to obtain a drug:polymer ratio of 1:1. The mixture was mixed with a magnetic stirrer until all drug substance was dissolved. A solid carrier of choice (sample 101X1 = partially pregelatinized starch, sample 101X2 = microcrystalline cellulose, sample 101 X3 = lactose) was added to the solution in a ratio of 1:2 = carrier:abiraterone acetate, mixed and dried in a vacuum dryer for 4 hours at 40°C. The compositions of the final mixtures are given in Table 3.
Table 3: Composition of solid dispersion 101X1, 101X2 and 101X3

<table>
<thead>
<tr>
<th></th>
<th>101X1</th>
<th>101X2</th>
<th>101X3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abiraterone acetate</td>
<td>250 mg</td>
<td>250 mg</td>
<td>250 mg</td>
</tr>
<tr>
<td>Eudragit L100</td>
<td>250 mg</td>
<td>250 mg</td>
<td>250 mg</td>
</tr>
<tr>
<td>Starch</td>
<td>125 mg</td>
<td>/</td>
<td>/</td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
<td>/</td>
<td>125 mg</td>
<td>/</td>
</tr>
<tr>
<td>Lactose</td>
<td>/</td>
<td>/</td>
<td>125 mg</td>
</tr>
</tbody>
</table>

Example 2 (102X1, 102X2, 102X3)
The polymer of choice (sample 102X1 = Eudragit L100, sample 102X2 = polyvinylpyrrolidone, sample 102X3 = hydroxypropyl cellulose) was mixed with ethanol until it dissolved entirely. Butylated hydroxytoluene (BHT) was added to the solution and the solution was stirred until all butylated hydroxytoluene was dissolved. Abiraterone acetate was added to the solution and the solution was stirred until all abiraterone acetate was dissolved. The resulting solution was added drop wise to microcrystalline cellulose until a wet mass was formed, the mass was dried in a vacuum dryer at 30°C, crushed and again wetted with the ethanol solution. The procedure was repeated until all solution was used up. The final mass was dried at the conditions described above, crushed and sieved through a 0.7 mm sieve. The final composition of the granulates is given in Table 4.

Table 4: Composition of solid dispersion 102X1, 102X2 and 102X3

<table>
<thead>
<tr>
<th></th>
<th>102X1</th>
<th>102X2</th>
<th>102X3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abiraterone acetate</td>
<td>250 mg</td>
<td>250 mg</td>
<td>250 mg</td>
</tr>
<tr>
<td>Eudragit L100</td>
<td>250 mg</td>
<td>/</td>
<td>/</td>
</tr>
<tr>
<td>Polynvinylpyrrolidone</td>
<td>/</td>
<td>250 mg</td>
<td>/</td>
</tr>
<tr>
<td>Hydroxypropyl cellulose</td>
<td>/</td>
<td>/</td>
<td>250 mg</td>
</tr>
<tr>
<td>Butylated hydroxytoluene</td>
<td>0.4 mg</td>
<td>0.4 mg</td>
<td>0.4 mg</td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
<td>500 mg</td>
<td>500 mg</td>
<td>500 mg</td>
</tr>
</tbody>
</table>

Example 3 (103X1, 103X2, 103X3)
The granulates from example 2 were mixed with croscarmellose sodium, colloidal silica and magnesium stearate and compressed into tablets. The granulate from sample 102X1 was used to prepare tablet sample 103X1, the granulate from sample 102X2 was used to prepare tablet sample 103X2 and the granulate from sample 102X3 was used to prepare tablet sample 103X3. The final compositions are given in Table 5.

| Table 5: Composition of tablets 103X1, 103X2 and 103X3 |
|----------------|----------------|----------------|
|                | 103X1           | 103X2           | 103X3           |
| Abiraterone acetate | 250 mg          | 250 mg          | 250 mg          |
| Eudragit L100      | 250 mg          | /               | /               |
| Polyvinylpyrrolidone | /               | 250 mg          | /               |
| Hydroxypropyl cellulose | /             | /               | 250 mg          |
| Butylated hydroxytoluene | 0.4 mg        | 0.4 mg          | 0.4 mg          |
| Microcrystalline cellulose | 500 mg        | 500 mg          | 500 mg          |
| Croscarmellose Sodium | 30 mg          | 30 mg           | 30 mg           |
| Colloidal silica   | 2.5 mg          | 2.5 mg          | 2.5 mg          |
| Mg stearate        | 5 mg            | 5 mg            | 5 mg            |

Stability evaluation of solid dispersions and final dosage forms

Example 4
Samples from examples 1-3 were put on different storage condition for stability evaluation. To accelerate ageing the samples were stored at the following accelerate and stress storage conditions:

- elevated temperature of 60 °C under nitrogen, air and oxygen atmosphere for 7 days
- accelerated condition of 40 °C under air for 1 month.

The samples were analyzed after sampling from storage conditions. The marketed product (Zytiga®) and the pure active pharmaceutical ingredient (API) were used as reference products and treated in the same manner as the samples from the examples. The results are shown in Figures 3-4. The increase in total impurities was
measured. The increase of impurities was calculated as a difference between the amount of total impurities of each sample before and after storage.

Results in Figures 3-4 show an increase in total impurities during storage in some of the samples (101X1, 101X2, 101X3 - prepared without antioxidant, Example 1) in the presence of oxygen as well as in the reference product Zytiga®. Instead, no increase in degradation products was observed in the sample with the starting API at the same stability conditions. From these results it is evident that the preparation of solid dispersions has an extremely negative effect on the chemical stability of abiraterone acetate. Abiraterone acetate in solid dispersion is prone to oxidative degradation, which can be derived from the fact, that no instability was observed in inert (nitrogen) atmosphere. Additionally, the stability of prepared solid dispersion and their respective formulations was significantly improved by addition of the antioxidant butylated hydroxytoluene to the solid dispersions and the respective tablet formulations (102X1, 102X2, 102X3 - Example 2; 103X1, 103X2, 103X3 - Example 3). Superior stability of all samples with butylated hydroxytoluene as antioxidant was observed at all tested temperature conditions (60 °C, and 40 °C) under air conditions (Figures 3-4). Moreover, the results presented in Figure 3 demonstrate the stabilization effect of an antioxidant even when the samples were stored under pure oxygen atmosphere. Beside this, the stability of all samples - including the reference product Zytiga® and samples without antioxidant - was exceptionally improved by storage under nitrogen atmosphere, no significant increase in degradation products was detected in all samples stored under nitrogen.

Preparation of Nanosuspensions and pharmaceutical composition/dosage forms

Example 5 (002X1 tablet)

In a glass beaker 1 g hydroxypropyl methylcellulose was mixed with 17 of demineralized water to prepare a clear, slightly viscous solution. 2 g abiraterone acetate were suspended in the prepared HPMC solution, the suspension was transferred to a milling jar containing 90 g zirconium balls with the diameter in range 0,6-0,8 mm and milled in a planetary ball mill for 4 hours at 500 RPM. The resulting suspension was separated from the milling balls with a 0,4 mm sieve and the balls
were further washed with 50 g demineralized water, which was added to the milled suspension. The final suspension was centrifuged, supernatant was removed and sediment dried in a vacuum dryer at 40°C for 3 hours, grinded with pestle and mortar and sieved through a 0.315 mm sieve. The resulting granulate was mixed with lactose, colloidal silica and magnesium stearate and compressed into tablets containing 250 mg of abiraterone acetate.

Example 6 (001X4)
In a glass beaker 0.4 g polysorbate 80 was mixed with 17.6 g of demineralized water to prepare a clear, yellowish solution. 2 g abiraterone acetate were suspended in the prepared polysorbate solution, the suspension was transferred to a milling jar containing 90 g zirconium balls with the diameter in range 0.6-0.8 mm and milled in a planetary ball mill for 4 hours at 500 RPM. The resulting suspension was separated from the milling balls with a 0.4 mm sieve and the balls were further washed with 75 g of demineralized water, which was added to the milled suspension.

Example 7 (001X5)
In a glass beaker 2 g hydroxypropyl methylcellulose (HPMC) was mixed with 16 g demineralized water to prepare a clear, slightly viscous solution. 2 g abiraterone acetate were suspended in the prepared HPMC solution, the suspension was transferred to a milling jar containing 90 g zirconium balls with the diameter in range 0.6-0.8 mm and milled in a planetary ball mill for 4 hours at 500 RPM. The resulting suspension was separated from the milling balls with a 0.4 mm sieve and the balls were further washed with 75 g of demineralized water, which was added to the milled suspension.

Example 8 (001X6)
In a glass beaker 1 g poloxamer 188 was mixed with 17 g demineralized water to prepare a clear solution. 2 g abiraterone acetate were suspended in the prepared poloxamer solution, the suspension was transferred to a milling jar containing 90 g zirconium balls with the diameter in range 0.6-0.8 mm and milled in a planetary ball mill for 4 hours at 500 RPM. The resulting suspension was separated from the milling
balls with a 0,4 mm sieve and the balls were further washed with 75 g demineralized water, which was added to the milled suspension.

Example 9 (003X1, 003X2, 003X3)
Sucrose was added to final suspensions from examples 6, 7 and 8. The ratio sucrose:abiraterone acetate was 1:1. When the sucrose was dissolved the suspensions were frozen with liquid nitrogen and freeze-dried. Resulting granulate was grinded with pestle and mortar, sieved through a 1,0 mm sieve, mixed with microcrystalline cellulose, colloidal silica and magnesium stearate and compressed into tablets containing 250 mg abiraterone acetate. Suspension 001X4 was used to prepare tablet sample 003X1, suspension 001X5 was used to prepare tablet sample 003X2 and suspension 001X6 was used to prepare tablet sample 003X3.

Example 10 (001X1 0)
In a glass beaker 2 g abiraterone acetate were suspended in McIlvaine buffer with pH 3, the suspension was transferred to a milling jar containing 90 g of zirconium balls with the diameter in range 0,6-0,8 mm and milled in a planetary ball mill for 1 hour at 500 RPM. In a glass beaker 1 g of poloxamer 188 was mixed with 2 g McIlvaine buffer with pH 3 to prepare a clear solution. The resulting solution was transferred to the suspension in the milling jar and further milled for 4 hours. The resulting suspension was separated from the milling balls with a 0,4 mm sieve and the balls were further washed with 75 g of demineralized water, which was added to the milled suspension.

Example 11 (004X1)
Sucrose was added to final suspension from example 10. The ratio sucrose:abiraterone acetate was 1:1. When the sucrose was dissolved the suspension was frozen with liquid nitrogen and freeze-dried. Resulting granulate was grinded with pestle and mortar, sieved through a 0,7 mm sieve, mixed with croscarmellose, colloidal silica and magnesium stearate and compressed into tablets containing 250 mg of abiraterone acetate.
Example 12 (001X1 6)

In a glass beaker 1 g of hydroxypropyl methylcellulose was mixed with 17 g of demineralized water to prepare a clear, slightly viscous solution. 2 g abiraterone acetate mesylate were suspended in the prepared HPMC solution, the suspension was transferred to a milling jar containing 90 g zirconium balls with the diameter in range 0,6-0,8 mm and milled in a planetary ball mill for 4 hours at 500 RPM. The resulting suspension was separated from the milling balls with a 0,4 mm sieve and the balls were further washed with 50 g demineralized water, which was added to the milled suspension.

Example 13 (008X1)

The nanosuspension from example 12 was added to 0,60 g lactose in a ratio of 6:5=lactose:abiraterone acetate. The mixture was mixed and left to stand for 15 minutes, 0,32 g sodium starch glycolate was added, mixed and left to stand for 15 minutes. The mixture was transferred to vacuum dryer and dried at 40°C. Resulting granulate was grinded with pestle and mortar, sieved through a 0,3 mm sieve, mixed with microcrystalline cellulose, colloidal silica and magnesium stearate and compressed into tablets containing 250 mg of abiraterone acetate (as abiraterone acetate mesylate).

Stability evaluation of dry nanosuspensions and final dosage forms

Example 14

The final suspensions from examples 6-8, 10 and 12 were centrifuged, supernatant was removed and sediment dried in a vacuum dryer at 40 °C for 3 hours. The dry suspensions and tablets from examples 5, 9, 11, 13 were put on stress stability conditions and analyzed. The samples were stored at elevated temperature of 60 °C under nitrogen, air and oxygen atmosphere for 7 days. After sampling from storage conditions, the samples were analyzed. As reference products, the marketed product (Zytiga®) and API were treated in the same manner as the samples from the examples and analyzed. The results are shown in Figure 5. The increase in total impurities was measured. The increase of impurities was calculated as a difference between the amount of total impurities of each sample before and after storage. The
results in Figure 6 show an increase in total impurities during storage in the Zytiga®
tablets and in the majority of the nanosuspensions and tablets in the presence of
oxygen - oxygen atmosphere and air. Instead, no increase in degradation products
was observed for all samples when stored under nitrogen.

Preparation of liquid pharmaceutical compositions

Example 15

Different liquid, lipidic formulations were prepared. The preparation was the same in
all cases: the respective surfactants were mixed in the prescribed ratio (in case of
two surfactants) and the oil phases were added. The mixture was mixed on a
magnetic stirrer after each addition to form a homogeneous mixture. The final
compositions were mixed until a homogeneous mixture was obtained. The final
mixtures did not exhibit any phase separation under room temperature conditions.
The exact compositions of the lipidic mixtures are shown in Table 6. Samples of the
mixtures were further saturated with abiraterone acetate. The amount of dissolved
abiraterone acetate was measured; the concentrations of abiraterone acetate in the
mixtures are shown in Table 6.

Further samples were prepared starting from the 7 mixtures, by adding as antioxidant
butylated hydroxytoluene (BHT) in a concentration of 0.05 %. The resulting mixtures
with antioxidant were then also saturated with abiraterone acetate.

Table 6

<table>
<thead>
<tr>
<th>Sample</th>
<th>Oil (lipid) phase (ratio)</th>
<th>Surfactant (ratio)</th>
<th>Ratio (Oil/surfactant)</th>
<th>Assay of abiraterone acetate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mixture 1</td>
<td>Castor oil/Capmul MCM = 1/1</td>
<td>Span 80/Cremophor EL = 1/1</td>
<td>40/60</td>
<td>6.8%</td>
</tr>
<tr>
<td>Mixture 2</td>
<td>Castor oil/Capmul MCM = 1/1</td>
<td>Tween 80/Cremophor EL = 1/1</td>
<td>50/50</td>
<td>5.8%</td>
</tr>
<tr>
<td>Mixture 3</td>
<td>Castor oil/Capmul MCM = 1/1</td>
<td>Cremophor EL</td>
<td>50/50</td>
<td>6.3%</td>
</tr>
<tr>
<td>Mixture 4</td>
<td>Castor oil/Peceol = 1/1</td>
<td>Cremophor EL/Cremophor RH 40 = 1/1</td>
<td>70/30</td>
<td>7.7%</td>
</tr>
<tr>
<td>Mixture 5</td>
<td>Captex 355/Capmul MCM = 1/2</td>
<td>Cremophor EL</td>
<td>50/50</td>
<td>6.5%</td>
</tr>
<tr>
<td>Mixture 6</td>
<td>Captex 355/Capmul</td>
<td>Tween 20/Solutol HS =</td>
<td>50/50</td>
<td>6.4%</td>
</tr>
</tbody>
</table>
Stability of liquid pharmaceutical compositions

Example 16
The following lipidic mixtures from example 15 comprising abiraterone acetate were put on storage for stability evaluation:
Mixture 1 - Mixture 7, without antioxidants
Mixture 1 - Mixture 7, with butylated hydroxytoluene (BHT)

The lipidic mixtures without antioxidants were stored under air and nitrogen atmosphere at elevated temperature of 60°C for 7 days and at accelerated temperature of 40°C for 1 month. The mixtures containing antioxidant BHT were stored only under air at 60°C for 7 days and at 40°C for 1 month. After sampling from storage conditions, samples of all mixtures were analyzed. Increase in total impurities of abiraterone acetate was measured. The increase of impurities was calculated as a difference between the amount of total impurities of each sample before and after storage. The results are shown in Figures 6 and 7.

The results in Figures 6 and Figure 7 show that abiraterone acetate dissolved in majority of tested mixtures is prone to extensive degradation during storage under air. The stability of abiraterone acetate in all tested mixtures was significantly improved when stored under nitrogen. It can be concluded that the chemical instability of abiraterone acetate is due to oxidative instability since there is no instability in inert (nitrogen) atmosphere. Additionally an increased stability can be observed when antioxidant is used. The results show an excellent stabilization and prevention of the oxidation of abiraterone acetate in mixtures containing butylated hydroxytoluene.
Preparation of adsorbates

Example 17
1 g abiraterone acetate was dissolved in 50 ml dichloromethane. To the solution of abiraterone acetate 10 g Syloid AL 1 and 100 ml n-pentane was added and the suspension was mixed. The solvents were further removed under reduced pressure. Presence of amorphous abiraterone acetate in prepared adsorbate was confirmed by x-ray diffraction.

Stability evaluation of the adsorbates

Example 18
The dry sample of abiraterone acetate adsorbate from example 17 was put on stress stability conditions. The sample was stored at elevated temperature of 60°C under nitrogen, air and oxygen atmosphere for 7 days. After sampling from storage conditions, the sample was analyzed. As a reference product, the starting API was treated in the same manner as the adsorbate sample and analyzed. The increase in total impurities was measured. The increase of impurities was calculated as a difference between the amount of total impurities of each sample before and after storage. The results shown in Figure 8 show a significant increase in total impurities during storage of the adsorbate in the presence of oxygen - in comparison to starting API adsorbate is prone to oxidative degradation. Nevertheless, the storage of the adsorbate under nitrogen showed a stabilization effect on the chemical stability of abiraterone acetate, only a negligible increase of degradation products was observed, when the sample was stored under nitrogen.
The present invention also relates to the following items.

1. Process for the preparation of a pharmaceutical composition comprising abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof, in which pharmaceutical composition the abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof is stabilized against oxidative degradation, wherein said abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof is mixed with one or more excipients and processed to provide a pharmaceutical composition, and characterized in that means are employed which stabilize the abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof against oxidative degradation.

2. The process of item 1, characterized in that the pharmaceutical composition is a packaged pharmaceutical composition.

3. The process of item 1 or item 2, characterized in that the abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof is stabilized against oxidative degradation by the addition of at least one antioxidant.

4. The process of any of items 1-3, characterized in that the abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof is stabilized against oxidative degradation by means of pH adjustment.

5. The process of any of items 1-4, characterized in that the abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof is stabilized against oxidative degradation by means of an oxygen impermeable coating.

6. The process of any of items 1-5, characterized in that the abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof is stabilized against oxidative degradation by means of preparation under inert atmosphere.
7. The process of any of items 1-6, characterized in that the abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof is stabilized against oxidative degradation by means of special packaging and/or storage.

8. The process of item 7, characterized in that the abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof is stabilized against oxidative degradation by means of packaging with at least one oxygen scavenger/absorber.

9. The process of item 7, characterized in that the abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof is stabilized against oxidative degradation by means of packaging using oxygen barrier packaging material.

10. Pharmaceutical composition comprising abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof, characterized in that the abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof is stabilized against oxidative degradation.

11. The pharmaceutical composition of item 10, characterized in that the pharmaceutical composition is a packaged pharmaceutical composition.

12. The pharmaceutical composition of item 10 or item 11, characterized in that the abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof is stabilized against oxidative degradation by the addition of at least one antioxidant.

13. The pharmaceutical composition of item 12, characterized in that the antioxidant is selected from the group consisting of butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), ascorbyl palmitate (AP), propyl gallate, alpha tocopherol or any mixtures thereof.
14. The pharmaceutical composition of item 12 or item 13, characterized in that the antioxidant is present in an amount of 0.0001% to 5% by weight, based on the weight of the composition.

15. The pharmaceutical composition of any of items 10-14, characterized in that the abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof is stabilized against oxidative degradation by means of pH adjustment.

16. The pharmaceutical composition of item 15, characterized in that the pH is adjusted to be within a range of 1 to 9, preferably to be within a range of 1.5 to 8.5, more preferably to be within a range of 2 to 8, even more preferably to be about 3.

17. The pharmaceutical composition of any of items 10-16, characterized in that the abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof is stabilized against oxidative degradation by means of an oxygen impermeable coating.

18. The pharmaceutical composition of item 17, characterized in that the oxygen impermeable coating is selected from the group consisting of polyvinyl alcohol, and cellulose derivatives.

19. The pharmaceutical composition of any of items 10-18, characterized in that the abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof is stabilized against oxidative degradation by means of preparation under inert atmosphere.

20. The pharmaceutical composition of item 19, characterized in that the inert atmosphere comprises less than 5% oxygen, preferably less than 3% oxygen, more preferably less than 1% oxygen, even more preferably less than 0.5% oxygen, most preferably the inert atmosphere comprises less than 0.2% oxygen.
21. The pharmaceutical composition of item 19 or item 20, characterized in that the inert atmosphere is a nitrogen atmosphere, which contains at least 95% of nitrogen, preferably at least 98% of nitrogen, more preferably at least 99.5% of nitrogen.

22. The pharmaceutical composition of any of items 10-21, characterized in that the abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof is stabilized against oxidative degradation by means of special packaging and/or storage.

23. The pharmaceutical composition of item 22, wherein the special packaging and/or storage is achieved by packaging and/or storage under vacuum.

24. The pharmaceutical composition of item 23, characterized in that the special packaging and/or storage is selected from packaging and/or storage under inert atmosphere, packaging with at least one oxygen scavenger/absorber and oxygen barrier packaging.

25. The pharmaceutical composition of item 24, characterized in that the oxygen barrier packaging comprises glass or/and metal or/and packaging materials containing ethylene vinyl alcohol copolymers, polyvinylidene chloride copolymers, polyvinyl alcohol films or polyethylene terephthalate polyester.

26. The pharmaceutical composition of item 24, characterized in that it is packaged with at least one oxygen scavenger/absorber, wherein the oxygen absorption capacity of the at least one scavenger/absorber is more than 5 ml of oxygen per 1 g of scavenger/absorber, preferably more than 10 ml, preferably more than 30 ml, even more preferably the oxygen absorption capacity of the at least one oxygen scavenger/absorber is more than 50 ml of oxygen per 1 g of scavenger/absorber.

27. The pharmaceutical composition of any of the previous items, characterized in
that it is in the form of a solid dispersion, a nanosuspension, an adsorbate, a liquid lipidic formulation or a pharmaceutical preparation comprising or derived from a solid dispersion, a nanosuspension, an adsorbate, a liquid lipidic formulation.

28. The pharmaceutical composition of any of the previous items, characterized in that the abiraterone acetate is in the form of the free base or the mesylate salt.

29. The pharmaceutical composition of any of the previous items, characterized in that it further comprises one or more excipients selected from fillers, diluents, lubricants, binders, disintegrating agents, colorants, flavoring agents, sweeteners, glidants, preservatives, stabilizers, solubilizers, antioxidants and buffers.

30. The pharmaceutical composition of any of the previous items, characterized in that it said pharmaceutical composition is an oral dosage form, preferably selected from the group consisting, a tablet, a capsule, a sachet, a powder, a syrup or a liquid.

31. The pharmaceutical composition of any of the previous items for use in the treatment of cancer, preferably metastatic prostate cancer.
Claims

1. Process for the preparation of a pharmaceutical composition comprising abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof, in which pharmaceutical composition the abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof is stabilized against oxidative degradation, wherein said abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof is mixed with one or more excipients and processed to provide a pharmaceutical composition, and characterized in that means are employed which stabilize the abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof against oxidative degradation.

2. The process of claim 1, characterized in that the pharmaceutical composition is a packaged pharmaceutical composition.

3. The process of claim 1 or claim 2, characterized in that the abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof is stabilized against oxidative degradation by the addition of at least one antioxidant.

4. The process of any of claims 1-3, characterized in that the abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof is stabilized against oxidative degradation by means of special packaging and/or storage.

5. The process of claim 4, characterized in that the abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof is stabilized against oxidative degradation by means of packaging using oxygen barrier packaging material.

6. Pharmaceutical composition comprising abiraterone acetate or a
pharmaceutically acceptable salt, hydrate or solvate thereof, characterized in that the abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof is stabilized against oxidative degradation.

7. The pharmaceutical composition of claim 6, characterized in that the pharmaceutical composition is a packaged pharmaceutical composition.

8. The pharmaceutical composition of claim 6 or claim 7, characterized in that the abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof is stabilized against oxidative degradation by the addition of at least one antioxidant.

9. The pharmaceutical composition of claim 8, characterized in that the antioxidant is selected from the group consisting of butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), ascorbyl palmitate (AP), propyl gallate, alpha tocopherol or any mixtures thereof.

10. The pharmaceutical composition of claim 8 or claim 9, characterized in that the antioxidant is present in an amount of 0.0001% to 5% by weight, based on the weight of the composition.

11. The pharmaceutical composition of any of claims 6-10, characterized in that the abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof is stabilized against oxidative degradation by means of preparation under inert atmosphere.

12. The pharmaceutical composition of claim 11, characterized in that the inert atmosphere comprises less than 5% oxygen, preferably less than 3% oxygen, more preferably less than 1% oxygen, even more preferably less than 0.5% oxygen, most preferably the inert atmosphere comprises less than 0.2% oxygen.

13. The pharmaceutical composition of any of claims 6-12, characterized in that
the abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof is stabilized against oxidative degradation by means of special packaging and/or storage.

14. The pharmaceutical composition of claim 13, characterized in that the special packaging and/or storage is selected from packaging and/or storage under inert atmosphere, packaging with at least one oxygen scavenger/absorber and oxygen barrier packaging.

15. The pharmaceutical composition of claim 14, characterized in that it is packaged with at least one oxygen scavenger/absorber, wherein the oxygen absorption capacity of the at least one scavenger/absorber is more than 5 ml of oxygen per 1 g of scavenger/absorber, preferably more than 10 ml, preferably more than 30 ml, even more preferably the oxygen absorption capacity of the at least one oxygen scavenger/absorber is more than 50 ml of oxygen per 1 g of scavenger/absorber.
Figure 1: Chromatograms of Zytiga® samples stored at 60°C after 7 days under different atmosphere conditions. Sensitivity of Zytiga® tablets to oxygen is observed. No increase of hydrolytic degradation product is detected (free abiraterone impurity is eluted at Rt-2.347).
Figure 2: Stability trend for total impurities in Zytiga® tablets at accelerated stability condition
<table>
<thead>
<tr>
<th>Sample Description</th>
<th>Total Impurities (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zytiga®</td>
<td>0.9</td>
</tr>
<tr>
<td>101X1 dispersion</td>
<td>15.4</td>
</tr>
<tr>
<td>101X2 dispersion</td>
<td>9.6</td>
</tr>
<tr>
<td>101X3 dispersion</td>
<td>17.8</td>
</tr>
<tr>
<td>102X1 dispersion (BHT)</td>
<td>0.3</td>
</tr>
<tr>
<td>103X1 tablet (BHT)</td>
<td>0.3</td>
</tr>
<tr>
<td>102X2 dispersion (BHT)</td>
<td>0.0</td>
</tr>
<tr>
<td>103X3 tablet (BHT)</td>
<td>0.1</td>
</tr>
<tr>
<td>102X3 dispersion (BHT)</td>
<td>0.1</td>
</tr>
<tr>
<td>103X3 tablet (BHT)</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Figure 3: Increase in total impurities of abiraterone acetate in samples of solid dispersions, tablets prepared from solid dispersions, the reference product Zytiga® and the starting API after storage at 60°C for 7 days under air, nitrogen and oxygen atmosphere.
<table>
<thead>
<tr>
<th></th>
<th>% Increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zytiga®</td>
<td>0.2</td>
</tr>
<tr>
<td>starting API</td>
<td>0.0</td>
</tr>
<tr>
<td>101X1 dispersion</td>
<td>9.1</td>
</tr>
<tr>
<td>101X2 dispersion</td>
<td>5.8</td>
</tr>
<tr>
<td>101X3 dispersion</td>
<td>3.2</td>
</tr>
<tr>
<td>102X1 dispersion (BHT)</td>
<td>0.2</td>
</tr>
<tr>
<td>103X1 tablet (BHT)</td>
<td>0.2</td>
</tr>
<tr>
<td>102X2 dispersion (BHT)</td>
<td>0.0</td>
</tr>
<tr>
<td>103X3 tablet (BHT)</td>
<td>0.0</td>
</tr>
<tr>
<td>102X3 dispersion (BHT)</td>
<td>0.0</td>
</tr>
<tr>
<td>103X3 tablet (BHT)</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Figure 4: Increase in total impurities of abiraterone acetate in samples of solid dispersions, tablets prepared from solid dispersions, the reference product Zytiga® and the starting API after storage at 40°C for 1 month under air.
Figure 5: Increase in total impurities of abiraterone acetate in samples of nanosuspensions, tablets prepared from nanosuspensions, the reference product Zytiga® and the starting API after storage at 60°C for 1 month under air.
Figure 6: Increase in total impurities of abiraterone acetate after storage at 60°C for 7 days under air and nitrogen in mixtures with abiraterone acetate (with and without butylated hydroxytoluene (BHT)).
Figure 7: Increase in total impurities of abiraterone acetate after storage at 40°C for 1 month under air and nitrogen in mixtures with abiraterone acetate (with and without butylated hydroxytoluene (BHT)).
Figure 8: Increase in total impurities in abiraterone acetate adsorbate and starting active pharmaceutical ingredient (API) after storage at 60°C for 7 days under oxygen, air and nitrogen.
INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2013/064622

A. CLASSIFICATION OF SUBJECT MATTER

A61K47/10

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

B. FIELDS SEARCHED

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

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

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

EPO-Internal, BIOSIS, EMBASE, WPI Data

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>
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* Special categories of cited documents :
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<td></td>
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<td>US 5618807 A</td>
<td>08-04-1997</td>
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