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Nanosuspension of abiraterone acetate

Description

The present invention relates to a nanosuspension of abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof and a method of preparing the same. It further relates to a pharmaceutical composition comprising a nanosuspension of abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof, and a method of preparing the same.

Abiraterone is a selective inhibitor of 17 a-hydroxylase/C1 7,20 lyase (CYP1 7A1), an enzyme which is known to be essential for the biosynthesis of androgens and oestrogens. CYP1 7 is expressed in testicular, adrenal, and prostatic tumor tissues. Said enzyme complex catalyzes the conversion of pregnenolone and progesterone to their 17-a-hydroxy derivatives by its 17 a-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 CYP1 7 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 17-(pyridin-3-yl)androsta-5,1 6-dien-33-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 of abiraterone acetate](image)

Abiraterone acetate is a white to off-white, non-hygroscopic, crystalline powder. Its molecular formula is C26H33NO2 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.

Pharmaceutically active salts are known in the art from WO 2006/021777 and WO 09/0091132.

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 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. 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. 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 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 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 therapeutic effect.

Accordingly, it would be desirable to improve the bioavailability of abiraterone acetate and to reduce the administered daily dose of abiraterone acetate.

Additionally, abiraterone acetate is known to exhibit a very strong food effect, when administered orally (Zytiga® prescribing information). In particular, administration with food increases absorption of the drug and thus potentially results in increased and highly variable exposures. In particular, the drug uptake may vary up to 5- to 10-fold between fasted and fed state, depending on the fat content of the meal. To control the drug uptake, abiraterone acetate is labeled to be taken fasting, i.e. patients must take abiraterone acetate on empty stomach only. No food should have been consumed for 2 h prior to dosing and for 1 h afterwards.

There is therefore a need to reduce the food effect of abiraterone acetate.

Accordingly, it is one object of the present invention to improve the solubility and dissolution rate of abiraterone acetate. It is another object of the invention, to provide a formulation with improved bioavailability of abiraterone acetate. It is a further object of the invention to reduce the necessary daily dose of abiraterone acetate. It is an additional object of the invention to reduce the food effect of abiraterone acetate.

Nanocrystallization techniques have been used previously to increase the dissolution rate and thus the bioavailability of poorly soluble drugs. For example, nanocrystallization has been used for the drugs sirolimus, aprepitant, fenofibrate, megestrol acetate and paliperidone acetate (Peltonen and Hirvonen, J. Pharm.
Pharmacol. 2010 Nov;62(11):1569-79. In order to obtain a nanosuspension in most cases a media milling technique has been applied but also a high-pressure homogenization technique has been proven useful. As a further technique for the production of nanocrystals precipitation has been suggested.

However, in initial attempts aimed at the preparation of nanosuspensions of abiraterone acetate it was found, that the abiraterone acetate particles after nanomilling have a strong tendency to aggregate and flocculate. Aggregation and flocculation are adversely affecting the physical stability of the nanosuspension or any product derived thereof. Thus, it became clear during initial experiments that it would not be trivial to obtain a nanosuspension of abiraterone acetate.

Additionally it was found that abiraterone acetate may degrade to abiraterone during preparation of the nanosuspension due to ester hydrolysis. Degradation of abiraterone acetate is adversely affecting the chemical stability of the nanosuspension or any product derived thereof.

Surprisingly, it was found, that the degradation of abiraterone acetate and the aggregation of the particles could be significantly reduced or even inhibited by the use of a stabilizing agent during the nanomilling process. Such stabilizers are described in more detail hereinafter.

Additionally, it was found that, e.g., the type and amount of stabilizing agent has a pronounced effect on the physical and chemical stability and in vivo behavior (which is related to changes in Cmax, tmax, AUC) of the nanosuspension or a pharmaceutical composition comprising the nanosuspension or a concentrated nanosuspension derived thereof or the solid components thereof.

Therefore, the present invention provides a nanosuspension comprising particles of abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof having a mean particle size d(0.5) of less than 1000 nm.

It was found that the nanosuspension of the present invention results in an increased solubility and dissolution rate of abiraterone acetate compared to conventional
compositions or micronized compositions. Further the nanosuspension also advantageously exhibits a reduced food effect.

In particular, the increased solubility and dissolution rate of abiraterone acetate result in an increased bioavailability and improved pharmacokinetic profile of the drug. This results in a reduction of the required daily dose of abiraterone acetate. In particular, a reduction of about 10 wt%, preferably about 20 wt%, about 25 wt%, about 30 wt%, about 35 wt% and more preferably of up to 40 wt% of the required daily dose of abiraterone acetate can be achieved by the nanosuspension of the invention.

Apart from improving bioavailability, nanoparticulate compositions of abiraterone acetate exhibit a reduced fed/fasted state variability and consequently a reduced food effect. Therefore, it is not necessary to take abiraterone acetate in the form of the inventive nanosuspension or a pharmaceutical composition comprising the inventive nanosuspension or a concentrated nanosuspension derived thereof or the solid components thereof on empty stomach only. The inventive nanosuspension comprising abiraterone acetate or a pharmaceutical composition comprising the inventive nanosuspension can thus be taken without having regard to the subject's eating regimen.

Benefits of a dosage form which substantially eliminates the effect of food include an increase in subject convenience, thereby increasing subject compliance, as the subject does not need to ensure that they are taking a dose either with or without food. This is significant, as with poor subject compliance an increase in the medical condition for which the drug is being prescribed may be observed.

According to the present invention it was surprisingly found that the inventive nanosuspension comprising particles of abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof having a d(0.5) of less than 1000 nm not only provides for an increased dissolution rate and bioavailability of the poorly soluble drug abiraterone acetate but also results in a decreased food effect and an increased stability of the drug.
It has been found that the drug abiraterone acetate per se and in the form of the commercially available product Zytiga® is prone to oxidation degradation and further ester hydrolysis occurs at basic and extremely acidic pH.

However, according to the present invention ester hydrolysis is significantly reduced or is substantially not observed in the inventive nanosuspension and during the inventive process for preparation of the inventive nanosuspension compared to abiraterone acetate per se and in the form of the commercially available product Zytiga®.

In a first aspect, the present invention is therefore directed to a nanosuspension comprising abiraterone, abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof.

As used herein, the term "nanosuspension" can be defined as a colloidal dispersion of nano-sized drug particles.

The terms "nanoparticles", "nanoparticulate" or "nano-sized particles", which are used interchangeably herein, refer to a plurality of particles possessing a d(0.5) of less than 1000 nm.

The nanosuspension of the present invention comprises particles of abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof having a d(0.5) of less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 150 nm.

Preferably the nanosuspension of the present invention comprises particles of abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof having a d(0.5) of from 50 nm to 1000 nm, from 50 nm to 900 nm, from 50 nm to 800 nm, from 50 nm to 700 nm, from 50 nm to 600 nm, from 50 nm to 500 nm, from 50 nm to 400 nm, from 50 nm to 300 nm, from 50 nm to 250 nm, from 50 nm to 200 nm or from 50 nm to 150 nm. Also preferably, the nanosuspension of the present
invention comprises particles of abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof having a d(0.5) of from 100 nm to 1000 nm, from 100 nm to 900 nm, from 100 nm to 800 nm, from 100 nm to 700 nm, from 100 nm to 600 nm, from 100 nm to 500 nm, from 100 nm to 400 nm, from 100 nm to 300 nm or from 100 nm to 200 nm.

In a preferred embodiment the nanosuspension of the present invention comprises particles of abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof having a particle size d(0.9) of less than about 5000 nm, less than about 2500 nm, less than about 1500 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm. Preferably the nanosuspension of the present invention comprises particles of abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof having a particle size d(0.9) of from 100 nm to 5000 nm, from 100 nm to 2500 nm, from 100 nm to 1500 nm, from 100 nm to 1000 nm, from 200 nm to 1000 nm, from 200 nm to 800 nm, from 300 nm to 800 nm, from 400 nm to 800 nm, from 500 nm to 800 nm, from 500 nm to 750 nm or from 550 nm to 750 nm.

According to the invention a particle size d(0.5) of less than 500 nm is preferred, more preferably the particle size d(0.5) is less than 400 nm, even more preferably less than 300 nm.

According to the invention a particle size d(0.5) of more than 50 nm is preferred, more preferably the particle size d(0.5) is more than 80 nm, even more preferably more than 100 nm.

According to the invention a particle size d(0.9) of less than 5000 nm is preferred, more preferably the particle size d(0.9) is less than 1000 nm, even more preferably less than 800 nm.

According to the invention a particle size d(0.9) of more than 100 nm is preferred, more preferably the particle size d(0.9) is more than 300 nm, even more preferably more than 500 nm.
The terms "particle size" or "size", as used herein, refer to the volume average particle diameter as measured by laser diffraction method (e.g. Malvern Mastersizer). Further, the values given for the particle size refer to all particles of abiraterone or abiraterone acetate and pharmaceutically acceptable salts, hydrates or solvates thereof which are present in the nanosuspension. The particle size can be measured by a laser diffraction method, microscopy, photon correlation spectroscopy or other appropriate methods known in the art. The particle size is preferably measured using a laser diffraction method.

As used herein, the term "d(0.9)" means that at least 90% of the particles based on volume have a particle size equivalent to or below the indicated value.

As used herein, the term "d(0.5)" refers to the mean particle size, i.e. at least 50% of the particles based on volume have a particle size equivalent to or below the indicated value.

As used herein, the term "d(0.1)" means that at least 10% of the particles based on volume have a particle size equivalent to or below the indicated value.

According to the invention it is preferred that the span, i.e. the width of the particle size distribution, is narrow.

The term "particle-size distribution" (PSD), as used herein, refers to the relative amounts of particles present, sorted according to size.

As used throughout the present disclosure, "span" refers to the width of the particle size distribution based on the d(0.1), d(0.5) and d(0.9). The span is calculated by dividing the difference between d(0.9) and d(0.1) by d(0.5).

In one embodiment, the nanoparticles of abiraterone acetate are being obtained in a consistent and narrow particle size range, i.e. the nanoparticles of abiraterone acetate obtained according to the invention exhibit a narrow span. In particular, a
narrow span results in a better reproducibility of results from batch to batch. In addition, less crystal growth is observed if the span is narrow.

According to the invention the span is from 30 to 0.01, preferably from 15 to 0.01, more preferably from 10 to 0.01, even more preferably from 5 to 0.01, most preferably from 2 to 0.01.

In one embodiment of the invention the nanosuspension comprises abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof, in the form of particles having a particle size in a range of less than 5000 to 10 nm, less than 2500 to 20 nm, less than 1500 to 30 nm, less than 1000 to 40 nm, less than 800 to 40 nm, less than 500 to 50 nm, wherein the upper range is defined by d(0.9) and the lower range by d(0.1).

In another embodiment of the invention the nanosuspension comprises abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof, in the form of particles having a particle size in a range of less than 1000 to 10 nm, less than 900 to 10 nm, less than 800 to 10 nm, less than 700 to 10 nm, less than 600 to 10 nm, less than 500 to 10 nm, wherein the upper range is defined by d(0.9) and the lower range by d(0.1).

In one embodiment, the nanoparticles are in the form of crystalline drug particles.

According to the invention abiraterone or 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, isobutyrate, caproate, 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, phenylbutyrate, 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 or 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 salt). More preferably, abiraterone acetate is in the form of the free base, in particular the crystalline free base.

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.

In one embodiment the present invention relates to a stable nanosuspension comprising abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof.

As used herein with reference to stable abiraterone acetate particles, stable abiraterone acetate nanosuspensions or stable nanoparticulate abiraterone acetate, "stable" means that the particles do not appreciably flocculate or agglomerate due to interparticle attractive forces or otherwise increase in particle size during and after preparation of the nanosuspension.

"Stable" connotes, but is not limited to one or more of the following parameters: (1) the particles do not appreciably flocculate or agglomerate due to interparticle attractive forces or otherwise significantly, i.e. ± 10% increase in particle size over one week at room conditions; (2) the physical structure of the abiraterone acetate particles is not altered over time, such as by conversion from an amorphous phase to a crystalline phase; (3) the abiraterone acetate particles are chemically stable, which means that no more than 5% of total impurities including the metabolite abiraterone can be detected by HPLC.

In a further embodiment of the invention the nanosuspension comprises at least one stabilizing agent, also termed stabilizer. A stabilizer is an additive which renders a nanosuspension of abiraterone acetate stable during and/or after preparation of the
nanosuspension and thus preferably prevents aggregation and/or flocculation during and/or after nanomilling.

Preferably, the stabilizing agent is a surface modifying agent or/and a buffer, more preferably the stabilizing agent is a surface modifying agent.

In one embodiment the stabilizing agent is a surface modifying agent, also termed "surface modifier". The surface modifying agent, without wishing to be bound to any theory, interacts with the surface of the abiraterone acetate nanoparticles in such a way so as to prevent agglomeration and/or flocculation. The term surface modifying agent includes for example various polymers, low molecular weight oligomers, natural products and surfactants. Thus, examples of stabilizing agents which may be employed include: polyoxyethylene sorbitan fatty acid esters, e.g. Tweens and Spans; polyoxyethylene stearates; polyoxyethylene alkyl esters; polyethylene glycols; castor oil derivatives (e.g. Cremophor EL®, Cremophor RH40®, Cremophor RH60®); block polymers and block copolymers such as poloxamers, e.g Lutrol F68, and poloxamines; lecithins of various origin (e.g. egg-lecithin or soya-lecithin), chemically-modified lecithins (e.g. hydrated lecithin), as well as phospholipids and sphingolipids, sterols (e.g. cholesterol derivatives, as well as stigmasterin), esters and ethers of sugars or sugar alcohols with fatty acids or fatty alcohols (e.g. saccharose monostearate); ethoxylated mono- and diglycerides, ethoxylated lipids and lipoids, dicetyl phosphate, phosphatidyl glycerine, sodium cholate, sodium glycolcholate, sodium taurocholate; sodium citrate; cellulose ethers and cellulose esters (e.g. methylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, sodium carboxymethylcellulose), polyvinyl derivatives such as polyvinyl alcohol, polyvinyl pyrrolidone, polyvinyl acetate, alginites, polyacrylates (e.g. carbopol), xanthanes; pectins, gelatin, casein, gum acacia, cholesterol, tragacanth, stearic acid, calcium stearate, glyceryl monostearate, dioctyl sodium sulfo succinate (sodium docusate); sodium dodecyl sulphate, benzalkonium chloride, alkyl aryl polyether sulfonate, polyethylene glycols. The term surface modifying agent also includes certain inorganic excipients, for example colloidal silicon dioxide, magnesium aluminium silicate; and phosphates.
Most of these compounds are described in detail as excipients in the Handbook of Pharmaceutical Excipients, published jointly by the American Pharmaceutical Association and The Pharmaceutical Society of Great Britain, the Pharmaceutical Press, 1986, the disclosure of which is hereby incorporated by reference in its entirety. The surface modifiers are commercially available or/and can be prepared by techniques known in the art.

In a preferred embodiment of the invention the surface modifying agent is a cellulose derivative selected from the group consisting of hydroxypropyl methylcellulose (HPMC), methylcellulose, hydroxypropylcellulose (HPC), hydroxyethylcellulose, sodium carboxymethylcellulose. HPMC is particularly preferred as the surface modifying agent and/or emulsifier. It has been found that HPMC conveys particularly advantageous properties to an inventive nanosuspension comprising HPMC (see examples).

The term "cellulose derivative" as used herein in particular refers to those compounds listed in the "Fiedler Encyclopedia of Excipients for Pharmaceuticals, Cosmetics and Related Areas" and described therein as cellulose derivatives, in particular to a cellulose derivative selected from hydroxypropyl methylcellulose (HPMC), methylcellulose, hydroxypropylcellulose (HPC), hydroxyethylcellulose and sodium carboxymethylcellulose.

In another preferred embodiment of the invention the surface modifying agent is a surfactant. The surfactant can be an nonionic surfactant or an ionic surfactant, and in particular the surfactant is selected from the group consisting of polyoxyethylene products of hydrogenated vegetable oils, polyoxyethylated castor oils or polyethoxylated hydrogenated castor oil, polyoxyethylene-sorbitan-fatty acid esters, polyoxyethylene castor oil derivatives, sorbitan esters, sucrose esters, polyoxamers, poloxamers, polyglycolyzed glycerides (as caprylocapryl macrogol glyceride (Labrasol), linoleaoyl macrogol glycerides (Labrafil), polyglyceryl oleate (Plurol)), gelucires, sodium dodecyl sulfate (SDS), sodium cholate, sodium glycolcholate, sodium taurocholate, saccharose monostearate, lecithin, dioctyl sodium sulfosuccinate or a combination thereof.
In still another preferred embodiment of the invention the surface modifying agent is a polymer selected from the group consisting of polyvinyl alcohol, polyvinyl pyrrolidone, polyvinyl acetate, alginates, polyacrylates and pectins.

The following Table 1 summarizes particularly preferred stabilizers used for the nanosuspensions of the invention.

Table 1

<table>
<thead>
<tr>
<th>Chemical name</th>
<th>Common name</th>
<th>Trade name</th>
<th>Structural Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cellulose hydroxypropyl methyl ether</td>
<td>hydroxypropyl methylcellulose (HPMC)</td>
<td>Pharmacoat</td>
<td><img src="image" alt="Structural formula for HPMC" /></td>
</tr>
<tr>
<td>Polyoxylene 20 sorbitan monooleate</td>
<td>Polysorbate 80</td>
<td>Tween 80</td>
<td><img src="image" alt="Structural formula for Polysorbate" /></td>
</tr>
<tr>
<td>α-Hydro-ω-hydroxy(poly(oxyethylene) poly(oxypropylene) block copolymer</td>
<td>Poloxamer 188</td>
<td>Lutrol F68</td>
<td><img src="image" alt="Structural formula for Poloxamer" /></td>
</tr>
<tr>
<td>Sulfuric acid monododecyl ester sodium salt</td>
<td>sodium dodecyl sulfate (SDS)</td>
<td>Texapon</td>
<td><img src="image" alt="Structural formula for SDS" /></td>
</tr>
<tr>
<td>Cremophor EL is made by reacting castor oil with ethylene oxide in a molar ratio of 1:35.</td>
<td>Cremophor EL</td>
<td></td>
<td><img src="image" alt="Structural formula for Cremophor EL" /></td>
</tr>
</tbody>
</table>

According to the present invention it has surprisingly been found that when a cellulose derivative, in particular HPMC, is used as the stabilizing agent a considerable reduction of the formation of impurities during milling is achieved.
compared to other stabilizing agents tested such as polysorbate 80, poloxamer 188, SDS and cremophor EL. In particular, substantially no degradation of abiraterone acetate to abiraterone has been observed after milling in the presence of HPMC.

Most surprisingly, in the inventive nanosuspension comprising a cellulose derivative, in particular HPMC, as the stabilizing agent substantially no abiraterone degradation product and a reduced amount of total impurities is observed even compared to the commercially available Zytiga® tablets which were assessed for impurities as reference materials. In the case of Zytiga® tablets a low amount of abiraterone degradation product and of total impurities was detected while in the case of the starting API only a certain amount of total impurities but no abiraterone degradation product was observed.

It has further been found that the use of a cellulose derivative, in particular HPMC, as the stabilizing agent results in superior stability of the inventive nanosuspension upon storage. In particular, no significant increase of degradation products has been observed during storage.

The inventive nanosuspension comprising a cellulose derivative, in particular HPMC, as the stabilizing agent exhibits a storage stability comparable to or even better than the commercially available Zytiga® tablets which were assessed for impurities as reference materials. Importantly, when a cellulose derivative, in particular HPMC, is used as the stabilizing agent substantially no oxidation degradation is observed in the presence of air, while oxidation degradation is frequently observed with other stabilizing agents and even for the commercially available Zytiga® tablets.

Additionally or alternatively, the stabilizing agent may be a buffer. The buffer serves to modify or buffer the pH to maintain optimal conditions for the preparation of the inventive nanosuspension.

In one embodiment of the invention, the stabilizing agent is a buffer providing a pH in the range of 1 to 9, preferably providing a pH of 1.5 to 8.5, more preferably providing a pH of 2 to 8, even more preferably providing a pH of about 3.
Suitable pH modifying agents or buffers include an inorganic acid such as hydrochloric acid, sulfuric acid and phosphoric acid; an inorganic base such as sodium hydroxide, potassium hydroxide and calcium hydroxide; an organic acid such as citric acid, acetic acid, tartaric acid, succinic acid, boric acid, edetic acid, gluuronic acid, glutaric acid, malic acid, formic acid, gluconic acid, ascorbic acid and fatty acids; or/and an organic base such as ethanolamine and triethanolamine; or a mixture thereof, all of which may be used either with or without a corresponding counterion, i.e. salt of inorganic acid, salt of organic acid, salt of inorganic base or salt of organic base.

According to the present invention it has surprisingly been found that adjustment of the pH exerts a stabilizing effect, with or without using a further stabilizing agent.

Thus, in another embodiment the invention relates to a nanosuspension, wherein the pH of the nanosuspension 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.

In particular, when the pH is adjusted within a range of 1 to 9, preferably 1.5 to 8.5, more preferably within a range of 2 to 8, even more preferably to about 3, in certain cases a considerable reduction of the formation of impurities during milling can be achieved compared to the addition of a stabilizing agent alone.

Thus, in one embodiment, the invention relates to a nanosuspension as described hereinabove, wherein the nanosuspension has a pH in the range of 1 to 9, preferably a pH of 1.5 to 8.5, more preferably a pH of 2 to 8, even more preferably a pH of about 3.

Similar observations were made with respect to storage stability. Adjustment of the pH within a range of 1 to 9, preferably 1.5 to 8.5, more preferably within a range of 2 to 8, even more preferably to about 3, and optionally further using a stabilizing agent can result in an improved storage stability compared to use of a further stabilizing agent alone.
Thus, in a preferred embodiment of the invention, the nanosuspension comprises as a stabilizing agent a surface modifying agent and/or a buffer. For example, the nanosuspension comprises as a stabilizing agent a surface modifying agent or/and the pH of the nanosuspension is adjusted within a range of 1 to 9, preferably 1.5 to 8.5, more preferably within a range of 2 to 8, even more preferably to about 3.

In a preferred embodiment, the buffer serves to adjust the pH within a range of 1 to 9, preferably 1.5 to 8.5, more preferably within a range of 2 to 8, even more preferably to about 3 and the surface modifying agent which is optionally present is a cellulose derivative, in particular HPMC. However, if the pH of the nanosuspension is adjusted as outlined above, any stabilizing agent can be used in order to obtain the reduction of impurities and improved storage stability described hereinabove.

The concentration of the at least one stabilizing agent, when the stabilizing agent is a surface modifier and/or emulsifier, either in the coarse suspension or the nanosuspension may be in the range of about 0 to 20% (based on the weight of the final suspension).

As used herein, the term "coarse suspension" relates to the suspension which is used for nanomilling as described herein below.

The relative amount of stabilizing agent can vary widely and the optimal amount of the stabilizing agent can depend, for example, upon the particular stabilizing agent selected, the critical micelle concentration of the stabilizing agent, molecular mass of the stabilizing agent, etc. The weight ratio of abiraterone acetate to stabilizing agent in the inventive nanosuspension ranges from 20:1 to 1:20, preferably from 10:1 to 1:10.

In another embodiment of the invention, the nanosuspension comprises a liquid agent. A preferred liquid agent for the preparation of the nanosuspension of the present invention is water.

In another embodiment the liquid agent comprises water, in particular the liquid agent comprises at least 80 wt% water, based on the total weight of liquid agent, preferably
at least 90 wt%, more preferably at least 95 wt%, most preferably at least 99 wt% water, based on the total weight of liquid agent.

However, the invention can be practiced with other liquid agents in which abiraterone acetate is poorly soluble and dispersible, e.g. in which 0.1 mg/mL or less abiraterone acetate is soluble, including, for example, a liquid agent selected from the group consisting of an aqueous solution, an acid, a base, a polyethylene glycol, glycerol, propylene glycol and mixtures thereof. Determination of suitable liquid agents in which abiraterone acetate is poorly soluble and dispersible is well within the skill of the art.

Suitable aqueous solutions include without limitation buffers such as McIlvaine's buffer, citrate-HCl buffer pH 2, citrate-NaOH buffer pH 5, phosphate buffer pH 7, borate-KCl-NaOH buffer pH 9 or phosphate-NaOH buffer pH 12. Examples of suitable acids are without limitation 0.1 N HCl and 0.01 N HCl. An example of a suitable base is without limitation 0.1 N NaOH.

In one embodiment of the invention the liquid agent is a buffer.

The pH of the liquid agent or/and of the nanosuspension can be adjusted by techniques known to the skilled person, if required.

In a further aspect the present invention relates to a nanosuspension comprising:

- 0.1 -60 wt%, preferably 5-15 wt% of particles of abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof having a d(0.5) of less than 1000 nm, preferably less than 500 nm, more preferably less than 400 nm, most preferably less than 300 nm;
- 30-99 wt%, preferably 70-90 wt% of a liquid agent, preferably selected from the group consisting of water, an aqueous solution, an acid, a base, a polyethylene glycol, glycerol, propylene glycol and combinations thereof; and
- 0.1 -60 wt%, preferably 5-15 wt% of at least one stabilizing agent, preferably selected from a surface modifying agent and a buffer.
In said nanosuspension, it is preferred that the particles of abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof have a \(d(0.9)\) of less than 5000 nm, preferably less than 1000 nm, more preferably less than 500 nm, most preferably less than 400 nm.

It is further preferred that the nanosuspension has a pH in the range of 1 to 9, preferably a pH of 1.5 to 8.5, more preferably a pH of 2 to 8, even more preferably a pH of about 3.

In a further aspect the present invention relates to a process for preparing a nanosuspension comprising particles of abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof having a \(d(0.5)\) of less than 1000 nm, preferably a \(d(0.9)\) of less than 5000 nm, more preferably a \(d(0.9)\) of less than 1000 nm.

In the first step of the inventive process abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof is suspended in a liquid agent, resulting in a coarse suspension. The liquid agent is preferably selected from the group consisting of water, an aqueous solution, an acid, a base, a polyethylene glycol, glycerol, propylene glycol and combinations thereof. Said liquid agent optionally contains a stabilizing agent and/or an emulsifier.

For the preparation of the nanosuspension it is preferred that the abiraterone acetate starting material is utilized in the form of coarse particles, preferably having a particle size in a range of 300 to 10 \(\mu\)m. If necessary, the particle size of abiraterone acetate may be reduced to this level by conventional means, known to the skilled person, e.g. dry powder milling or jet milling. The coarse particles of abiraterone acetate are preferably suspended in a liquid agent comprising a solvent in which the drug substance is essentially insoluble. In the case of abiraterone acetate the liquid agent preferably comprises an aqueous solution and most preferably consists essentially of water. The concentration of abiraterone acetate in the said suspension of coarse particles may be in the range 0.1 to 60% by weight, preferably 5 to 15% by weight, based on the weight of the suspension of coarse particles.
To the coarse suspension obtained in the first step, milling balls are added to obtain a slurry for nanomilling, and the suspension is then subjected to nanomilling, e.g. a wet milling process under conditions sufficient to provide a nanosuspension with a mean particle size $d(0.5)$ of less than 1000 nm, preferably a $d(0.9)$ of less than 5000 nm, more preferably a $d(0.9)$ of less than 1000 nm. Preferably the wet milling process is wet ball milling.

A wet ball milling process commonly used in the art typically uses a media mill such as a Dyno® Mill (Glen Mills Inc., Clifton, NJ) that circulates the suspension through a chamber containing beads made from extremely hard, durable and essentially inert materials (e.g., zirconium). The high-energy movement and collisions of milling media with suspended pharmaceutically active ingredient lead to significant reductions in particle size of the pharmaceutically active ingredient.

According to the invention the following process was used for nanomilling. In a glass beaker a stabilizing agent, e.g. hydroxypropyl methylcellulose, was mixed with a liquid agent, e.g. demineralized water, to prepare a clear, slightly viscous solution. Abiraterone or abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof was suspended in the prepared stabilizing agent-liquid agent-solution, the suspension was transferred to a milling jar containing zirconium balls and milled in a planetary ball mill. The resulting suspension was separated from the milling balls, e.g. with a 0.4 mm sieve. Optionally, the balls were further washed with liquid agent, e.g. demineralized water, which was added to the milled suspension.

The above described beads used for wet ball milling are also referred to as "milling balls", "milling pearls" or "milling beads" herein.

Thus, in one embodiment the present invention relates to a process for preparing a nanosuspension comprising particles of abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof having a mean particle size $d(0.5)$ of less than 1000 nm, preferably a $d(0.9)$ of less than 5000 nm, more preferably a $d(0.9)$ of less than 1000 nm, the process comprising the following steps:

(a) preparing a suspension of abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof in a liquid agent, preferably selected from
the group consisting of water, an aqueous solution, an acid, a base, a polyethylene glycol, glycerol, propylene glycol and combinations thereof;
(b) adding milling balls to the suspension of step (a) in order to obtain a slurry for nanomilling, and
(c) nanomilling the slurry to provide a nanosuspension with a mean particle size d(0.5) of less than 1000 nm, preferably a d(0.9) of less than 5000 nm, more preferably a d(0.9) of less than 1000 nm.

In one embodiment the suspension of step (a) further comprises a stabilizing agent and/or an emulsifier.

In another embodiment the process for preparing a nanosuspension further comprises the following step after steps (a) - (c):
(d) separating the resulting nanosuspension from the milling balls.

In a further embodiment the process for preparing a nanosuspension further comprises the following step after step (d):
(e) washing the milling balls with a liquid agent selected from the group consisting of water, an aqueous solution, an acid, a base, a polyethylene glycol, glycerol, propylene glycol and combinations thereof, separating the liquid agent from the milling balls and adding the separated liquid agent to the milled nanosuspension obtained in step (d).

In one embodiment a solution of a liquid agent and a stabilizing agent is prepared prior to step (a).

In the inventive process for preparing a nanosuspension an amount of 0.1-60 wt%, preferably 5-15 wt% of abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof is used, based on the weight of the slurry used for nanomilling in step (c).

In the inventive process for preparing a nanosuspension an amount of 5-90 wt%, preferably 50-90 wt%, more preferably 70-90 wt% of milling balls is used, based on
the weight of the slurry used for nanomilling in step (c), with a diameter of the milling balls in the range of 0.1 - 5 mm, preferably 0.1 - 3 mm, more preferably 0.1 - 1 mm.

According to the invention, the amount of milling balls in the slurry is in particular important in case a planetary ball mill is used for nanomilling. However, for certain types of mills such as the above-described Dyno® Mill, the amount of milling balls is not critical, since the suspension is circulated through the balls.

The nanomilling of step (c) used in the inventive process for preparing a nanosuspension is carried out under conditions sufficient to provide a nanosuspension with a mean particle size d(0.5) of less than 1000 nm, preferably a d(0.9) of less than 5000 nm, more preferably a d(0.9) of less than 1000 nm. Suitable conditions are, for example, a milling speed of 300-600 rpm, preferably 500 rpm, for a milling time of 2-5 h, preferably 3-4 h, at room temperature in a planetary ball mill. However, the exact conditions depend on the type of equipment used and can be determined by a person skilled in the art by routine experimentation.

In one embodiment of the invention the pH of the suspension of step (a) is adjusted to 1 to 9, preferably 1.5 to 8.5, more preferably 2 to 8, even more preferably to 3.

In the inventive process for preparing a nanosuspension a stabilizing agent may be used as described hereinabove. Said stabilizing agent, e.g. a surface modifier, may be introduced at any suitable stage during the manufacture of the nanosuspension. Thus, for example, the surface modifying agent may be added to the initial coarse dispersion prior to the formation of the nanosuspension or after reduction of the particle size has taken place. Alternatively a portion of the stabilizing agent may be added before and a portion after the step of particle size reduction. Preferably the stabilizing agent is present in the coarse dispersion.

The invention further relates, in a preferred embodiment to a nanosuspension comprising particles of abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof, in particular particles of crystalline abiraterone acetate free base, having a d(0.5) of less than 1000 nm, and further comprising an emulsifier.
Preferably the nanosuspension comprising particles of abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof, in particular particles of crystalline abiraterone acetate free base, having a d(0.5) of less than 1000 nm, and further comprising an emulsifier, comprises particles of abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof, in particular particles of crystalline abiraterone acetate free base, having a d(0.5) of from 50 nm to 1000 nm, from 50 nm to 900 nm, from 50 nm to 800 nm, from 50 nm to 700 nm, from 50 nm to 600 nm, from 50 nm to 500 nm, from 50 nm to 400 nm, from 50 nm to 300 nm, from 50 nm to 250 nm, from 50 nm to 200 nm or from 50 nm to 150 nm or alternatively particles of abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof, in particular particles of crystalline abiraterone acetate free base, having a d(0.5) of from 100 nm to 1000 nm, from 100 nm to 900 nm, from 100 nm to 800 nm, from 100 nm to 700 nm, from 100 nm to 600 nm, from 100 nm to 500 nm, from 100 nm to 400 nm, from 100 nm to 300 nm or from 100 nm to 200 nm.

Preferably the nanosuspension comprising particles of abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof, in particular particles of crystalline abiraterone acetate free base, having a d(0.9) of less than 1000 nm, and further comprising an emulsifier, comprises particles of abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof, in particular particles of crystalline abiraterone acetate free base, having a d(0.9) of from 100 nm to 5000 nm, from 100 nm to 2500 nm, from 100 nm to 1500 nm, from 100 nm to 1000 nm, from 200 nm to 1000 nm, from 200 nm to 800 nm, from 300 nm to 800 nm, from 400 nm to 800 nm, from 500 nm to 800 nm, from 500 nm to 750 nm or from 550 nm to 750 nm.

In a preferred embodiment, abiraterone or 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 salt). More preferably, abiraterone acetate is in the form of the free base, in particular the crystalline free base.

Thus, in one embodiment the present invention relates to a stable nanosuspension comprising abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof.
An "emulsifier", as used herein is a substance that can stabilize an emulsion by increasing its kinetic stability. Preferred emulsifiers are those compounds listed in the "Fiedler Encyclopedia of Excipients for Pharmaceuticals, Cosmetics and Related Areas" and described therein as having an application as an emulsifier, solubilizer and/or surfactant, preferably as an emulsifier. Thus, examples of emulsifiers which may be employed include: polyoxyethylene sorbitan fatty acid esters, e.g. Tweens and Spans; polyoxyethylene stearates; polyoxyethylene alkyl esters; castor oil derivatives (e.g. Cremophor EL®, Cremophor RH40®, Cremophor P.H60®); block polymers and block copolymers such as poloxamers, e.g. Lutrol F68, and poloxamines; lecithins of various origin (e.g. egg-lecithin or soya-lecithin), chemically-modified lecithins (e.g. hydrated lecithin), as well as phospholipids and sphingolipids, sterols (e.g. cholesterol derivatives, as well as stigmasterin), esters and ethers of sugars or sugar alcohols with fatty acids or fatty alcohols (e.g. saccharose monostearate); ethoxylated mono- and diglycerides, ethoxylated lipids and lipoids, dicetyl phosphate, phosphatidyl glycerine, sodium cholate, sodium glycolcholate, sodium taurocholate; cellulose ethers and cellulose esters (e.g. methylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, sodium carboxymethylcellulose), polyvinyl derivatives such as polyvinyl alcohol, polyvinyl pyrrolidone, polyvinyl acetate, alginates, polyacrylates (e.g. carbopol), xanthanes; pectins, casein, gum acacia, cholesterol, tragacanth, stearic acid, calcium stearate, glyceryl monostearate, dioctyl sodium sulfosuccinate (sodium docusate); sodium dodecyl sulphate, benzalkonium chloride, alkyl aryl polyether sulfonate, polyethylene glycols.

One class of emulsifiers are surfactants. Surfactants are compounds which lower the surface tension of water at ambient conditions. The preferred non-ionic surfactants do not comprise a charged moiety in water at pH 7 and 20 °C. SDS is an example of an ionic surfactant while Cremophor EL is an example of a non-ionic surfactant.

Most of these compounds are described in detail as excipients in the Handbook of Pharmaceutical Excipients, published jointly by the American Pharmaceutical Association and The Pharmaceutical Society of Great Britain, the Pharmaceutical Press, 1986, the disclosure of which is hereby incorporated by reference in its entirety. The emulsifier are commercially available or/and can be prepared by techniques known in the art.
In one preferred embodiment the emulsifier is a cellulose derivative.

In a preferred embodiment of the invention the emulsifier is a cellulose derivative selected from the group consisting of hydroxypropyl methylcellulose (HPMC), methylcellulose, hydroxypropylcellulose (HPC), hydroxyethylcellulose, sodium carboxymethylcellulose. HPMC is particularly preferred as the surface modifying agent and/or emulsifier. It has been found that HPMC conveys particularly advantageous properties to an inventive nanosuspension comprising HPMC (see examples).

The term "cellulose derivative" as used herein in particular refers to those compounds listed in the "Fiedler Encyclopedia of Excipients for Pharmaceuticals, Cosmetics and Related Areas" and described therein as cellulose derivatives, in particular to a cellulose derivative selected from hydroxypropyl methylcellulose (HPMC), methylcellulose, hydroxypropylcellulose (HPC), hydroxyethylcellulose and sodium carboxymethylcellulose.

According to the present invention it has surprisingly been found that when a cellulose derivative, in particular HPMC, is used as emulsifier a considerable reduction of the formation of impurities during milling is achieved compared to other stabilizing agents tested such as polysorbate 80, poloxamer 188, SDS and cremophor EL. In particular, substantially no degradation of abiraterone acetate to abiraterone has been observed after milling in the presence of HPMC.

Most surprisingly, in the inventive nanosuspension comprising a cellulose derivative, in particular HPMC, as emulsifier substantially no abiraterone degradation product and a reduced amount of total impurities is observed even compared to the commercially available Zytiga® tablets which were assessed for impurities as reference materials. In the case of Zytiga® tablets a low amount of abiraterone degradation product and of total impurities was detected while in the case of the starting API only a certain amount of total impurities but no abiraterone degradation product was observed.
It has further been found that the use of a cellulose derivative, in particular HPMC, as the emulsifier results in superior stability of the inventive nanosuspension upon storage. In particular, no significant increase of degradation products has been observed during storage.

The inventive nanosuspension comprising a cellulose derivative, in particular HPMC, as the emulsifier exhibits a storage stability comparable to or even better than the commercially available Zytiga® tablets which were assessed for impurities as reference materials. Importantly, when a cellulose derivative, in particular HPMC, is used as the emulsifier substantially no oxidation degradation is observed in the presence of air, while oxidation degradation is frequently observed with other emulsifier and even for the commercially available Zytiga® tablets.

According to the present invention it has surprisingly been found that adjustment of the pH exerts a stabilizing effect, when used together with an emulsifier.

Thus, in another embodiment the invention relates to a nanosuspension, wherein the pH of the nanosuspension 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.

In particular, when the pH is adjusted within a range of 1 to 9, preferably 1.5 to 8.5, more preferably within a range of 2 to 8, even more preferably to about 3, in certain cases a considerable reduction of the formation of impurities during milling can be achieved compared to the addition of an emulsifier alone.

Thus, in one embodiment, the invention relates to a nanosuspension as described hereinabove, wherein the nanosuspension has a pH in the range of 1 to 9, preferably a pH of 1.5 to 8.5, more preferably a pH of 2 to 8, even more preferably a pH of about 3.

Similar observations were made with respect to storage stability. Adjustment of the pH within a range of 1 to 9, preferably 1.5 to 8.5, more preferably within a range of 2 to 8, even more preferably to about 3, and optionally further using a stabilizing agent
can result in an improved storage stability compared to use of an emulsifier agent alone.

Thus, in a preferred embodiment of the invention, the nanosuspension comprises as an emulsifier and a buffer. For example, the nanosuspension comprises as an emulsifier, preferably a non-ionic emulsifier or/and the pH of the nanosuspension is adjusted within a range of 1 to 9, preferably 1.5 to 8.5, more preferably within a range of 2 to 8, even more preferably to about 3.

In a preferred embodiment, the buffer serves to adjust the pH within a range of 1 to 9, preferably 1.5 to 8.5, more preferably within a range of 2 to 8, even more preferably to about 3 and the emulsifier which is optionally present is a cellulose derivative, in particular HPMC. However, if the pH of the nanosuspension is adjusted as outlined above, any emulsifier can be used in order to obtain the reduction of impurities and improved storage stability described hereinabove.

The concentration of the at least one emulsifier, either in the coarse suspension or the nanosuspension may be in the range of about 0 to 20% (based on the weight of the final suspension).

As used herein, the term "coarse suspension" relates to the suspension which is used for nanomilling as described herein below.

The relative amount of emulsifier can vary widely and the optimal amount of the emulsifier can depend, for example, upon the emulsifier selected, the critical micelle concentration of the emulsifier, molecular mass of the emulsifier, etc. The weight ratio of abiraterone acetate to emulsifier in the inventive nanosuspension ranges from 20:1 to 1:20, preferably from 10:1 to 1:10.

In another embodiment of the invention, the nanosuspension comprises a liquid agent. A preferred liquid agent for the preparation of the nanosuspension of the present invention is water.
In another embodiment the liquid agent comprises water, in particular the liquid agent comprises at least 80 wt% water, based on the total weight of liquid agent, preferably at least 90 wt%, more preferably at least 95 wt%, most preferably at least 99 wt% water, based on the total weight of liquid agent.

However, the invention can be practiced with other liquid agents in which abiraterone acetate is poorly soluble and dispersible, e.g. in which 0.1 mg/mL or less abiraterone acetate is soluble, including, for example, a liquid agent selected from the group consisting of an aqueous solution, an acid, a base, a polyethylene glycol, glycerol, propylene glycol and mixtures thereof. Determination of suitable liquid agents in which abiraterone acetate is poorly soluble and dispersible is well within the skill of the art.

Suitable aqueous solutions include without limitation buffers such as McIlvaine's buffer, citrate-HCl buffer pH 2, citrate-NaOH buffer pH 5, phosphate buffer pH 7, borate-KCl-NaOH buffer pH 9 or phosphate-NaOH buffer pH 12. Examples of suitable acids are without limitation 0.1 N HCl and 0.01 N HCl. An example of a suitable base is without limitation 0.1 N NaOH.

In one embodiment of the invention the liquid agent is a buffer.

The pH of the liquid agent or/and of the nanosuspension can be adjusted by techniques known to the skilled person, if required.

In a further aspect the present invention relates to a nanosuspension comprising:

- 0.1 -60 wt%, preferably 5-15 wt% of particles of abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof having a d(0.5) of less than 1000 nm, preferably less than 500 nm, more preferably less than 400 nm, most preferably less than 300 nm;
- 30-99 wt%, preferably 70-90 wt% of a liquid agent, preferably selected from the group consisting of water, an aqueous solution, an acid, a base, a polyethylene glycol, glycerol, propylene glycol and combinations thereof; and
- 0.1 -60 wt%, preferably 5-15 wt% of at least one emulsifier, preferably being a non-ionic emulsifier.
In said nanosuspension, it is preferred that the particles of abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof have a \(d(0.9)\) of less than 5000 nm, preferably less than 1000 nm, more preferably less than 500 nm, most preferably less than 400 nm.

It is further preferred that the nanosuspension has a pH in the range of 1 to 9, preferably a pH of 1.5 to 8.5, more preferably a pH of 2 to 8, even more preferably a pH of about 3.

In a further aspect the present invention relates to a process for preparing a nanosuspension comprising particles of abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof having a \(d(0.5)\) of less than 1000 nm, preferably a \(d(0.9)\) of less than 5000 nm, more preferably a \(d(0.9)\) of less than 1000 nm.

In the first step of the inventive process abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof is suspended in a liquid agent, resulting in a coarse suspension. The liquid agent is preferably selected from the group consisting of water, an aqueous solution, an acid, a base, a polyethylene glycol, glycerol, propylene glycol and combinations thereof. Said liquid agent optionally contains an emulsifier, preferably and non-ionic emulsifier.

For the preparation of the nanosuspension it is preferred that the abiraterone acetate starting material is utilized in the form of coarse particles, preferably having a particle size in a range of 300 to 10 \(\mu\)m. If necessary, the particle size of abiraterone acetate may be reduced to this level by conventional means, known to the skilled person, e.g. dry powder milling or jet milling. The coarse particles of abiraterone acetate are preferably suspended in a liquid agent comprising a solvent in which the drug substance is essentially insoluble. In the case of abiraterone acetate the liquid agent preferably comprises an aqueous solution and most preferably consists essentially of water. The concentration of abiraterone acetate in the said suspension of coarse particles may be in the range 0.1 to 60% by weight, preferably 5 to 15% by weight, based on the weight of the suspension of coarse particles.
To the coarse suspension obtained in the first step, milling balls are added to obtain a slurry for nanomilling, and the suspension is then subjected to nanomilling, e.g. a wet milling process under conditions sufficient to provide a nanosuspension with a mean particle size \(d(0.5)\) of less than 1000 nm, preferably a \(d(0.9)\) of less than 5000 nm, more preferably a \(d(0.9)\) of less than 1000 nm. Preferably the wet milling process is wet ball milling.

A wet ball milling process commonly used in the art typically uses a media mill such as a Dyno®Mill (Glen Mills Inc., Clifton, NJ) that circulates the suspension through a chamber containing beads made from extremely hard, durable and essentially inert materials (e.g., zirconium). The high-energy movement and collisions of milling media with suspended pharmaceutically active ingredient lead to significant reductions in particle size of the pharmaceutically active ingredient.

According to the invention the following process was used for nanomilling. In a glass beaker an emulsifier, preferably an non-ionic emulsifier, e.g. hydroxypropyl methylcellulose, was mixed with a liquid agent, e.g. demineralized water, to prepare a clear, slightly viscous solution. Abiraterone or abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof was suspended in the prepared emulsifier -liquid agent-solution, the suspension was transferred to a milling jar containing zirconium balls and milled in a planetary ball mill. The resulting suspension was separated from the milling balls, e.g. with a 0.4 mm sieve. Optionally, the balls were further washed with liquid agent, e.g. demineralized water, which was added to the milled suspension.

The above described beads used for wet ball milling are also referred to as "milling balls", "milling pearls" or "milling beads" herein.

Thus, in one embodiment the present invention relates to a process for preparing a nanosuspension comprising particles of abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof having a mean particle size \(d(0.5)\) of less than 1000 nm, preferably a \(d(0.9)\) of less than 5000 nm, more preferably a \(d(0.9)\) of less than 1000 nm, the process comprising the following steps:
(a) preparing a suspension of abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof in a liquid agent, preferably selected from the group consisting of water, an aqueous solution, an acid, a base, a polyethylene glycol, glycerol, propylene glycol and combinations thereof;

(b) adding milling balls to the suspension of step (a) in order to obtain a slurry for nanomilling, and

(c) nanomilling the slurry to provide a nanosuspension with a mean particle size \(d(0.5)\) of less than 1000 nm, preferably a \(d(0.9)\) of less than 5000 nm, more preferably a \(d(0.9)\) of less than 1000 nm.

In another embodiment the process for preparing a nanosuspension further comprises the following step after steps (a) - (c):

(d) separating the resulting nanosuspension from the milling balls.

In a further embodiment the process for preparing a nanosuspension further comprises the following step after step (d):

(e) washing the milling balls with a liquid agent selected from the group consisting of water, an aqueous solution, an acid, a base, a polyethylene glycol, glycerol, propylene glycol and combinations thereof, separating the liquid agent from the milling balls and adding the separated liquid agent to the milled nanosuspension obtained in step (d).

In one embodiment a solution of a liquid agent and an emulsifier is prepared prior to step (a).

In the inventive process for preparing a nanosuspension an amount of 0.1 - 60 wt%, preferably 5-15 wt% of abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof is used, based on the weight of the slurry used for nanomilling in step (c).

In the inventive process for preparing a nanosuspension an amount of 5-90 wt%, preferably 50-90 wt%, more preferably 70-90 wt% of milling balls is used, based on the weight of the slurry used for nanomilling in step (c), with a diameter of the milling balls in the range of 0.1 - 5 mm, preferably 0.1-3 mm, more preferably 0.1 - 1 mm.
According to the invention, the amount of milling balls in the slurry is in particular important in case a planetary ball mill is used for nanomilling. However, for certain types of mills such as the above-described Dyno® Mill, the amount of milling balls is not critical, since the suspension is circulated through the balls.

The nanomilling of step (c) used in the inventive process for preparing a nanosuspension is carried out under conditions sufficient to provide a nanosuspension with a mean particle size d(0.5) of less than 1000 nm, preferably a d(0.9) of less than 5000 nm, more preferably a d(0.9) of less than 1000 nm. Suitable conditions are, for example, a milling speed of 300-600 rpm, preferably 500 rpm, for a milling time of 2-5 h, preferably 3-4 h, at room temperature in a planetary ball mill. However, the exact conditions depend on the type of equipment used and can be determined by a person skilled in the art by routine experimentation.

In one embodiment of the invention the pH of the suspension of step (a) is adjusted to 1 to 9, preferably 1.5 to 8.5, more preferably 2 to 8, even more preferably to 3.

In the inventive process for preparing a nanosuspension an emulsifier may be used as described hereinabove. Said emulsifier may be introduced at any suitable stage during the manufacture of the nanosuspension. Thus, for example, the emulsifier may be added to the initial coarse dispersion prior to the formation of the nanosuspension or after reduction of the particle size has taken place. Alternatively a portion of the emulsifier may be added before and a portion after the step of particle size reduction. Preferably the an emulsifier is present in the coarse dispersion.

In another aspect the present invention relates to a pharmaceutical composition comprising a nanosuspension as described hereinabove or a concentrated nanosuspension derived thereof or the solid components thereof.

In one embodiment of the invention, the nanosuspension can be prepared for direct administration to a patient.
In an alternative embodiment of the invention, the nanosuspension can be incorporated into a pharmaceutical composition by standard manufacturing techniques.

The composition can be prepared for parenteral injection, oral administration, local, buccal, nasal, rectal, ocular administration and the like.

The pharmaceutical composition according to the present invention can take various forms such as, but not limited to, solutions, suspensions, emulsions, tablets, pills, capsules, granules, powders or sustained-release formulations, depending on the intended route of administration.

For oral administration, the composition may be formulated as a tablet, a pill, a dragee, a troche, a capsule, a liquid, a gel, a syrup, a slurry, a suspension and the like.

For topical or transdermal administration, the composition can be formulated as a solution, a gel, an ointment, a cream, a suspension or a salve.

In a preferred embodiment, the nanosuspension of the invention is converted into a concentrated nanosuspension or into a solid particle formulation.

The term "concentrated nanosuspension", as used herein, refers to a nanosuspension from which the liquid agent has at least been partly removed, i.e. the concentrated nanosuspension is less dilute than the original nanosuspension from which it is prepared and still comprises an amount of liquid agent.

The terms "solid particle formulation" or "solid components of the nanosuspension", as used herein, refer to a nanosuspension from which the liquid agent has substantially been removed, i.e. only the solid components of the original nanosuspension from which they are prepared remain.

Thus, in one embodiment of the present invention the nanosuspension is further processed to provide a concentrated nanosuspension or solid nanoparticles of
abiraterone acetate, i.e. the solid components of the nanosuspension, which can then be included into pharmaceutical compositions.

In a preferred embodiment, the liquid agent is at least partly removed from the nanosuspension by conventional drying methods such as lyophilisation or spray drying in order to obtain a concentrated nanosuspension or the solid components of the nanosuspension.

During the development of pharmaceutical compositions, it was observed, that the nanoparticles of abiraterone acetate tend to aggregate in the process of drying. It was surprisingly found, that the stability of the nanoparticles of abiraterone acetate could be increased and the particles could be stabilized by the use of at least one redispersant (i.e. redispersing agent), especially if the redispersant is dissolved in the nanosuspension prior to at least partly removing the liquid agent from the nanosuspension, e.g. prior to drying the nanosuspension.

Therefore, in a further embodiment of the invention, the pharmaceutical composition comprises at least one redispersing agent. The redispersing agent is selected from the group consisting of reducing and non-reducing sugars and sugar alcohols.

Examples of non-reducing sugars are sucrose and trehalose, examples for reducing sugars are glucose, galactose, lactose and maltose and examples for sugar alcohols are xylitol, mannitol, sorbitol and isomalt.

According to the invention non-reducing sugars are preferred and in particular sucrose is preferred. The redispersing agent is preferably added to the nanosuspension prior to removing the liquid agent.

According to the invention it was found that tablets prepared from the inventive nanosuspension exhibit a stability comparable to or better than that of Zytiga® tablets when a cellulose derivative, in particular HPMC, is used as the stabilizing agent and/or an emulsifier in the preparation of the nanosuspension. Surprisingly, the stability of tablets with a cellulose derivative, in particular HPMC, was significantly improved with the addition of a non-reducing sugar, e.g. sucrose, as a redispersing
agent to the nanosuspension that was used for the preparation of tablets. Further surprisingly, the stability of tablets with poloxamer 188 used as the stabilizing agent and/or an emulsifier in the preparation of the nanosuspension was improved when the tablets were prepared from the nanosuspension prepared in buffer pH 3. Thus, it is concluded that the stability of tablets is improved when the tablets are prepared from a nanosuspension with or without a stabilizing agent, wherein the pH of the nanosuspension has been adjusted as described hereinabove, and wherein a non-reducing sugar, e.g. sucrose is added as a redispersing agent to the nanosuspension that was used for the preparation of tablets.

The pharmaceutical compositions according to the present invention may optionally include one or more additional excipients generally used in the art.

Examples of such pharmaceutical excipients include, but are not limited to, bulking agents (e.g., lactose monohydrate, anhydrous lactose, sucrose, trehalose, fructose, glucose, maltose, mannitol, isomalt, glycine, maltodextrin, microcrystalline cellulose), chemical stability enhancers (e.g., anti-oxidants, chelating agents, ion-exchange resins, cyclodextrins and their derivatives), disintegrants (e.g., croscarmellose sodium, crospovidone, sodium starch glycolate, starch, modified starch), viscosity modifiers (e.g., bovine gelatin, porcine gelatin, alginates, carrageenan gum, gellan gum, guar gum, xanthan gum, pullulan, methyl cellulose, ethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, cellulose acetate phthalate), precipitation inhibitors (e.g., hydroxypropyl methylcellulose, polysorbate 80, sodium lauryl sulfate, Gelucire 44/14, Cremophor EL, Cremophor RH40), sweeteners (e.g., aspartame, acesulfame potassium, sucralose, sorbitol, xylitol, Magnasweet, thaumatin), flavoring agents of artificial or natural origin, coloring agents, diluents, lubricants, binders, granulating aids, glidants, preservatives or buffers and combinations thereof depending on the route of administration and the dosage form used.

The pharmaceutical compositions according to the present invention may optionally comprise an external coating. Said external coating may provide a function such as enteric coating or oxygen protection. Suitable enteric or oxygen protective coatings are known in the art. Besides the coating, for the purpose of oxygen protection, i.e. in
order to prevent oxidation degradation, other methods can be used, for example packaging under inert atmosphere, oxygen impermeable packaging, oxygen scavengers or combinations thereof.

In another aspect the present invention relates to a process for preparing a pharmaceutical composition comprising nanoparticulate abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof comprising the following steps:
(a) providing a nanosuspension as described hereinabove or preparing a nanosuspension according to the process as described hereinabove;
(b) at least partly removing the liquid agent from the nanosuspension in order to obtain a concentrated nanosuspension or solid; and
(c) performing at least one additional process step selected from grinding, sieving, mixing, roller compaction, screening, granulating, tableting or a combination thereof with the obtained concentrated nanosuspension or solid.

Suitable methods to at least partly remove the liquid agent from the nanosuspension in order to obtain a concentrated nanosuspension or solid are, for example, decantation, centrifugation and decantation, centrifugation and vacuum drying, vacuum or tray drying, spray drying, lyophilization, wet granulation, fluid bed granulation, moisture activated granulation.

In one embodiment of the inventive process for preparing a pharmaceutical composition prior to step (b) or prior to step (c) a redispersing agent selected from the group consisting of reducing and non-reducing sugars and sugar alcohols, preferably a non-reducing sugar, e.g. sucrose, is added to the nanosuspension.

In one embodiment of the inventive process for preparing a pharmaceutical composition the weight ratio of redispersing agent and abiraterone acetate is from 1:10 to 10:1, preferably 1:1.

According to the invention lyophilization or wet granulation with the prior addition of a redispersing agent, preferably a non-reducing sugar, e.g. sucrose, are preferred as
the method used in order to at least partly remove the liquid agent from the nanosuspension.

In yet another aspect the present invention relates to a pharmaceutical composition comprising the inventive nanosuspension or a concentrated nanosuspension derived thereof or the solid components thereof prepared by a process as described hereinabove.

In one embodiment of the invention the pharmaceutical composition comprising nanoparticulate abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof is for use in the treatment of cancer, wherein the composition provides:

(a) min 6% of dose dissolved from 250 mg of abiraterone acetate in a dosage form in 45 min, measured by USP paddle apparatus at 50 RPM in 900 ml of Fassif media;

(b) min 30% of dose dissolved from 250 mg of abiraterone acetate in a dosage form in 45 min, measured by USP paddle apparatus at 50 RPM in 900 ml of Fassif media;

(c) ratio between AUCt values for the dosage form disclosed in this invention versus Zytiga® higher than 1.1, higher than 1.2, higher than 1.3, after single dose administration to healthy human subjects;

(d) ratio between Cmax values for the dosage form disclosed in this invention versus Zytiga® higher than 1.1, higher than 1.2, higher than 1.3, after single dose administration to healthy human subjects.

In a further embodiment of the invention the pharmaceutical composition comprising a nanosuspension as described hereinabove or prepared according to the process as described hereinabove is for use in the treatment of cancer, preferably metastatic prostate cancer.
Figures

The accompanying figures, which are incorporated and form part of the specification, merely illustrate certain embodiments of the present invention and should not be construed as limiting the invention. They are meant to serve to explain specific modes of the present invention to those skilled in the art.

Figure 1: Level of total impurities after storage at 40 °C and 60 °C in pharmaceutical compositions prepared from nanosuspensions compared to commercially available Zytiga® tablets.

Figure 2: Dissolution of abiraterone acetate in Fassif and Fessif media for a nanosuspension and the pharmaceutical dosage form (tablet) made of the nanosuspension compared to the dissolution of commercially available Zytiga® tablets.
Examples

Preparation of Nanosuspensions

Example 1 (Sample 001X1)
In a glass beaker 1 g of hydroxypropyl methylcellulose (HPMC) was mixed with 17 g of demineralized water to prepare a clear, slightly viscous solution. 2 g of abiraterone acetate were suspended in the prepared HPMC solution and milled in a high pressure homogenizer in a high pressure homogenizer at 300 bar for 2 cycles, 800 bar for 2 cycles and 1600 bar for 6 cycles.

Example 2 (Samples 001 X2, 001 X11, 001 X14, 001 X15)
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 of abiraterone acetate were suspended in the prepared HPMC solution, 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 at 500 RPM. Milling times was 180 minutes for sample 001 X2 and 240 minutes for samples 001 X11, 001 X14, 001 X15. The resulting suspension was separated from the milling balls with a 0.4 mm sieve and the balls were further washed with 50 g of demineralized water, which was added to the milled suspension.

Example 3 (Sample 001X3)
In a glass beaker 0.5 g of hydroxypropyl methylcellulose was mixed with 17.5 g of demineralized water to prepare a clear, slightly viscous solution. 2 g of abiraterone acetate were suspended in the prepared HPMC solution, 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 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 4 (Sample 001X4)
In a glass beaker 0.4 g of polysorbate 80 was mixed with 17.6 g of demineralized water to prepare a clear, yellowish solution. 2 g of abiraterone acetate were suspended in the prepared polysorbate solution, 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 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 5 (Sample 001X5)
In a glass beaker 2 g of hydroxypropyl methylcellulose (HPMC) was mixed with 16 g of demineralized water to prepare a clear, slightly viscous solution. 2 g of abiraterone acetate were suspended in the prepared HPMC solution, 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 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 6 (Sample 001X6)
In a glass beaker 1 g of poloxamer 188 was mixed with 17 g of demineralized water to prepare a clear solution. 2 g of abiraterone acetate were suspended in the prepared poloxamer solution, 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 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 (Sample 001X8)
In a glass beaker 0.4 g of sodium dodecyl sulfate (SDS) was mixed with 17.6 g of demineralized water to prepare a clear solution. 2 g of abiraterone acetate were suspended in the prepared SDS solution, 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 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 (Sample 001X9)
In a glass beaker 1 g of Cremophor EL was mixed with 17 g of demineralized water to prepare a clear, yellowish solution. 2 g of abiraterone acetate were suspended in the prepared Cremophor EL solution, 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 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 9 (Sample 001X10)
In a glass beaker 2 g of abiraterone acetate were suspended in 17 g of McIlvaine buffer with pH 3. McIlvaine buffer is prepared by mixing 20.55 mL of 0.2M Na₂HP0₄ and 79.45 mL of 0.1 M citric acid and adjusting to pH 3, if necessary. 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 of 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 10 (Sample 001X12)
In a glass beaker 1 g of hydroxypropyl methylcellulose (HPMC) was mixed with 17 g McIlvaine buffer with pH 3 to prepare a clear, slightly viscous solution. 2 g of abiraterone acetate were suspended in the prepared HPMC solution, 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 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 of demineralized water, which was added to the milled suspension.
Example 11 (Sample 001 X 13)
In a glass beaker 1 g of poloxamer 188 was mixed with 17 g of demineralized water to prepare a clear, slightly viscous solution. 0.62 g of acetic acid (100%) were added and the solution was mixed further. 2 g of abiraterone acetate were suspended in the prepared poloxamer 188 solution, 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 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 of demineralized water, which was added to the milled suspension.

Example 12 (Sample 001X16)
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 of abiraterone acetate mesylate were suspended in the prepared HPMC solution, 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 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 of demineralized water, which was added to the milled suspension.

Characterization of nanosuspension

Particle size determination

Example 13
Particle size of final suspensions from examples 1-9 and example 12 were measured by a laser diffraction method (Mastersizer, Malvern UK). The results are shown in Table 2. d(0.1) refers to the value below which 10% of the particles have a volume average diameter equivalent or below that value. d(0.5) refers to the value below which 50% of the particles have a volume average diameter equivalent or below that value. d(0.9) refers to the value below which 90% of the particles have a volume average diameter equivalent or below that value. Span is the width of the distribution based on the d(0.1), d(0.5) and d(0.9) and is calculated by dividing the difference between d(0.9) and d(0.1) by d(0.5).
<table>
<thead>
<tr>
<th>Example</th>
<th>Sample</th>
<th>Stabilizer</th>
<th>Particle size (d0,1)</th>
<th>Particle size (d0,5)</th>
<th>Particle size (d0,9)</th>
<th>Span</th>
<th>Fassif % dissolved in 10 min</th>
<th>Fassif % dissolved in 120 min</th>
<th>Fassif % dissolved in 10 min</th>
<th>Fassif % dissolved in 120 min</th>
<th>% free abiraterone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Example 1</td>
<td>001X1</td>
<td>HPMC</td>
<td>0.85</td>
<td>1.74</td>
<td>3.38</td>
<td>1,461</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Example 2</td>
<td>001X2</td>
<td>HPMC</td>
<td>0.07</td>
<td>0.16</td>
<td>0.86</td>
<td>27,271</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>/</td>
</tr>
<tr>
<td>Example 3</td>
<td>001X3</td>
<td>HPMC</td>
<td>0.34</td>
<td>3.63</td>
<td>17.06</td>
<td>4,602</td>
<td>10.6</td>
<td>8.7</td>
<td>39.6</td>
<td>37.9</td>
<td>/</td>
</tr>
<tr>
<td>Example 4</td>
<td>001X4</td>
<td>Polysorbate 80</td>
<td>0.07</td>
<td>0.13</td>
<td>0.32</td>
<td>1,897</td>
<td>8.1</td>
<td>8.3</td>
<td>35.6</td>
<td>34.9</td>
<td>0.84</td>
</tr>
<tr>
<td>Example 5</td>
<td>001X5</td>
<td>HPMC</td>
<td>0.07</td>
<td>0.14</td>
<td>0.65</td>
<td>4,217</td>
<td>7.6</td>
<td>7.8</td>
<td>31.2</td>
<td>31.3</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Example 6</td>
<td>001X6</td>
<td>Poloxamer</td>
<td>0.07</td>
<td>0.13</td>
<td>0.25</td>
<td>1,475</td>
<td>7.6</td>
<td>7.2</td>
<td>34.3</td>
<td>34.7</td>
<td>1.43</td>
</tr>
<tr>
<td>Example 7</td>
<td>001X7</td>
<td>SDS</td>
<td>0.07</td>
<td>0.15</td>
<td>1.91</td>
<td>12,594</td>
<td>3.9</td>
<td>4.3</td>
<td>20.1</td>
<td>20.2</td>
<td>0.88</td>
</tr>
<tr>
<td>Example 8</td>
<td>001X9</td>
<td>Cremophor EL</td>
<td>0.07</td>
<td>0.13</td>
<td>0.32</td>
<td>1,891</td>
<td>4.9</td>
<td>4.9</td>
<td>21.3</td>
<td>21.3</td>
<td>0.71</td>
</tr>
<tr>
<td>Example 9</td>
<td>001X10</td>
<td>Poloxamer</td>
<td>1.75</td>
<td>3.69</td>
<td>7.39</td>
<td>1,528</td>
<td>4.1</td>
<td>4.2</td>
<td>18.6</td>
<td>17.7</td>
<td>0.24</td>
</tr>
<tr>
<td>Example 10</td>
<td>001X11</td>
<td>HPMC</td>
<td>0.07</td>
<td>0.14</td>
<td>1.4</td>
<td>7,513</td>
<td>11.5</td>
<td>7.8</td>
<td>38.7</td>
<td>38.1</td>
<td>0.80</td>
</tr>
<tr>
<td>Example 11</td>
<td>001X12</td>
<td>HPMC</td>
<td>0.07</td>
<td>0.19</td>
<td>1.6</td>
<td>7,955</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>0.50</td>
</tr>
<tr>
<td>Example 12</td>
<td>001X13</td>
<td>Poloxamer</td>
<td>0.07</td>
<td>0.13</td>
<td>0.28</td>
<td>1,595</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>0.94</td>
</tr>
<tr>
<td>Example 13</td>
<td>001X14</td>
<td>HPMC</td>
<td>0.07</td>
<td>0.13</td>
<td>0.26</td>
<td>1.63</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>0.97</td>
</tr>
<tr>
<td>Example 14</td>
<td>001X15</td>
<td>HPMC</td>
<td>0.07</td>
<td>0.13</td>
<td>0.35</td>
<td>2,193</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>/</td>
</tr>
<tr>
<td>Example 15</td>
<td>001X16</td>
<td>HPMC</td>
<td>0.08</td>
<td>0.22</td>
<td>2.33</td>
<td>10,164</td>
<td>7.5</td>
<td>7.9</td>
<td>35.9</td>
<td>34.9</td>
<td>0.96</td>
</tr>
<tr>
<td>Zytiga</td>
<td>Zytiga</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.0</td>
<td>5.9</td>
<td>8.6</td>
<td>25.7</td>
<td>0.08</td>
</tr>
<tr>
<td>API</td>
<td>API</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.3</td>
<td>5.4</td>
<td>20.2</td>
<td>26.8</td>
<td>&lt; 0.05</td>
</tr>
</tbody>
</table>
Measurement of physical and chemical stability

Example 14
Final suspensions from examples 4-9 were centrifuged, supernatant was removed and sediment dried in a vacuum dryer at 40°C for 3 hours and analyzed. Marketed product (Zytiga®) and starting API (active pharmaceutical ingredient) were also analyzed. As the starting API commercially available abiraterone acetate with a particle size of d(0.5)=27 μm was used. Results are shown in Table 3. Abiraterone and total impurities were measured - abiraterone is derived from abiraterone acetate (starting substance) via ester bond cleavage. Total impurities are a sum of free abiraterone and all other impurities.

<table>
<thead>
<tr>
<th>Sample</th>
<th>Abiraterone (%)</th>
<th>Total impurities (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zytiga® tablets</td>
<td>0.08 %</td>
<td>0.15 %</td>
</tr>
<tr>
<td>Abiraterone acetate API</td>
<td>&lt; 0.05 %</td>
<td>0.16 %</td>
</tr>
<tr>
<td>Example 1 (001X1)</td>
<td>&lt; 0.05%</td>
<td>0.06 %</td>
</tr>
<tr>
<td>Example 4 (001X4)</td>
<td>0.84 %</td>
<td>0.84 %</td>
</tr>
<tr>
<td>Example 5 (001X5)</td>
<td>&lt; 0.05 %</td>
<td>0.05 %</td>
</tr>
<tr>
<td>Example 6 (001X6)</td>
<td>1.43 %</td>
<td>1.48 %</td>
</tr>
<tr>
<td>Example 7 (001X8)</td>
<td>0.88 %</td>
<td>0.93 %</td>
</tr>
<tr>
<td>Example 8 (001X9)</td>
<td>0.71 %</td>
<td>0.77 %</td>
</tr>
<tr>
<td>Example 9 (001X10)</td>
<td>0.24 %</td>
<td>0.29 %</td>
</tr>
<tr>
<td>Example 11 (001X13)</td>
<td>0.94 %</td>
<td>1.01 %</td>
</tr>
</tbody>
</table>

Results in Table 3 demonstrate a significant increase of abiraterone impurity in some of the nanosuspensions after milling in comparison to starting API. Surprisingly, no increase of free abiraterone was detected in the samples 001X1 (Example 1) and 001 X5 (Example 5) where HPMC was used as stabilizer. Moreover, the comparison of samples prepared with Poloxamer 188 (001X6 - Example 6, 001 X10 - Example 9) indicates that formation of abiraterone during milling could be reduced by appropriate pH modification (i.e. buffer with pH 3 or use of acetic acid).

Example 15
Final suspensions from examples 4-9 were centrifuged, supernatant was removed and sediment dried in a vacuum dryer at 40°C for 3 hours. Dry samples were put on
different storage condition. Samples were stored at elevated temperature of 60 °C under nitrogen, air and oxygen atmosphere for 7 days and at accelerated condition of 40 °C under air for 1 month. After sampling from storage conditions samples were analyzed. Marketed product (Zytiga®) and starting API were also treated as samples from the examples and analyzed. Results are shown in Table 4. Increase in total impurities was measured. Total impurities are a sum of abiraterone and all other impurities. The increase of impurities was calculated as a difference between the result for total impurities of samples from specific storage condition and the result of initial analysis (sample analyzed before storage at stability conditions).

Table 4

<table>
<thead>
<tr>
<th>Sample</th>
<th>Increase of total impurities (%) at storage conditions:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>60 °C, nitrogen, 7 days</td>
</tr>
<tr>
<td>Zytiga® tablets</td>
<td>0.08 %</td>
</tr>
<tr>
<td>Abiraterone acetate API</td>
<td>0</td>
</tr>
<tr>
<td>Example 4 (001X4)</td>
<td>0</td>
</tr>
<tr>
<td>Example 5 (001X5)</td>
<td>0.06 %</td>
</tr>
<tr>
<td>Example 6 (001X6)</td>
<td>0</td>
</tr>
<tr>
<td>Example 7 (001X8)</td>
<td>0.04 %</td>
</tr>
<tr>
<td>Example 8 (001X9)</td>
<td>0</td>
</tr>
<tr>
<td>Example 9 (001X10)</td>
<td>0.08 %</td>
</tr>
<tr>
<td>Example 10 (001X12)</td>
<td>0</td>
</tr>
<tr>
<td>Example 11 (001X13)</td>
<td>0</td>
</tr>
<tr>
<td>Example 12 (001X16)</td>
<td>0.01 %</td>
</tr>
</tbody>
</table>

Results in Table 4 show increase in total impurities during storage in Zytiga® tablets and in some of the nanosuspensions in the presence of oxygen. On the contrary no increase in degradation products was observed for all samples when stored under nitrogen.
Superior stability of sample with HPMC (001X5 - Example 5 and 001X1 2 - Example 10) was observed, no significant increase of impurities was detected when stored under air at 60°C and 40°C.

Dissolution studies

Example 16
Final suspensions from examples 2-9 and example 12 were tested in terms of the dissolution profile of abiraterone acetate. Samples were tested using bio relevant dissolution media FaSSIF and FeSSIF. Test conditions were as follows: 900 ml media, Apparatus 2 at 50 rpm, 10 ml samples were withdrawn at prescribed time points and filtered through 0.2 micron filter prior to HPLC analysis. Marketed product (Zytiga®) was also tested as reference. Dissolution profiles are shown in Table 2.

Preparation of pharmaceutical composition/dosage forms (drying and tabletting)

Example 17 (Sample 002X1)
Final suspension from example 2 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. Resulting granulate was mixed with lactose, colloidal silica and magnesium stearate and compressed into tablets containing 250 mg of abiraterone acetate.

Example 18 (Samples 003X1, 003X2, 003X3)
Sucrose was added to final suspensions from examples 4, 5 and 6. Sample from example 4 was labeled 003X1, sample from example 5 was labeled 003X2, sample from example 6 was labeled 003X3. The weight 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 of abiraterone acetate.
Example 19 (Sample 004X1)
Sucrose was added to final suspension from example 9. The weight 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 20 (Sample 005X1)
70 g of nanosuspension from example 10 was carefully weighted. 3.2 g of lactose was wetted with the nanosuspension to obtain a wet mass. The mass was placed in a vacuum dryer and dried at 40°C. Dried mass was wetted again with the nanosuspension to obtain a wet mass and dried as described. The steps were repeated until all nanosuspension was used up. To a person skilled in the art the process is known as wet granulation. Final dry mass was crushed with pestle and mortar and sieved through a 0.7 mm sieve.

Example 21 (Sample 005X2)
70 g of nanosuspension from example 11 was carefully weighted. 3.2 g of lactose was wetted with the nanosuspension to obtain a wet mass. The mass was placed in a vacuum dryer and dried at 40°C. Dried mass was wetted again with the nanosuspension to obtain a wet mass and dried as described. The steps were repeated until all nanosuspension was used up. To a person skilled in the art the process is known as wet granulation. Final dry mass was crushed with pestle and mortar and sieved through a 0.7 mm sieve.

Example 22 (Sample 006X1)
Nanosuspension from example 2 was added to 0.990 g of lactose in a weight ratio 6:5=lactose:abiraterone acetate. The mixture was mixed and left to stand for 15 minutes, 0.528 g of 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.
Example 23 (Sample 007X1)
Nanosuspension from example 2 was added to 0.990 g of lactose in a weight ratio 6:5= lactose:abiraterone acetate. The mixture was mixed and left to stand for 15 minutes, 0.363 g of citric acid 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, magnesium stearate and 0.156 g of sodium dihydrogen phosphate and compressed into tablets containing 250 mg of abiraterone acetate.

Example 24 (Sample 008X1)
Nanosuspension from example 12 was added to 0.60 g of lactose in a weight ratio 6:5= lactose:abiraterone acetate. The mixture was mixed and left to stand for 15 minutes, 0.32 g of 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.

Characterization of dosage forms

Example 25
Tablets and blends from examples 17-24 were put on stress and accelerated stability and analyzed. The samples were stored at elevated temperature of 60 °C under nitrogen and air for 7 days and at accelerated condition of 40°C under air for 1 month. Marketed product (Zytiga®) was also treated as samples from the examples and analyzed. Results are shown in Figure 2. The increase in total impurities was measured. The total impurities are a sum of abiraterone and all other impurities. The increase of impurities was calculated as a difference between the result for total impurities of samples from specific storage condition and the result of initial analysis (sample analyzed before storage at stability conditions).

The results show an increase in total impurities during storage in majority of the samples in the presence of oxygen. On the contrary no increase in degradation
products was observed for all samples (tablets and granules) when stored under nitrogen.

Stability of samples with HPMC (sample 002X1, Example 17 and sample 005X1, Example 20) was comparable to stability of Zytiga® tablets. Stability of tablets with HPMC was significantly improved with addition of sucrose to the suspension that was used for the preparation of tablets (sample 003X2, Example 18 - example 5). Tablets with poloxamer 188 (sample 003X3, Example 18 - example 6) were extremely unstable in the presence of oxygen. Nevertheless, the stability of the samples with Poloxamer 188 was improved when the tablets were prepared from the nanosuspension prepared in buffer pH 3 (sample 004X1, Example 19) or with addition of acetic acid (sample 005X2, Example 21).

Dissolution studies

Example 26

Tablets from examples 18 and 20-23 were tested in terms of the dissolution profile of abiraterone acetate. Samples were tested using bio relevant dissolution media FaSSIF and FeSSIF. Test conditions were as follows: 900 ml media, Apparatus 2 at 50 rpm, 10 ml samples were withdrawn at prescribed time points and filtered through 0.2 micron filter prior to HPLC analysis. Marketed product (Zytiga®) was also tested as reference. Dissolution profiles are shown in Table 5.

An exemplary dissolution profile for a nanosuspension and the pharmaceutical composition made out of the respective nanosuspension, compared to commercially available Zytiga® tablets is shown in Figure 2, based on example 2 (001X11) and example 22 (006X1).
**Table 5**

<table>
<thead>
<tr>
<th>Example</th>
<th>Sample</th>
<th>Fassif % dissolved in 10 min</th>
<th>Fassif % dissolved in 120 min</th>
<th>Fessif % dissolved in 10 min</th>
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<td>2.1</td>
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<td>17</td>
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<tr>
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<td>005X2</td>
<td>6.8</td>
<td>9</td>
<td>/</td>
<td>/</td>
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<td>Example 22</td>
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<td>0.8</td>
<td>8.5</td>
<td>12.8</td>
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<td>1.3</td>
<td>5.4</td>
<td>20.2</td>
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The invention is further characterized by the following items:

1. Nanosuspension comprising particles of abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof having a d(0.5) of less than 1000 nm.

2. Nanosuspension comprising particles of abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof having a d(0.9) of less than 1000 nm.

3. Nanosuspension according to item 1 or 2 comprising at least one stabilizing agent.

4. Nanosuspension according to item 3, wherein the stabilizing agent is a surface modifying agent or/and a buffer.

5. Nanosuspension according to item 3 or 4, wherein the stabilizing agent is a surface modifying agent.

6. Nanosuspension according to item 4 or 5, wherein the surface modifying agent is a cellulose derivative, a polymer or a surfactant.

7. Nanosuspension according to item 4-6, wherein the surface modifying agent is a cellulose derivative selected from the group consisting of hydroxypropyl methylcellulose (HPMC), methylcellulose, hydroxypropylcellulose (HPC), hydroxyethylcellulose, sodium carboxymethylcellulose.

8. Nanosuspension according to any of items 4-7, wherein the surface modifying agent is HPMC.

9. Nanosuspension according to item 4 or 5, wherein the surface modifying agent is a polymer selected from the group consisting of polyvinyl alcohol, polyvinyl pyrrolidone, polyvinyl acetate, alginates, polyacrylates, pectins.
10. Nanosuspension according to item 4 or 5, wherein the surface modifying agent is a surfactant selected from the group consisting of polyoxyethylene products of hydrogenated vegetable oils, polyoxyethylated castor oils or polyethoxylated hydrogenated castor oil, polyoxyethylene-sorbitan-fatty acid esters, polyoxyethylene castor oil derivatives, sorbitan esters, sucrose esters, polyoxamers, poloxamers, polyglycolyzed glycerides (as caprylocaproyl macrogol glyceride (Labrasol), linoleaoyl macrogol glycerides (Labrafil), polyglyceryl oleate (Plurrol)), gelucires, sodium dodecyl sulfate (SDS), sodium cholate, sodium glycolcholate, sodium taurocholate, saccharose monostearate, lecithin, dioctyl sodium sulfosuccinate or a combination thereof.

11. Nanosuspension according to item 3 or 4, wherein the stabilizing agent is a buffer providing a pH in the range of 1 to 9.

12. Nanosuspension according to any of items 3-10, wherein the weight ratio of abiraterone acetate to stabilizing agent ranges from 20:1 to 1:20, preferably from 10:1 to 1:10.

13. Nanosuspension according to any of the previous items, wherein the nanosuspension is a stable nanosuspension.

14. Nanosuspension according to any of the previous items, wherein the nanosuspension has a pH in the range of 1 to 9.

15. Nanosuspension according to any of the previous items, wherein the nanosuspension comprises a liquid agent selected from the group consisting of water, an aqueous solution, an acid, a base, a polyethylene glycol, glycerol, propylene glycol and combinations thereof.

16. Nanosuspension according to item 15, wherein the liquid agent comprises water.
17. Nanosuspension according to item 15, wherein the liquid agent is a buffer.

18. Nanosuspension according to any of the previous items wherein the abiraterone acetate is in the form of the free base or the mesylate salt.

19. Nanosuspension according to items 1-18 comprising:
   - 0.1 -60 wt% of particles of abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof having a d(0.5) of less than 1000 nm;
   - 30-99 wt% of a liquid agent; and
   - 0.1 -60 wt% of at least one stabilizing agent.

20. Nanosuspension according to item 19, wherein the particles of abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof have a d(0.9) of less than 1000 nm, preferably less than 500 nm, more preferably less than 400 nm, most preferably less than 300 nm.

21. Nanosuspension according to item 19 or 20, wherein the nanosuspension has a pH in the range of 1 to 9, preferably a pH of 1.5 to 8.5, more preferably a pH of 2 to 8, even more preferably a pH of about 3.

22. Process for preparing a nanosuspension, the process comprising the following steps:
   (a) preparing a suspension of abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof in a liquid agent;
   (b) adding milling balls to the suspension of step (a) in order to obtain a slurry for nanomilling, and
   (c) nanomilling the slurry to provide a nanosuspension with a d(0.5) of less than 1000 nm.

23. Process for preparing a nanosuspension according to item 22, wherein the suspension of step (a) further comprises a stabilizing agent.
24. Process for preparing a nanosuspension according to item 22 or 23, further comprising (d) separating the resulting nanosuspension from the milling balls.

25. Process for preparing a nanosuspension according to item 24, further comprising (e) washing the milling balls with a liquid agent, separating the liquid agent from the milling balls and adding the separated liquid agent to the milled nanosuspension obtained in step (d).

26. Process for preparing a nanosuspension according to any of items 22-25, wherein prior to step (a) a solution of a liquid agent and a stabilizing agent is prepared.

27. Process for preparing a nanosuspension according to any of items 22-26, wherein an amount of 0.1 - 60 wt% of abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof is used, based on the weight/volume of the slurry used for nanomilling in step (c).

28. Process for preparing a nanosuspension according to any of items 22-27, wherein an amount of 5-90 wt% of milling balls is used, based on the weight/volume of the slurry used for nanomilling in step (c), with a diameter of the milling balls in the range of 0.1 - 5 mm.

29. Process for preparing a nanosuspension according to any of items 22-28, wherein the nanomilling of step (c) is carried out at a milling speed of 300-600 rpm for a milling time of 2-5 h, at room temperature.

30. Process for preparing a nanosuspension according to any of items 22-29, wherein the pH of the suspension of step (a) is adjusted to 1-9, preferably 1.5 to 8.5, more preferably 2 to 8, even more preferably preferably to 3.

31. Nanosuspension comprising particles of abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof having a d(0.5) of less than 1000 nm and an emulsifier.
32. Nanosuspension according to item 31 comprising particles of abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof having a d(0.9) of less than 1000 nm and an emulsifier.

33. Nanosuspension according to item 31 or 32, wherein the emulsifier is a cellulose derivative, a polymer or a surfactant.

34. Nanosuspension according to items 31-33, wherein the emulsifier is a non-ionic emulsifier.

35. Nanosuspension according to items 31-34, wherein the emulsifier is a cellulose derivative selected from the group consisting of hydroxypropyl methylcellulose (HPMC), methylcellulose, hydroxypropylcellulose (HPC), hydroxyethylcellulose, sodium carboxymethylcellulose.

36. Nanosuspension according to items 31-35, wherein the emulsifier is HPMC.

37. Nanosuspension according to items 31-36, wherein the weight ratio of abiraterone acetate to emulsifier ranges from 20:1 to 1:20, preferably from 10:1 to 1:10.

38. Nanosuspension according to items 31-37, wherein the nanosuspension is a stable nanosuspension.

39. Nanosuspension according to items 31-38, wherein the nanosuspension has a pH in the range of 1 to 9.

40. Nanosuspension according to items 31-39, wherein the nanosuspension comprises a liquid agent selected from the group consisting of water, an aqueous solution, an acid, a base, a polyethylene glycol, glycerol, propylene glycol and combinations thereof.
41. Nanosuspension according to item 40, wherein the liquid agent comprises water.

42. Nanosuspension according to item 40, wherein the liquid agent is a buffer.

43. Nanosuspension according to any of the items 31-42, wherein the abiraterone acetate is in the form of the free base or the mesylate salt.

44. Nanosuspension according to items 31-43 comprising:
   - 0.1-60 wt% of particles of abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof having a \( d(0.5) \) of less than 1000 nm;
   - 30-99 wt% of a liquid agent; and
   - 0.1-60 wt% of at least one emulsifier

45. Nanosuspension according to item 44, wherein the particles of abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof have a \( d(0.9) \) of less than 1000 nm, preferably less than 500 nm, more preferably less than 400 nm, most preferably less than 300 nm.

46. Process for preparing a nanosuspension, the process comprising the following steps:
   (a) preparing a suspension of abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof in a liquid agent;
   (b) adding milling balls to the suspension of step (a) in order to obtain a slurry for nanomilling, and
   (c) nanomilling the slurry to provide a nanosuspension with a \( d(0.5) \) of less than 1000 nm.

47. Process for preparing a nanosuspension according to item 46, wherein the suspension of step (a) further comprises an emulsifier.
48. Process for preparing a nanosuspension according to item 46 or 47, further comprising (d) separating the resulting nanosuspension from the milling balls.

49. Process for preparing a nanosuspension according to item 48 further comprising (e) washing the milling balls with a liquid agent, separating the liquid agent from the milling balls and adding the separated liquid agent to the milled nanosuspension obtained in step (d).

50. Process for preparing a nanosuspension according to any of items 46-49, wherein prior to step (a) a solution of a liquid agent and an emulsifier is prepared.

51. Process for preparing a nanosuspension according to any of items 46-50, wherein an amount of 0.1 -60 wt% of abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof is used, based on the weight/volume of the slurry used for nanomilling in step (c).

52. Process for preparing a nanosuspension according to any of items 46-51, wherein an amount of 5-90 wt% of milling balls is used, based on the weight/volume of the slurry used for nanomilling in step (c), with a diameter of the milling balls in the range of 0.1 -5 mm.

53. Process for preparing a nanosuspension according to any of items 46-52, wherein the nanomilling of step (c) is carried out at a milling speed of 300-600 rpm for a milling time of 2-5 h, at room temperature.

54. Process for preparing a nanosuspension according to any of items 46-53, wherein the pH of the suspension of step (a) is adjusted to 1-9, preferably 1.5 to 8.5, more preferably 2 to 8, even more preferably preferably to 3.

55. Pharmaceutical composition comprising a nanosuspension according to items 1-21 or items 31- 45, a concentrated nanosuspension derived thereof or the solid components thereof.
56. Pharmaceutical composition according to item 55, wherein the composition comprises a redispersing agent selected from the group consisting of reducing and non-reducing sugars and sugar alcohols.

57. Pharmaceutical composition according to item 55 or 56, wherein the composition further comprises one or more excipients selected from fillers, diluents, lubricants, binders, granulating aids, disintegrating agents, colorants, flavoring agents, sweeteners, glidants, preservatives, precipitation inhibitors or buffers.

58. Process for preparing a pharmaceutical composition comprising nanoparticulate abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof comprising the following steps:

(a) providing a nanosuspension according to any of items 1-21 or items 31-45, preparing a nanosuspension according to the process of any of items 22-30 or items 46-54;

(b) at least partly removing the liquid agent from the nanosuspension, in order to obtain a concentrated nanosuspension or solid; and

(c) performing at least one additional process step selected from grinding, sieving, mixing, roller compaction, screening, granulating, tableting or a combination thereof with the obtained concentrated nanosuspension or solid.

59. Process for preparing a pharmaceutical composition according to item 58, wherein prior to step (b) or prior to step (c) at least one redispersing agent selected from the group consisting of reducing and non-reducing sugars and sugar alcohols is added to said nanosuspension.

60. Process for preparing a pharmaceutical composition according to item 58 or 59, wherein the weight ratio of redispersing agent and abiraterone acetate is from 10:1 to 1:10, preferably 1:1.

61. Pharmaceutical composition comprising nanoparticulate abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof for use in the treatment of cancer, wherein the composition provides:

(a) min 6% of dose dissolved from 250 mg of abiraterone acetate in a dosage
form in 45 min, measured by USP paddle apparatus at 50 RPM in 900 ml of Fassif media;
(b) min 30% of dose dissolved from 250 mg of abiraterone acetate in a dosage form in 45 min, measured by USP paddle apparatus at 50 RPM in 900 ml of Fassif media;
(c) ratio between AUCt values for the dosage form disclosed in this invention versus Zytiga® higher than 1.1, higher than 1.2, higher than 1.3, after single dose administration to healthy human subjects;
   ratio between Cmax values for the dosage form disclosed in this invention versus Zytiga® higher than 1.1, higher than 1.2, higher than 1.3, after single dose administration to healthy human subjects.

62. Pharmaceutical composition comprising a nanosuspension according to any of items 1-21 or 31-45, prepared according to the process of any of items 22-30 or 46-54 for use in the treatment of cancer, preferably metastatic prostate cancer.
Claims

1. Nanosuspension comprising particles of abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof having a d(0.5) of less than 1000 nm.

2. Nanosuspension according to claim 1 comprising at least one stabilizing agent.

3. Nanosuspension according to claim 2, wherein the stabilizing agent is a surface modifying agent or/and a buffer.

4. Nanosuspension according to claim 3, wherein the surface modifying agent is a cellulose derivative, a polymer or a surfactant.

5. Nanosuspension according to claim 3 or 4, wherein the surface modifying agent is a cellulose derivative selected from the group consisting of hydroxypropyl methylcellulose (HPMC), methylcellulose, hydroxypropylcellulose (HPC), hydroxyethylcellulose, sodium carboxymethylcellulose.

6. Nanosuspension according to any of claims 3-5, wherein the surface modifying agent is HPMC.

7. Nanosuspension according to claim 3 or 4, wherein the surface modifying agent is a surfactant selected from the group consisting of polyoxyethylene products of hydrogenated vegetable oils, polyoxyethylated castor oils or polyethoxylated hydrogenated castor oil, polyoxyethylene-sorbitan-fatty acid esters, polyoxyethylene castor oil derivatives, sorbitan esters, sucrose esters, polyoxamers, poloxamers, polyglycolyzed glycerides (as caprylocaproyl macrogol glyceride (Labrasol), linoleaoyl macrogol glycerides (Labrafil), polyglyceryl oleate (Plurol)), gelucires, sodium dodecyl sulfate (SDS), sodium cholate, sodium glycolcholate, sodium taurocholate, saccharose monostearate, lecithin, dioctyl sodium sulfosuccinate or a combination thereof.
8. Nanosuspension according to claim 2 or 3, wherein the stabilizing agent is a buffer providing a pH in the range of 1 to 9.

9. Nanosuspension according to any of the previous claims, wherein the nanosuspension has a pH in the range of 1 to 9.

10. Nanosuspension according to any of the previous claims, wherein the nanosuspension comprises a liquid agent selected from the group consisting of water, an aqueous solution, an acid, a base, a polyethylene glycol, glycerol, propylene glycol and combinations thereof.

11. Nanosuspension according to any of claims 1-10 comprising:
   - 0.1-60 wt% of particles of abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof having a d(0.5) of less than 1000 nm;
   - 30-99 wt% of a liquid agent; and
   - 0.1-60 wt% of at least one stabilizing agent.

12. Process for preparing a nanosuspension, the process comprising the following steps:
   (a) preparing a suspension of abiraterone acetate or a pharmaceutically acceptable salt, hydrate or solvate thereof in a liquid agent;
   (b) adding milling balls to the suspension of step (a) in order to obtain a slurry for nanomilling, and
   (c) nanomilling the slurry to provide a nanosuspension with a d(0.5) of less than 1000 nm.

13. Process for preparing a nanosuspension according to claim 12, wherein the suspension of step (a) further comprises a stabilizing agent.

14. Pharmaceutical composition comprising a nanosuspension according to claims 1-11 or a concentrated nanosuspension derived thereof or the solid components thereof.
15. Pharmaceutical composition according to claim 14, wherein the composition comprises a redispersing agent selected from the group consisting of reducing and non-reducing sugars and sugar alcohols.
Figure 1

Increase of abiraterone acetate impurities (%) at 40°C after 1 month

Zytiga® 250 mg
- 0.22
- 0.06
- 0.35
- 0
- 5.63
- 0.09
- 0.36
- 0.27
- 1.01

Increase of abiraterone acetate impurities (%) at 60°C after 7 days

Zytiga® 250 mg
- 0.93
- 0.08
- 0.37
- 0.05
- 0.45
- 0.00
- 0.01
- 0.02
- 13.66
- 0.13
- 0.02
- 0.72
- 0.10
- 0.12
- 0.00
- 2.28
- 2.87
- 9.96
Figure 2
A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/16 A61K9/20 A61K31/58
ADD.
According to International Patent Classification (IPC) 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

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<th>Relevant to claim No.</th>
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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) on which 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
I* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
S* document member of the same patent family

Date of the actual completion of the international search 1 October 2013
Date of mailing of the international search report 08/10/2013

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