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(54) Title: STABLE PHARMACEUTICAL COMPOSITIONS COMPRISING ABIRATERONE ACETATE AND PROCESS FOR THE PREPARATION THEREOF

(57) Abstract: The present invention relates to a safe manufacturing process for the preparation of stable pharmaceutical compositions comprising abiraterone acetate or pharmaceutically acceptable salts, hydrates or solvates thereof, and to the use of said compositions in the treatment of cancer.

STABLE PHARMACEUTICAL COMPOSITIONS COMPRISING ABIRATERONE ACETATE AND PROCESS FOR THE PREPARATION THEREOF

FIELD OF THE INVENTION

The present invention relates to a safe manufacturing process for the preparation of stable pharmaceutical compositions comprising abiraterone acetate or pharmaceutically acceptable salts, hydrates or solvates thereof, and to the use of said compositions in the treatment of cancer.

BACKGROUND OF THE INVENTION

Abiraterone is a selective inhibitor of CYP17A1, an enzyme complex, which manifests as two enzymes 17α-hydroxylase and C17,20-lyase. CYP17A1 is expressed in testicular, adrenal, and prostatic tumor tissues. Said enzyme complex catalyzes the conversion of pregnenolone and progesterone to their 17-α-hydroxy derivatives by its 17 α-hydroxylase activity, and the subsequent formation of dehydroepiandrosterone (DHEA) and androstenedione, by its C17,20-lyase activity. DHEA and androstenedione are precursors of testosterone, thus, the inhibition of CYP17A1 activity decreases circulating levels of testosterone and other androgens.

Abiraterone acetate is a white to off-white powder practically insoluble in aqueous media (pH range 2.0 to 12.9), very slightly soluble in 0.1N HCl solution and soluble to freely soluble in organic solvents. Abiraterone acetate is classified as a Class IV compound (low solubility and low permeability) according to the biopharmaceutical classification system (BCS).

According to the European regulatory classification criteria (Regulation (EC) No. 1272/2008) abiraterone acetate is a reproductive toxin. The risk of impaired fertility (R62) and the risk of harm to the unborn child (R63) is possible, as stated in the safety data sheet.

Abiraterone acetate was first approved by the FDA in April 2011 for the treatment of patients with metastatic castration-resistant prostate cancer (mCRPC), who had received prior chemotherapy. Abiraterone acetate was launched in the USA and in Europe by Johnson & Johnson under the trade name of Zytiga®.

Recent clinical trials proved, that abiraterone acetate is also useful in the treatment of advanced and metastatic breast cancer (Bonnefoi et. al *Annals of Oncology 27* (2016) 812-818).

The low solubility of abiraterone acetate in water is one of the factors leading to the low bioavailability of Zytiga®. Furthermore, it is not well absorbed over the intestinal mucosa, therefore a high variability of systemic exposure is expected *in vivo*. This means in consequence, that, from the daily dose of 1 g, only 10 % of the drug develops a therapeutic effect. Accordingly, high amount of high potency drug is required for the manufacture of the product, which requires particular care and attention to ensure the safety for those involved in the handling of the materials. High potency drugs are highly selective pharmacologically active ingredients that bind to specific receptors or enzymes and/or could cause cancer, mutations, developmental effects or reproductive toxicity at low doses. Therefore, either an active pharmaceutical ingredient (API) or a finished pharmaceutical composition requires special approaches in facility design, equipment selection, and manufacturing process to achieve the desired levels of containment and minimize operator exposure. Moreover, the manufacturing process must be designed to protect product quality and patient safety by preventing cross-contamination, and to protect the operators who participate in the manufacturing process by environmental, health, and safety controls.

The assessment report of Zytiga® (EMEA/H/C/002321) published by the European Medicines Agency discloses the composition and preparation of abiraterone drug product for use as a medicament treating metastatic advanced prostate cancer (castration resistant prostate cancer) in adult patients who have received prior chemotherapy. Abiraterone acetate tablets represent an immediate-release formulation for oral use packaged in high density polyethylene (HDPE) bottles of 120 tablets with polypropylene child resistant closure and foil induction seal. The excipients of Zytiga® are: lactose monohydrate and microcrystalline cellulose as diluents, croscarmellose sodium as a disintegrant, povidone as a binder, magnesium stearate as a lubricant, colloidal silicon dioxide as a glidant, and sodium lauryl sulfate as an anionic surfactant and wetting agent. The manufacture of the finished product involves conventional processes including (1) mixing, (2) granulation, (3) wet milling, (4) drying, (5) dry milling, (6) blending, (7) lubrication, (8) tablet compression, and (9) packaging.

Abiraterone molecule was first disclosed in the patent application **WO 93/20097 A1**. Other documents, e.g. **WO 95/09178 A1** and **WO 2006/021777 A1** disclose different routes for the synthesis of abiraterone acetate.

Pharmaceutically active salts of abiraterone acetate are known e.g. from **WO 2006/021777 A1** and from **WO 1993/020097A1**.

Abiraterone acetate salts are poorly soluble in the gastric environment, and the prior art teaches that micronisation of such compounds improves their bioavailability. On the other hand, it is difficult to handle the micronized active pharmaceutical substances during the manufacturing process, because it makes the active substance prone to agglomeration and sticking during the manufacturing process and storage, particularly in the case of high drug content (Chapter 1.5 – Biopharmaceutical importance of particle size; in..: Physicochemical Principles of Pharmacy: In Manufacture, Formulation and Clinical Use (Alexander T Florence, David Attwood) Pharmaceutical Press, 2016).

Moreover, due to the exceptionally high dose, the tablet size is larger than usual, thus, the improvement of the final product cannot be obtained by adding more excipients. There are several different difficulties during the production process, for example bad flow properties, unwanted agglomeration and sticking during granulation, and the necessity of wet milling before the drying step. Furthermore, it is difficult to granulate high volumes of micronized active substances, because excipients with higher density sediment during the process, which cause problems during the compression, and the inhomogeneous distribution of the excipients decrease the dissolution properties of the tablets. Fluid granulation is not applicable, because abiraterone acetate is a non-fluidizable material. High shear granulation is more suitable, nevertheless the formation of lumps or agglomeration is probable during this process. It is difficult to grind these agglomerates after the drying step, and the agglomeration causes local inhomogeneity; therefore the originator applied a wet milling step before drying, which makes the process unenclosed, dustier and longer. Due to the toxicology profile of abiraterone acetate this process is disadvantageous, uneconomical and hazardous to the operators.

WO 2016/001208 A1 discloses stable pharmaceutical compositions in the form of immediate release tablets comprising abiraterone acetate, characterized by improved solubility resulting in good bioavailability.

WO 2014/009437 A1 discloses a process for the preparation of a pharmaceutical composition, in which abiraterone acetate is stabilized against oxidative degradation by the addition of at least one antioxidant, wherein the antioxidant is selected from the group consisting of butylated hydroxytoluene, butylated hydroxyanisole, ascorbyl palmitate, propyl gallate, alpha tocopherol or any mixtures thereof in an amount of 0.0001 % to 5 % by weight. Furthermore, the product is stabilized against oxidative degradation by using oxygen barrier packaging material, and by preparation under inert atmosphere.

However, the use of antioxidants in pharmaceutical compositions is not advantageous, as the regulatory requirements increase the cost of the production and patients take unnecessary additives. According to the EMEA CPMP/QWP/419/03 guideline, the application for the registration should contain reason for inclusion for each antioxidant, proof of efficacy, the method of control in finished product, details of the labelling of the finished product and safety information.

Thus, the prior art discloses several different mechanisms to obtain pharmaceutical compositions with improved quality compared to Zytiga® tablets by different methods. Most of the prior art relates to the improvement of bioavailability in order to decrease the daily dose. However, products with improved bioavailability are not equivalent to the registered product, thus, this development is not desirable for the patients, as it requires long-term clinical trials, which prolongs the time of launching the product on the market. Moreover, biologically different formulations can cause undesirable adverse effects during the treatment, because of the much higher bioavailability compared to Zytiga®. Other prior developments aimed to improve the stability of the product in different ways, for example by manufacturing the product under inert atmosphere, and by the addition of at least one antioxidant, or by using oxygen barrier packaging material. These technological achievements make the new product uneconomic and/or *in vivo* dissimilar, therefore, they do not facilitate the access to an economically beneficial and *in vivo* equivalent therapy.

Considering the disadvantages of the known methods, there is a need to develop an improved and safer manufacturing process to decrease the harms and costs of the production, in order to obtain a product which is both *in vitro and in vivo* similar to Zytiga® tablets.

Moreover, it is desirable to provide a new manufacturing method for a stable product containing abiraterone acetate, in which cross-contamination and the exposure of the operator is minimized.

Therefore it was an object of the present invention to provide a manufacturing process for a pharmaceutical composition comprising abiraterone acetate or pharmaceutically acceptable salts, hydrates or solvates thereof, which exhibits an increased manufacturability and stability against degradation, in particular against oxidative degradation without the addition of special excipients.

It is further desirable, to provide a pharmaceutical composition with improved stability, which can be stored and used at room temperature for more than two years, and which can be stored in climate zones characterized by high temperature or high temperature and high humidity.

Additionally, there is also a need to provide simple preparation methods that can be scaled to industrial level, and the manufacture has to be economically feasible for a long term.

Consequently, the objective of the present invention is to provide a safe and economic manufacturing process for an oral pharmaceutical composition comprising abiraterone acetate or its pharmaceutically acceptable salts, hydrates and solvates with at least one organic solvent suitable for granulation of micronized active substance preventing the granules from forming lumps during the manufacturing process, wherein the composition is suitable for geographic regions with high relative humidity or elevated temperatures and *in vitro* and *in vivo* similar to Zytiga® tablets.

BRIEF DESCRIPTION OF THE DRAWINGS

An exemplary embodiment of the present invention is illustrated by way of example in the accompanying drawings in which like reference numbers indicate the same or similar elements and in which:

Figure 1 illustrates the comparative dissolution profile of Zytiga® tablets and tablets manufactured by wet granulation based on the process described in the EMEA/H/C/002321 public assessment report.

Figure 2 illustrates the comparative dissolution profile of Zytiga® tablets and tablets manufactured by the manufacturing process of the present invention.

Figure 3 illustrates the agglomerates and local inhomogeneity of the granules manufactured by wet granulation based on the process described in the EMEA/H/C/002321 public assessment report.

SUMMARY OF THE INVENTION

The present invention relates to a stable pharmaceutical composition with improved physicochemical characteristics and improved impurity profile comprising abiraterone acetate or pharmaceutically acceptable salts, hydrates or solvates thereof, and at least one pharmaceutically acceptable excipient; wherein said composition possesses the following features:

a) an increased stability compared to Zytiga;
b) the same *in vitro* behaviour as Zytiga.

In a further aspect the present invention provides a process for the preparation of a stable pharmaceutical composition comprising abiraterone acetate or pharmaceutically acceptable salts, hydrates or solvates thereof, said process comprising the steps of: high shear mixing and granulation with a pharmaceutically acceptable solvent or a mixture of solvents with a dielectric constant of about 20 to about 80; drying; blending; and direct compression into tablets.

In a further aspect the present invention provides a pharmaceutical composition comprising abiraterone acetate or pharmaceutically acceptable salts, hydrates or solvates thereof obtained by a process comprising the steps of: high

shear mixing and granulation with a pharmaceutically acceptable solvent or a mixture of solvents with a dielectric constant of about 20 to about 80; drying; blending; and direct compression into tablets.

In a further aspect the present invention provides a pharmaceutical composition with improved physicochemical characteristics and improved impurity profile comprising abiraterone acetate or pharmaceutically acceptable salts hydrates or solvates thereof, and at least one pharmaceutically acceptable excipient; wherein said composition possesses one or more of the following features:

a) an increased stability compared to Zytiga;
b) the same *in vitro* behaviour as Zytiga,
for use in the treatment of early stage or metastatic prostate cancer or breast cancer.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a stable pharmaceutical composition with improved physicochemical characteristics and improved impurity profile comprising abiraterone acetate or pharmaceutically acceptable salts, hydrates or solvates thereof, and at least one pharmaceutically acceptable excipient; wherein said composition possesses one or more of the following features:

a) it has an increased stability compared to Zytiga;
b) it has the same *in vitro* behaviour as Zytiga.

In one embodiment, the pharmaceutical composition has a lower abiraterone acetate related impurity level than Zytiga.

In another embodiment, the pharmaceutical composition has a lower abiraterone acetate related impurity level than Zytiga, wherein, the abiraterone acetate related impurities are selected from the group of 7-ketoabiraterone acetate, α-epoxyabiraterone acetate, ß-epoxyabiraterone acetate and abiraterone.

The USP (United States Pharmacopeia) acceptance criteria of impurities for abiraterone acetate is shown in Table 1.

Name	Acceptance Criteria NMT (%)
7-ketoabiraterone-acetate	0.50
abiraterone	0.40
α-epoxyabiraterone-acetate (%)	0.80
β-epoxyabiraterone-acetate (%)	0.80
abiraterone acetate related unspecified impurity (%)	0.20
abiraterone acetate related total impurity (%)	2.0

Table 1: The USP acceptance criteria of impurities for abiraterone acetate

In another embodiment the 7-ketoabiraterone acetate impurity level of the composition is about zero to about 0.5 % within 30 months of storage of the final pharmaceutical composition at 25 °C/65 % RH or 30 °C/65 % RH or 30 °C/75 % RH.

In another embodiment the abiraterone impurity level of the composition is about zero to about 0.4 % within 30 months of storage of the final pharmaceutical composition at 25 °C/65 % RH or 30 °C/65 % RH or 30 °C/75 % RH.

In another embodiment the α-epoxyabiraterone acetate impurity level is about zero to about 0.8 % within 30 months of storage of the final pharmaceutical composition at 25 °C/65 % RH or 30 °C/65 % RH or 30 °C/75 % RH.

In another embodiment the ß-epoxyabiraterone acetate impurity level is about zero to about 0.8 % within 30 months of storage of the final pharmaceutical composition at 25 °C/65 % RH or 30 °C/65 % RH or 30 °C/75 % RH.

In another embodiment the abiraterone acetate related unspecified impurity level is about zero to about 0.2 % within 30 months of storage of the final pharmaceutical composition at 25 °C/65 % RH or 30 °C/65 % RH or 30 °C/75 % RH.

In another embodiment the abiraterone acetate related total impurity level is about zero to about 2.0 % within 30 months of storage of the final pharmaceutical composition at 25 °C/65 % RH or 30 °C/65 % RH or 30 °C/75 % RH.

In another embodiment the 7-ketoabiraterone acetate impurity level of the composition is about zero to about 0.5 % within 36 months of storage of the final pharmaceutical composition at 25 °C/65 % RH or 30 °C/65 % RH or 30 °C/75 % RH.

In another embodiment the abiraterone impurity level of the composition is about zero to about 0.4 % within 36 months of storage of the final pharmaceutical composition at 25 °C/65 % RH or 30 °C/65 % RH or 30 °C/75 % RH.

In another embodiment the α-epoxyabiraterone acetate impurity level is about zero to about 0.8 % within 36 months of storage of the final pharmaceutical composition at 25 °C/65 % RH or 30 °C/65 % RH or 30 °C/75 % RH.

In another embodiment the ß-epoxyabiraterone acetate impurity level is about zero to about 0.8 % within 36 months of storage of the final pharmaceutical composition at 25 °C/65 % RH or 30 °C/65 % RH or 30 °C/75 % RH.

In another embodiment the abiraterone acetate related unspecified impurity level is about zero to about 0.2 % within 36 months of storage of the final pharmaceutical composition at 25 °C/65 % RH or 30 °C/65 % RH or 30 °C/75 % RH.

In another embodiment the abiraterone acetate related total impurity level is about zero to about 2.0 % within 36 months of storage of the final pharmaceutical composition at 25 °C/65 % RH or 30 °C/65 % RH or 30 °C/75 % RH.

In another embodiment, the pharmaceutical composition is stabilized against oxidative degradation without the use of a special package and/or storage conditions.

In another embodiment, the stable pharmaceutical compositions are suitable for oral administration.

In a further aspect, the present invention relates to the process for the preparation of a stable pharmaceutical composition with improved stability profile comprising abiraterone acetate or pharmaceutically acceptable salts, hydrates, or solvates thereof, comprising the steps of: high shear mixing and granulation with a pharmaceutically acceptable solvent or a mixture of solvents with a dielectric constant of about 20 to about 80; drying; blending; and direct compression into tablets.

In one embodiment, the process is performed in a high-shear granulator without wet milling.

In another embodiment, the process comprises the steps of:

(1) adding abiraterone acetate, lactose monohydrate, microcrystalline cellulose, povidone, sodium lauryl sulphate and croscarmellose sodium to the high shear mixer and the blend is mixed;
(2) preparing the solvent or solvent mixture with a dielectric constant of 20-80;
(3) adding the granulation solution obtained in step (2) to the blend obtained in step (1) and kneading;
(4) drying the granules obtained in step (3) in a high shear granulator;
(5) blending colloidal silicon dioxide with the granules obtained in step (4) in a blender and/or a high shear granulator;
(6) sieving the granules obtained in step (5);
(7) sieving and blending the lubricant with the granules obtained in step (6);
(8) compressing the final blend into tablets using a tablet press machine to obtain tablets.

In another embodiment, the pharmaceutically acceptable solvents are selected from the group of acetone, acetonitrile, dimethyl-sulfoxide, ethyl acetate, ethanol, isopropanol, n-propanol, methanol, methylene chloride, tetrahydrofuran, and water or any mixtures thereof.

In another embodiment, the dielectric constant of the applied solvent or solvent mixture is about 20 to about 80.

In another embodiment, the dielectric constant of the applied solvent or solvent mixture is about 25 to about 75.

In another embodiment, the dielectric constant of the applied solvent or solvent mixture is about 25 to about 70.

In another embodiment, the dielectric constant of the applied solvent or solvent mixture is about 25 to about 65.

In another embodiment, the dielectric constant of the applied solvent or solvent mixture is about 25 to about 60.

In another embodiment, the dielectric constant of the applied solvent or solvent mixture is about 25 to about 55.

In another embodiment, the dielectric constant of the applied solvent or solvent mixture is about 30 to about 55.

In another embodiment, the dielectric constant of the applied solvent or solvent mixture is about 30 to about 50.

In one embodiment, the pharmaceutically acceptable solvent mixture comprises purified water and at least one other pharmaceutically acceptable solvent selected from the group of acetone, acetonitrile, dimethyl-sulfoxide, ethyl acetate, ethanol, isopropanol, n-propanol, methanol, methylene chloride, and tetrahydrofuran.

In another embodiment, the pharmaceutically acceptable solvent mixture comprising water and at least one other pharmaceutically acceptable solvent, is characterized by a ratio of 6:1 % w/w, and a dielectric constant of approximately 65-75.

In another embodiment, the pharmaceutically acceptable solvent mixture comprising water and at least one other pharmaceutically acceptable solvent, is characterized by a ratio of 4:1 % w/w, and a dielectric constant of approximately 60-70.

In another embodiment, the pharmaceutically acceptable solvent mixture comprising water and at least one other pharmaceutically acceptable solvent, is characterized by a ratio of 2:1 % w/w, and a dielectric constant of approximately 55-65.

In another embodiment, the pharmaceutically acceptable solvent mixture comprising water and at least one other pharmaceutically acceptable solvent, is characterized by a ratio of 1:1 % w/w, and a dielectric constant of approximately 45-55.

In another embodiment, the pharmaceutically acceptable solvent mixture comprising water and at least one other pharmaceutically acceptable solvent, is characterized by a ratio of 1:2 % w/w, and a dielectric constant of approximately 35-45.

In another embodiment, the pharmaceutically acceptable solvent mixture comprising water and at least one other pharmaceutically acceptable solvent, is characterized by a ratio of 1:4 % w/w, and a dielectric constant of approximately 25-35.

In one embodiment, the granules obtained in step (3) are dried in a high shear granulator at a temperature of approximately 5 to 50 °C.

In another embodiment, the granules obtained in step (3) are dried in a high shear granulator at a temperature of approximately 5 to 45 °C.

In another embodiment, the granules obtained in step (3) are dried in a high shear granulator at a temperature of approximately 5 to 40 °C.

In another embodiment, the granules obtained in step (3) are dried in a high shear granulator at a temperature of approximately 5 to 35 °C.

In another embodiment, the granules obtained in step (3) are dried in a high shear granulator at a temperature of approximately 5 to 30 °C.

In one embodiment, the granules obtained in step (3) are dried in a high shear granulator under vacuum.

In one embodiment, the granules obtained in step (3) are dried in a high shear granulator under vacuum and/or using microwave energy and/or bowl heating.

In a further aspect, the present invention relates to a process for the preparation of pharmaceutical compositions, in which abiraterone acetate or

pharmaceutically acceptable salts, hydrates or solvates thereof is manufactured in an economical and safe way.

In one embodiment, the granules remain in the high shear equipment until the end of the process.

In a further aspect, the present invention provides a pharmaceutical composition with improved physicochemical characteristics and improved impurity profile comprising abiraterone acetate or pharmaceutically acceptable salts hydrates or solvates thereof, and at least one pharmaceutically acceptable excipient; wherein said composition possesses the following features:

a) an increased stability compared to Zytiga;
b) the same *in vitro* behaviour as Zytiga,
for use in the treatment of cancer, preferably early stage or metastatic prostate cancer or breast cancer.

In order to find a suitable manufacturing process for micronized abiraterone acetate and its pharmaceutically acceptable salts, hydrates and solvates a number of processes have been carried out and evaluated.

Taking into account the characteristics of abiraterone, the skilled person would expect that use of the manufacturing process described in the public assessment report of Zytiga® (EMEA/H/C/002321) is essential to achieve an *in vitro* and *in vivo* equivalent product.

Contrary to this, it has unexpectedly been found, that the difficult process used by the originator is completely unnecessary, and a simpler manufacturing process with the use of a solvent or solvent mixture with a dielectric constant of 20-80, and without using any special excipients is able to provide an *in vitro* equivalent and stable product. The tablet without any antioxidants and/or inert gas flow during the manufacturing process shows the same *in vitro* dissolution characteristics, however the impurity profile of the product stored under stressed conditions is much better than Zytiga® tablets.

It has been found, that the dielectric constant of the solvent or solvent mixture is critical during the granulation of abiraterone acetate, as it has the tendency to separate from polar granulating solvents. Therefore – especially in the

case of micronized abiraterone acetate – agglomeration occurs during solvent feeding, which deteriorates the granulation process and causes local inhomogeneity. Granulating with solvents or solvent mixtures with too low dielectric constants are also not preferable, because of their inability to dissolve the granulating polymer (e.g., PVP, HPMC, etc.). Improper dissolution of the granulating polymer and the improper wetting of the polar, hydrophilic excipient leads to incomplete granulation, which causes problems in the later phases of the tableting process. On the other hand, the use of solvents and solvent mixtures with low dielectric constant cause incomplete granule formation, decrease the adhesive properties of particles and cause difficulties and sticking during compression, because a significant part of micronized abiraterone acetate does not participate in the granule formation. Thus, the undesirable agglomeration during granulation, and sticking during compression can be avoided by using a solvent or solvent mixture with an appropriate dielectric constant.

Moreover, the use of a solvent or solvent mixture with a dielectric constant of 20-80 prevents lump formation within the granules, thus, the wet milling step used by the originator is not required.

It also leads to a closed process, as the drying step can be performed in the high shear granulator's vessel. Therefore, this simpler manufacturing process protects the product quality and patient safety by preventing cross-contamination; and by protecting the operators who participate in the manufacturing process through environmental, health, and safety controls.

Moreover, the oxidative degradation of abiraterone acetate is prevented by the manufacturing process, therefore, the use of any antioxidants in the pharmaceutical compositions of the present invention is not necessary. Furthermore, there is no need to manufacture the pharmaceutical compositions of the present invention under inert gas atmosphere, and there is no need to use oxygen scavengers/absorbers in the package.

This simple manufacturing process without wet milling and drying in the high shear granulator's vessel provides favourable stability profile, as it is able to increase the shelf life of the product, and the obtained products can be stored in Zone IV climate conditions with a longer shelf life as well.

The pharmaceutical compositions of the present invention maintain their stability in regions with high relative humidity and/or elevated temperatures for more than two years, without the addition of at least one antioxidant or without the preparation under inert gas atmosphere, and maintain their stability in regions with high relative humidity and/or elevated temperatures for more than two years.

"**Reproductive toxicity**" includes adverse effects on sexual function and fertility in adult males and females, as well as developmental toxicity in the offspring.

The category "**reproductive hazard is category 3 Reproductive toxicants (R62)**", includes substances which cause concern for human fertility, generally on the basis of results in appropriate animal studies which provide sufficient evidence to cause a strong suspicion of impaired fertility in the absence of toxic effects, or evidence of impaired fertility occurring at around the same dose levels as other toxic effects, but which is not a secondary non-specific consequence of the other toxic effects, but where the evidence is insufficient to place the substance in Category 2 (Regulation (EC) No 1272/2008).

The category "**reproductive hazard is category 3 - Reproductive toxicants (R63)**", includes substances which cause concern for humans owing to possible developmental toxic effects, generally on the basis of results in appropriate animal studies which provide sufficient evidence to cause a strong suspicion of developmental toxicity in the absence of signs of marked maternal toxicity, or at around the same dose levels as other toxic effects but which are not a secondary non-specific consequence of the other toxic effects, but where the evidence is insufficient to place the substance in Category 2 (Regulation (EC) No 1272/2008).

The "**Biopharmaceutics Classification System**" is a system to differentiate the drugs on the basis of their solubility and permeability. This system restricts the prediction using the parameters solubility and intestinal permeability. The solubility classification is based on a United States Pharmacopoeia (USP) aperture. The intestinal permeability classification is based on a comparison to the intravenous injection. Class IV compounds have low permeability and low solubility, thus they have poor bioavailability. Usually they are not well absorbed over the intestinal mucosa and a high variability is expected.

"**Micronisation**" is the process of reducing the average diameter of a solid material's particles. Traditional techniques for micronisation focus on mechanical means, such as milling and grinding. Modern techniques make use of the properties of supercritical fluids and manipulate the principles of solubility. The term micronisation usually refers to the reduction of average particle diameters to the micrometer range, but can also describe further reduction to the nanometer scale.

The term "**pharmaceutical composition**" as used herein refers to a finished dosage formulation, which contains the active agent abiraterone acetate or pharmaceutically acceptable salts, hydrates or solvates thereof and in the form in which it can be marketed.

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

The term „**inert gas**" is a gas which does not undergo chemical reactions under a set of given conditions, e.g. nitrogen or argon.

The term "**pharmaceutically acceptable**" describes an ingredient that is useful in preparing a pharmaceutical composition, is generally safe, non-toxic and neither biologically nor otherwise undesirable, and includes those acceptable for human pharmaceutical use.

The term "**salt**" means an ionic compound that can be formed by the neutralization reaction of an acid and a base. The salts include, but not limited to tartaric, acetic, malic, methanesulfonic, trifluoromethanesulfonic, ditoluoyl tartaric, hydrochloric, sulphuric, benzenesulfonic, p-toluenesulfonic and fumaric acid salts.

The term "**hydrate**" means non-covalent combinations between water and solute.

The term "**solvate**" means non-covalent combinations between solvent and solute. Solvents include, but are not limited to, ethanol, acetone, 2-propanol, acetonitrile and tetrahydrofuran.

The term „**solvent**" means an inorganic or an organic liquid used as a vehicle for the preparation of solutions or suspensions in the synthesis of a new drug

substance or the manufacture of a new drug product (ICH Topic Q 6 A, CPMP/ICH/367/96).

The term **"dielectric constant"** (DC) or relative permittivity is a property of materials. It is associated with the polarity of the solvent in the case of liquid materials. Usually, the higher the dielectric constant of a solvent the more polar it is. For example, water is very polar and has a dielectric constant at room temperature around 80, while n-hexane is non-polar and has a dielectric constant around 2.

The term "**release testing**" means a series of tests to ensure active ingredients are free of contaminants, is present in an appropriate amount and demonstrate compliance with regulatory guidelines.

The term "**shelf life**" means the length of time that a pharmaceutical product retains the functionality, effectiveness and safety.

The term "**acceptance criteria**" means numerical limits, ranges, or other suitable measures for acceptance of the results of analytical procedures (ICH Topic Q 6 A, CPMP/ICH/367/96).

The term "**degradation product**" means a molecule resulting from a chemical change in the drug molecule brought about over time and/or by the action of e.g., light, temperature, pH, water, or by reaction with an excipient and/or the immediate container/closure system. Also called decomposition product (ICH Topic Q 6 A, CPMP/ICH/367/96).

The term "**impurity**" means any component of the drug substance which is not the chemical entity defined as the drug substance and any component of the pharmaceutical composition which is not the chemical entity defined as the drug substance or an excipient in the pharmaceutical composition (ICH Topic Q 6 A, CPMP/ICH/367/96).

The term "**room temperature**" denotes a temperature in the range from 20°C to 25°C.

The term "**quantitation limit**" of an individual analytical procedure is the lowest amount of analyte in a sample which can be quantitatively determined with

suitable precision and accuracy. The quantitation limit is a parameter of quantitative assays for low levels of compounds in sample matrices, and is used particularly for the determination of impurities and/or degradation products (ICH Topic Q2(R1), CPMP/ICH281/95).

EXAMPLES

The invention is further explained in the following Examples. It should be understood that the Examples are given by way of illustration only. From the above discussion and the Examples, one skilled in the art can ascertain the essential characteristics of the invention, and without departing from the spirit and scope thereof, can make various changes and modifications to adapt the invention to various uses and conditions. As a result, the invention is not limited by the illustrative examples set forth herein below but rather defined by the claims appended hereto.

We have developed a safe and economical manufacturing process for the production of a product, which is essentially similar to the reference product, Zytiga® (Janssen-Cilag International N.V., Beerse, Belgium) containing 250 mg abiraterone acetate as an active ingredient. Furthermore, the stability of abiraterone product manufactured by this new, improved manufacturing process is much better than the stability of Zytiga®.

The qualitative and quantitative composition of Zytiga® 250 mg tablets is shown in Table 2:

Ingredients	Amount (mg)
Abirateron acetate	250.00
Lactose monohydrate	198.65
Microcrystalline cellulose	141.22
Croscarmellose sodium	42.90
Povidon K29/K32	35.75
Sodium lauryl sulfate	28.60
Colloidal silicon dioxide	7.15
Magnesium stearate	10.73
Σ	715

Table 2: The qualitative and quantitative composition of the Zytiga® 250 mg tablet

The qualitative and quantitative composition of the tablets of the present invention is shown in Table 3:

Ingredients	Amount
Abiraterone acetate	250 mg
Lactose monohydrate	15-30 % w/w
Microcrystalline cellulose	15-30 % w/w
Croscarmellose sodium	5-10 % w/w
Povidone	2-8 % w/w
Sodium lauryl sulfate	2-6 % w/w
Colloidal silicone dioxide	0.5-2 % w/w
Magnesium stearate	1-2 % w/w

Table 3: composition of the formulation containing micronized abiraterone acetate

Example 1: Granulation of abiraterone acetate with purified water

It was not possible to granulate the micronized abiraterone acetate in one step with an aqueous solution in a high shear granulator due to heavy agglomeration (see Figure 3), therefore, an alternative process was performed to investigate the feasibility of aqueous granulation based on the assessment report of Zytiga®. During the process the micronized abiraterone acetate agglomerates, because string bonds form between the material's particles, which causes serious operating difficulties.

The process comprises the steps of:

(1) Abiraterone acetate, lactose monohydrate, microcrystalline cellulose, sodium lauryl sulphate and croscarmellose sodium are mixed to form a homogenous blend;

(2) aqueous povidone solution is prepared;

(3) the granulation solution prepared in step (2) is slowly added to the blend of step (1) and the blend is granulated to form a wet mass;
(4) the wet mass is passed through a sieve, dried, and regranulated after drying;
(5) the dried granules are homogenously mixed with sieved colloidal silicon dioxide, and lubricated with magnesium stearate to prepare the final blend;
(6) the final blend is compressed into tablets with a tableting press equipment.

The product manufactured by the above described manufacturing process exhibits an *in vitro* release profile, wherein on average less than about 80 % of the total abiraterone acetate is released within 30 minutes in a standard dissolution test. In contrast, the Zytiga® tablet exhibits a faster *in vitro* release profile wherein, on average more than about 80 % of the total abiraterone acetate is released within 45 minutes in a standard dissolution test.

Dissolution method: Apparatus nr. 2 (paddle); Medium - 900 ml pH 4.5 phosphate buffer + 0.25 % sodium lauryl sulphate (SLS) – Run time 8 hours; Temperature: 37 ± 0.5 °C; Stirring rate: 50 rpm.

	Dissolution (%)/minutes				
	5	10	15	30	45
Tablet 5215	11	16	22	58	94
Zytiga®	21	37	55	90	97

Table 4: Dissolution test results of Tablet 5215 and Zytiga® tablet

Example 2: The effect of the granulation solution's composition on the final product

The granulation solution and the manufacturing process were modified in order to avoid the unwanted agglomeration and slow dissolution. The immediate release composition (see Table 3) was prepared by mixing abiraterone acetate with suitable excipients, high shear granulation with water miscible solvents and/or a mixture of water miscible solvents, vacuum and/or microwave drying and/or bowl heating, regranulation, homogenization with the external phase and compression of the mixture to tablets.

Tablet	5639	5740	5741	5742	5743	5744
Amount of water (g)	15	20	10	15	10	20
Amount of ethanol (g)	30	40	20	30	40	20
Water/ethanol weight ratio	1:2	1:2	1:2	1:2	1:4	1:1
Dielectric constant (approximate value)	39	39	39	39	33	49

Table 5: different solvent compositions for the granulation of abiraterone product

The process comprises the steps of:

(1) Abiraterone acetate, lactose monohydrate, microcrystalline cellulose, sodium lauryl sulphate are mixed to form a homogenous blend;

(2) ethanol – water mixture is prepared, the dielectric constant of the mixture is approximately about 30 to about 50 (see table 5);

(3) the granulation liquid prepared in step (2) is slowly added to the blend of step (1) and the blend is granulated to form a wet mass;

(4) the wet mass is dried by using vacuum and microwave energy;

(5) the dried granules are regranulated by using a sieve;

(6) the granules are homogenously mixed with sieved colloidal silicon dioxide and croscarmellose sodium then lubricated with magnesium stearate to prepare the final blend;

(7) the final blend is compressed into tablets with a tableting press equipment.

The product manufactured by the above described manufacturing process exhibits an *in vitro* release profile wherein on average more than about 80 % of the total abiraterone acetate is released within 45 minutes in a standard dissolution test.

Dissolution method: Apparatus nr. 2 (paddle); Medium - 900 ml pH 4.5 phosphate buffer + 0.25 % SLS – Run time 8 hours; Temperature: 37 ± 0.5 °C; Stirring rate: 50 rpm.

	Dissolution (%)/minutes				
	5	10	15	30	45
Tablet 5740	8	23	38	68	85
Tablet 5741	10	31	47	77	88

Table 6: Dissolution test results of Tablet 5740 and 5741

Example 3: The effect of extra-granular position of the superdisintegrant

The process comprises the steps of:

(1) Abiraterone acetate, lactose monohydrate, microcrystalline cellulose, sodium lauryl sulphate are mixed to form a homogenous blend;

(2) 2:1 (w/w) ethanol – water mixture is prepared, the dielectric constant of the mixture is approximately 39;

(3) the granulation liquid prepared in step (2) is slowly added to the blend of step (1) and the blend is granulated to form a wet mass;

(4) the wet mass is dried by using vacuum and microwave energy;

(5) the dried granules are regranulated by using a sieve;

(6) the granules are homogenously mixed with sieved colloidal silicon dioxide and croscarmellose sodium then lubricated with magnesium stearate to prepare the final blend;

(7) the final blend is compressed into tablets with a tableting press equipment.

Dissolution method: Apparatus nr. 2 (paddle); Medium - 900 ml pH 4.5 phosphate buffer + 0.25 % SLS – Run time 8 hours; Temperature: 37 ± 0.5 °C; Stirring rate: 50 rpm.

	Dissolution (%)/minutes				
	5	10	15	30	45
Tablet 5741	10	31	47	77	88

Table 7: Dissolution test results of Tablet 5741

Example 4: The effect of intra-granular position of the superdisintegrant

The process comprises the steps of:

(1) Abiraterone acetate, lactose monohydrate, microcrystalline cellulose, sodium lauryl sulphate and croscarmellose sodium are mixed to form a homogenous blend;

(2) 2:1 (w/w) ethanol – water mixture is prepared, the dielectric constant of the mixture is approximately 60;

(3) the granulation liquid prepared in step (2) is slowly added to the blend of step (1) and the blend is granulated to form a wet mass;

(4) the wet mass is dried by using vacuum and microwave energy;
(5) the dried granules are regranulated by using a sieve;
(6) the granules are homogenously mixed with sieved colloidal silicon dioxide, then lubricated with magnesium stearate to prepare the final blend;
(7) the final blend is compressed into tablets with a tableting press equipment.

The product manufactured by the above described manufacturing process exhibits an *in vitro* release profile wherein on average more than about 80 % of the total abiraterone acetate is released within 45 minutes in a standard dissolution test.

Dissolution method: Apparatus nr. 2 (paddle); Medium – 900 ml pH 4.5 phosphate buffer + 0.25 % SLS – Run time 8 hours; Temperature: 37 ± 0.5 °C; Stirring rate: 50 rpm.

	Dissolution (%)/minutes				
	5	10	15	30	45
Tablet 5746	12	36	56	89	100

Table 8: Dissolution test results of Tablet 5746

Example 5: The effect of intra- and extra-granular position of the superdisintegrant

The process comprises the steps of:
(1) Abiraterone acetate, lactose monohydrate, microcrystalline cellulose, sodium lauryl sulphate and half amount croscarmellose sodium are mixed to form a homogenous blend;
(2) 2:1 (w/w) ethanol – water mixture is prepared, the dielectric constant of the mixture is approximately 60;
(3) the granulation liquid prepared in step (2) is slowly added to the blend of step (1) and the blend is granulated to form a wet mass;
(4) the wet mass is dried by using vacuum and microwave energy;
(5) the dried granules are regranulated by using a sieve;
(6) the granules are homogenously mixed with sieved colloidal silicon dioxide and the half amount of croscarmellose sodium, then lubricated with magnesium stearate to prepare the final blend;
(7) the final blend is compressed into tablets with a tableting press equipment.

The product manufactured by the above described manufacturing process exhibits an *in vitro* release profile wherein on average more than about 80 % of the total abiraterone acetate is released within 45 minutes in a standard dissolution test.

Dissolution method: Apparatus nr. 2 (paddle); Medium - 900 ml pH 4.5 phosphate buffer + 0.25 % SLS – Run time 8 hours; Temperature: 37 ± 0.5 °C; Stirring rate: 50 rpm.

	Dissolution (%)/minutes				
	5	10	15	30	45
Tablet 5748	15	40	60	94	100

Table 9: Dissolution test results of Tablet 5748

Example 6: Product dried using vacuum and microwave energy – Tablet 7683

The process comprises the steps of:

(1) Abiraterone acetate, lactose monohydrate, microcrystalline cellulose, sodium lauryl sulphate and croscarmellose sodium are mixed to form a homogenous blend;

(2) 2:1 (w/w) ethanol – water mixture is prepared, the dielectric constant of the mixture is approximately 60;

(3) the granulation liquid prepared in step (2) is slowly added to the blend of step (1) and the blend is granulated to form a wet mass;

(4) the wet mass is dried by using vacuum and microwave energy;

(5) the dried granules are mixed with colloidal silicon dioxide.;

(6) the blend is regranulated by using a roto-sieve;

(7) the granules are lubricated with magnesium stearate to prepare the final blend.

(8) the final blend is compressed into tablets with a tableting press equipment.

Example 7: Product dried by using vacuum and intense (60 °C) bowl heating – Tablet 7684

The process comprises the steps of:

(1) Abiraterone acetate, lactose monohydrate, microcrystalline cellulose, sodium lauryl sulphate and croscarmellose sodium are mixed to form a homogenous blend;

(2) 2:1 (w/w) ethanol – water mixture is prepared, the dielectric constant of the mixture is approximately 60;

(3) the granulation liquid prepared in step (2) is slowly added to the blend of step (1) and the blend is granulated to form a wet mass;

(4) the wet mass is dried by using vacuum and intense (60 °C) bowl heating;

(5) the dried granules are mixed with colloidal silicon dioxide;

(6) the blend is regranulated by using a roto-sieve;

(7) the granules are lubricated with magnesium stearate to prepare the final blend;

(8) the final blend is compressed into tablets with a tableting press equipment.

Example 8: Pharmaceutical compositions (Tablet 6975 and Tablet 6673) for the comparative stability study of Zytiga® and the pharmaceutical composition of the present invention

Tablet 6975 and Tablet 6673	Amount (mg)
Abirateron acetate	250.00
Lactose monohydrate	198.65
Microcrystalline cellulose	141.22
Croscarmellose sodium	42.90
Povidon K29/K32	35.75
Sodium lauryl sulfate	28.60
Colloidal silicon dioxide	7.15
Magnesium stearate	10.73
Σ	715

Table 10: qualitative and quantitative composition of Tablet 6975 and Tablet 6673

Example 9: Manufacture of abiraterone acetate tablets of example 8 by high shear granulation in a closed system

The process comprises the steps of:

(1) Abiraterone acetate, lactose monohydrate, microcrystalline cellulose, povidone, sodium lauryl sulphate and croscarmellose sodium are added to the high shear mixer and the blend is mixed;

(2) a mixture of purified water and ethanol in a ratio 1:2 (w/w) is prepared, the dielectric constant of the mixture is approximately 40;

(3) the granulation solution prepared in step (2) is added to the blend obtained in step (1) and kneaded;

(4) the granules obtained in step (3) are dried in a high shear granulator at approximately 10°C to approximately 40°C;

(5) the colloidal silicon dioxide is blended with the granules obtained in step (4) in a blender;

(6) the granules obtained in step (5) are regranulated;

(7) magnesium stearate is sieved and blended with the granules from step (6) in a high shear granulator;

(8) the final blend is compressed into tablets with a tableting press equipment.

Example 10: comparative stability study of Tablet 6975 and Zytiga®

	Tablet 6975					Zytiga®
Samples and test points (months)	at the release	3	6	12	18	at the beginning of the study
7-ketoabiraterone-acetate	<QL	<QL	<QL	<QL	<QL	0.10
abiraterone	<QL	<QL	<QL	<QL	<QL	< QL
α-epoxyabiraterone-acetate (%)	<QL	<QL	<QL	<QL	<QL	0.06
β-epoxyabiraterone-acetate (%)	<QL	<QL	<QL	<QL	<QL	< QL
abiraterone acetate related impurity (%)	<QL	<QL	<QL	<QL	<QL	< QL
abiraterone acetate related total impurity (%)	na	na	na	na	na	0.16

Table 11: samples stored in HDPE bottle (25 °C/65 % RH; quantitation limit: QL=0.05 %, na: not applicable)

The Zytiga® tablets, used as a reference, were investigated 12 months after their manufacture. The reference composition was stored at room conditions (25 °C/65 % RH) prior to the investigation. Degradation profile of the pharmaceutical composition of the present invention (Tablet 11) was examined under storage at room conditions (25 °C/65 % RH). The pharmaceutical composition of the present invention did not show any degradation up to 18 months, as the abiraterone acetate related impurity level is under the quantitation limit (QL=0.05 %). On the contrary, the Zytiga® product showed higher impurity level and degradation, stored under identical conditions.

Samples and test points (months)	Tablet 6975		Zytiga®	
	at release	12	at the beginning of the study	12
7-ketoabiraterone-acetate	<QL	<QL	0.10	0,11
abiraterone	<QL	<QL	< QL	<QL
α-epoxyabiraterone-acetate (%)	<QL	<QL	0.06	0.42
β-epoxyabiraterone-acetate (%)	<QL	<QL	< QL	0.77
abiraterone acetate related other impurity (%)	<QL	<QL	< QL	0.39
abiraterone acetate related total impurity (%)	na	na	0.16	1.69

Table 12: samples stored in HDPE bottle (30 °C/75 65 % RH; quantitation limit: QL=0.05 %, na: not applicable)

The stability test with the reference Zytiga® tablets started 12 months after their manufacture, therefore, at the end of the test, the stored samples reached the shelf life of the Zytiga® product (24 months). The β-epoxyabiraterone-acetate and abiraterone acetate related total impurity levels of Zytiga® are close to the USP acceptance criteria (see Table 12).

The pharmaceutical composition of the present invention did not show any degradation during the 12 months of the stability study (30 °C/65 % RH), as the

abiraterone acetate related impurity level is under the quantitation limit. On the contrary, the Zytiga® product showed higher impurity level and degradation stored under identical conditions. There was a significant increase in the amount of total degradation, and new impurities also appeared, which were not present at the beginning of the stability test.

Samples and test points (months)	Tablet 6975			Zytiga®	
	at release	3	6	at the beginning of the study	6
7-ketoabiraterone-acetate	<QL	<QL	<QL	0.10	0.16
abiraterone	<QL	<QL	<QL	< QL	0.18
α-epoxyabiraterone-acetate (%)	<QL	<QL	<QL	0.06	0.65
β-epoxyabiraterone-acetate (%)	<QL	<QL	<QL	< QL	0.95
abiraterone acetate related unspecified impurity (%)	<QL	<QL	<QL	< QL	0.37
abiraterone acetate related total impurity (%)	na	na	na	0.16	2.31

Table 13: samples stored in HDPE bottle (40 °C/75 % RH; quantitation limit, QL=0.05 %, na.: not applicable)

The stability test with the reference Zytiga® tablets started 12 months after their manufacture. In order to compare the degree of change in degradation products, the samples were stored under accelerated condition. After 6 months of storage at 40 °C/70 % RH the β-epoxyabiraterone-acetate and abiraterone acetate related total impurity levels reached the USP acceptance criteria (see Table 13). On the contrary, the pharmaceutical composition of the present invention did not show any degradation during the 6 months of the stability study, while there was a significant increase in the amount of total degradation of the Zytiga® product and new impurities also appeared, which were not present at the beginning of the stability test.

Example 11: stability study of Tablet 6673

	Tablet 6673				
Samples and test points (months)	at the release	after 5 months	after 8 months	after 14 months	after 20 months
7-ketoabiraterone-acetate	<QL	<QL	<QL	<QL	<QL
abiraterone	<QL	<QL	<QL	<QL	<QL
α-epoxyabiraterone-acetate (%)	<QL	<QL	<QL	<QL	<QL
β-epoxyabiraterone-acetate (%)	<QL	<QL	<QL	<QL	<QL
abiraterone acetate related impurity (%)	<QL	<QL	<QL	<QL	<QL
abiraterone acetate related total impurity (%)	na	na	na	na	na

Table 14: samples stored in HDPE bottle (25 °C/65 % RH; quantitation limit: QL=0.05 %, na: not applicable)

The results of the stability studies can be extrapolated based on the ICH Harmonised Tripartite guideline (ICH HARMONISED TRIPARTITE GUIDELINE EVALUATION FOR STABILITY DATA Q1E), which states, that where the long-term data and accelerated data for an attribute show little or no change over time and little or no variability, it might be apparent that the drug substance or product will remain well within the acceptance criteria for that attribute during the proposed retest period or shelf life. In these circumstances, a statistical analysis is normally considered unnecessary, but justification for the omission should be provided. Justification can include a discussion of the change pattern or lack of change, relevance of the accelerated data, mass balance, and/or other supporting data as described in the parent guideline. Extrapolation of the retest period or shelf life beyond the period covered by long-term data can be proposed.

The test results obtained in the 18 months comparative stability study (Tablet 6975) can be extrapolated to 30 months, and the test results obtained in the 20 months stability study (Tablet 6673) can be extrapolated to 32 months. However,

considering that there is no change during the storage, it is also suitable for up to 36 months shelf life without any restrictions on storage.

Consequently, based on the stability test results, the predicted shelf life of the pharmaceutical composition of the present invention is at least 30 months, but rather 36 months which are both longer than the shelf life of the Zytiga® product (2 years).

CLAIMS

1. A stable pharmaceutical composition with improved physicochemical characteristics and improved impurity profile comprising abiraterone acetate or pharmaceutically acceptable salts, hydrates or solvates thereof, and at least one pharmaceutically acceptable excipient; wherein said composition possesses the following features:
a) an increased stability compared to Zytiga;
b) the same *in vitro* behaviour as Zytiga.

2. The pharmaceutical composition according to claim 1; wherein said composition has a lower abiraterone acetate related impurity level than Zytiga.

3. The pharmaceutical composition according to claim 2; wherein the abiraterone acetate related impurities are selected from the group of 7-ketoabiraterone acetate, α-epoxyabiraterone acetate, ß-epoxyabiraterone acetate, abiraterone and abiraterone acetate related unspecified impurity.

4. The pharmaceutical composition according to claim 3; wherein said 7-ketoabiraterone acetate impurity is about zero to about 0.5 % within 36 months of storage of the final pharmaceutical composition.

5. The pharmaceutical composition according to any one of claims 3 to 4; wherein said α-epoxyabiraterone acetate impurity is about zero to about 0.8 % within 36 months of storage of the final pharmaceutical composition.

6. The pharmaceutical composition according to any one of claims 3 to 5; wherein said ß-epoxyabiraterone acetate impurity is about zero to about 0.8 % within 36 months of storage of the final pharmaceutical composition.

7. The pharmaceutical composition according to any one of claims 3 to 6; wherein said abiraterone impurity is about zero to about 0.4 % within 36 months of storage of the final pharmaceutical composition.

8. The pharmaceutical composition according to any one of claims 3 to 7; wherein said abiraterone acetate related unspecified impurity is about zero to about 0.20 % within 36 months of storage of the final pharmaceutical composition.

9. The pharmaceutical composition according to any one of claims 3 to 8; wherein said abiraterone acetate related total impurity is about zero to about 2.0 % within 36 months of storage of the final pharmaceutical composition.

10. The pharmaceutical composition according to claim 3 characterized in, that abiraterone acetate or pharmaceutically acceptable salts, hydrates or solvates thereof, are stabilized against oxidative degradation without the use of a special package and/or storage conditions.

11. The pharmaceutical composition according to claim 3 characterized by, that abiraterone acetate or pharmaceutically acceptable salts, hydrates or solvates thereof, are stabilized against oxidative degradation without the addition of an antioxidant.

12. A process for the preparation of a stable pharmaceutical composition according to claim 1, said process comprising the steps of: high shear mixing and granulation with pharmaceutically acceptable solvents with a dielectric constant of about 20 to about 80; drying; blending; and compression into tablets.

13. The process according to claim 12, wherein said process is performed in a high-shear granulator without wet milling.

14. The process according to claim 13, wherein said pharmaceutically acceptable solvents are selected from the group of acetone, acetonitrile, dimethyl-sulfoxide, ethyl acetate, ethanol, isopropanol, n-propanol, methanol, methylene chloride, tetrahydrofuran, and water or any mixtures thereof.

15. The process according to claim 14, wherein the dielectric constant of said solvents is about 20 to about 80.

16. The process according to in claim 14, wherein the dielectric constant of said solvents is about 25 to about 75.

17. The process according to in claim 14, wherein the dielectric constant of said solvents is about 25 to about 70.

18. Pharmaceutical composition comprising abiraterone acetate or pharmaceutically acceptable salts, hydrates or solvates thereof obtained by the process of claim 12.

19. The pharmaceutical composition according to any of claim 1 to 11, wherein said composition is suitable for oral administration.

20. The pharmaceutical composition according to any of claims 1 to 11, for use in the treatment of cancer.

Figure 1

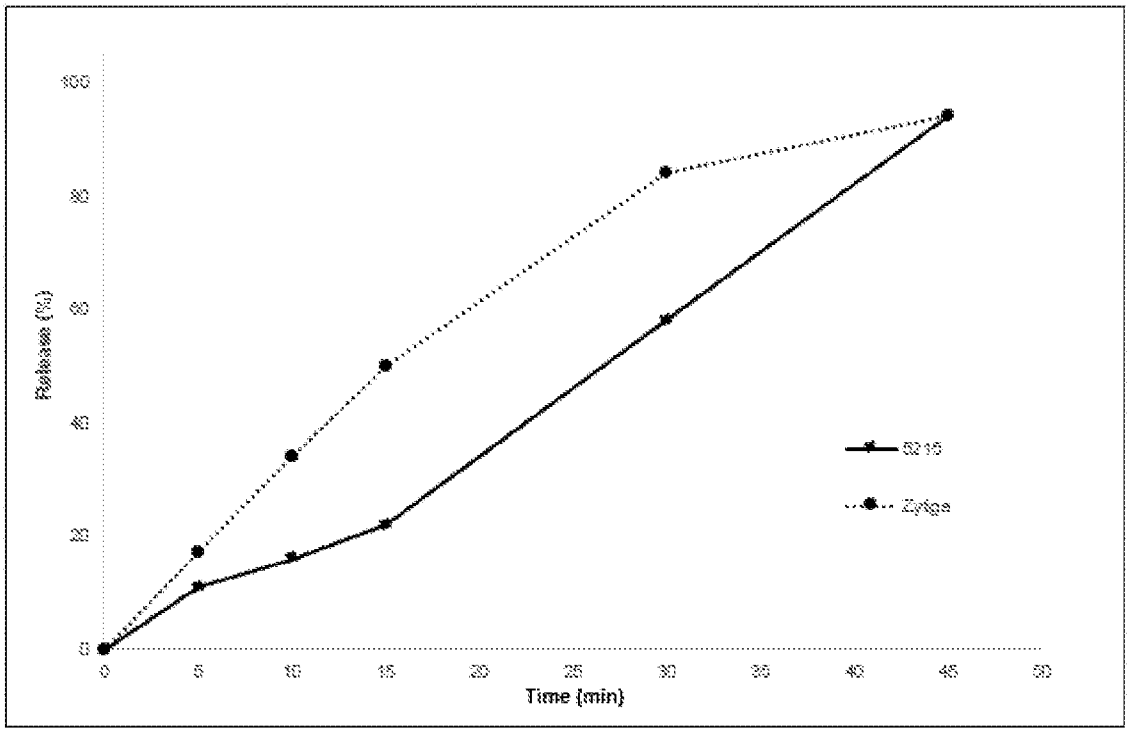


Figure 2

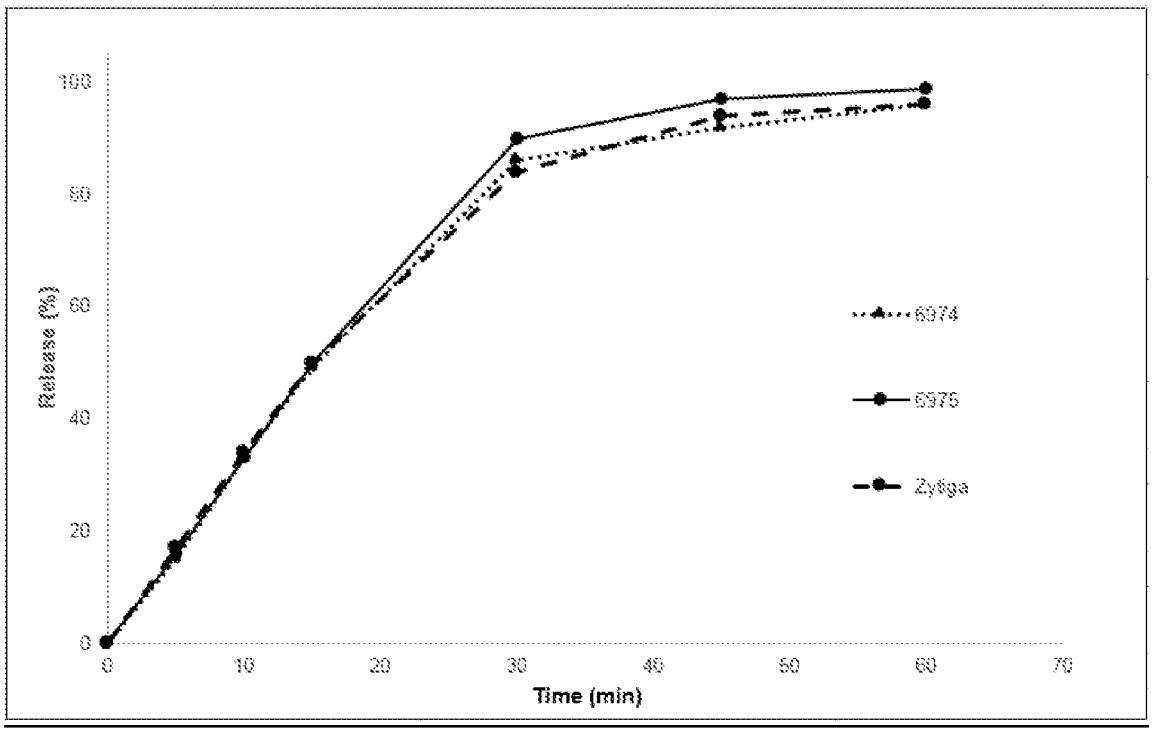
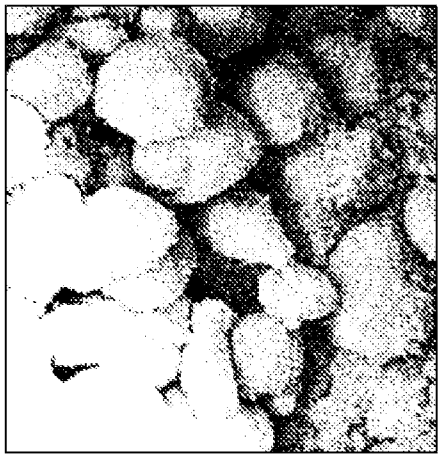
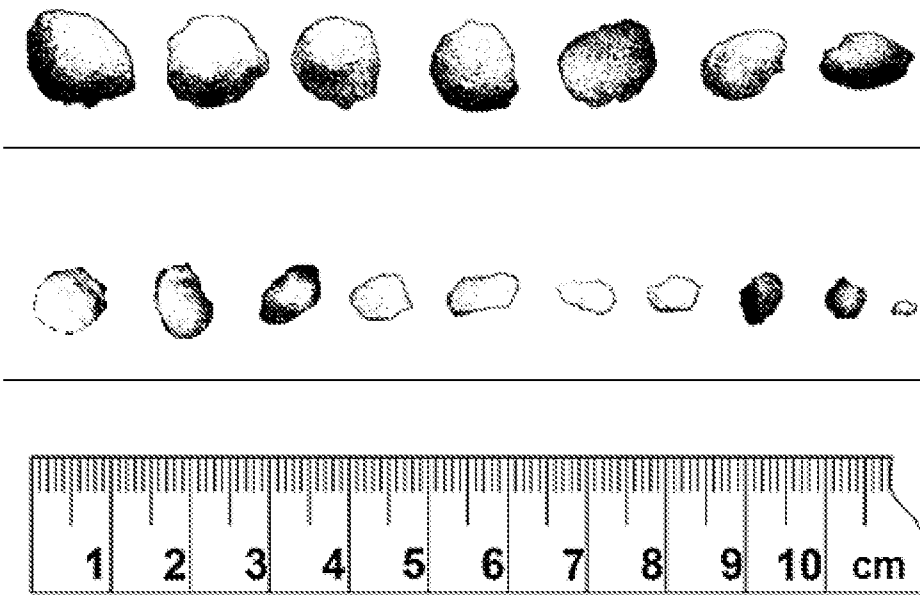


Figure 3





INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2019/056464

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/14 A61K9/16 A61K9/20 A61K31/573
ADD.

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

B. FIELDS SEARCHED

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

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, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 2 792 682 A1 (ZACH SYSTEM [FR]) 22 October 2014 (2014-10-22) claims paragraph [0082] - paragraph [0085] -----	1-20
X	WO 2015/032873 A1 (SYNTHON BV [NL]) 12 March 2015 (2015-03-12) claims examples -----	1-20
X	US 2015/246060 A1 (MURPHY MAURA [US] ET AL) 3 September 2015 (2015-09-03) example 6 example 13 claims paragraph [0006] - paragraph [0020] ----- -/--	1-20

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

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 December 2019	02/01/2020

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INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2019/056464

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2014/145813 A1 (ICEUTICA INC [US]) 18 September 2014 (2014-09-18) example 6 claims page 41, paragraph 1 - page 43, paragraph 3 -----	1-20

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
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