# COMPLEXES OF ABIRATERONE ACETATE, PROCESS FOR THE PREPARATION THEREOF AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

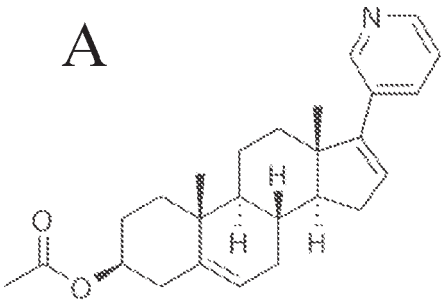
## FIELD OF THE INVENTION

The invention is directed to a stable complex with controlled particle size, increased apparent solubility and increased dissolution rate comprising as active compound Abiraterone acetate, which is useful in the treatment of a certain type of prostate cancer that has spread to other parts of the body. Abiraterone acetate might be used for earlier stages of prostate cancer and advanced breast cancer. More specifically, the complex of the present invention possesses increased apparent solubility and exhibits no positive food effect which allows significant dose reduction and the abandoning of the requirement of taking the drug on an empty stomach. The invention also relates to methods of formulating and manufacturing complex according to the invention, pharmaceutical compositions containing it, its uses and methods of treatment using the complex and its compositions.

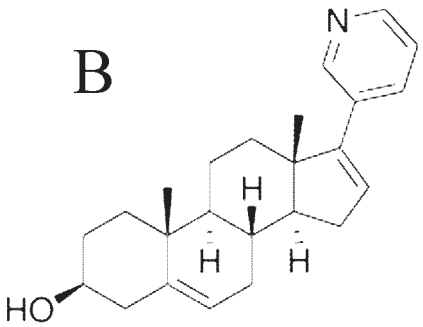
## BACKGROUND OF THE INVENTION

Abiraterone is a potent and selective inhibitor of CYP17 (17α-hydroxylase/C17,20-lyase). As Abiraterone was poorly bioavailable and also susceptible to hydrolysis by esterases, a prodrug was developed. Abiraterone acetate (**A**) was found to be resistant to esterases and was rapidly deacetylated to Abiraterone (**B**) *in vivo*, resulting in potent CYP17 inhibition. Abiraterone acetate is designated chemically as (3β)-17-(3-pyridinyl) androsta-5,16-dien-3-yl acetate and its structure is:

A




B



Abiraterone acetate is a white to off-white, non-hygroscopic, crystalline powder. Its molecular formula is $C_{26}H_{33}NO_2$ and it has a molecular weight of 391.55. Abiraterone acetate is a lipophilic compound with an octanol-water partition coefficient of 5.12 (Log P) and is practically insoluble in water. The pKa of the aromatic nitrogen is 5.19.

Inactive ingredients in the Zytiga® tablets are colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone, and sodium lauryl sulfate. ). Each Zytiga® tablet contains 250 mg of Abiraterone acetate.

Abiraterone acetate (ZYTIGA) is converted *in vivo* to Abiraterone, an androgen biosynthesis inhibitor, that inhibits 17α-hydroxylase/C17,20-lyase (CYP17). This enzyme is expressed in testicular, adrenal, and prostatic tumor tissues and is required for androgen biosynthesis.

CYP17 catalyzes two sequential reactions: 1) the conversion of pregnenolone and progesterone to their 17α-hydroxy derivatives by 17α-hydroxylase activity and 2) the subsequent formation of dehydroepiandrosterone (DHEA) and androstenedione, respectively, by C17,20 lyase activity. DHEA and androstenedione are androgens and are precursors of testosterone. Inhibition of CYP17 by Abiraterone can also result in increased mineralocorticoid production by the adrenals.

Androgen sensitive prostatic carcinoma responds to treatment that decreases androgen levels. Androgen deprivation therapies, such as treatment with GnRH agonists or orchiectomy, decrease androgen production in the testes but do not affect androgen production by the adrenals or in the tumor.

Abiraterone acetate decreased serum testosterone and other androgens in patients in the placebo-controlled phase 3 clinical trial. It is not necessary to monitor the effect of Abiraterone on serum testosterone levels.

Changes in serum prostate specific antigen (PSA) levels may be observed but have not been shown to correlate with clinical benefit in individual patients.

Following administration of Abiraterone acetate, the pharmacokinetics of Abiraterone and Abiraterone acetate have been studied in healthy subjects and in patients with metastatic castration-resistant prostate cancer (CRPC). *In vivo*, Abiraterone acetate is converted to Abiraterone. In clinical studies, Abiraterone acetate plasma concentrations were below detectable levels (< 0.2 ng/mL) in > 99% of the analyzed samples.

Following oral administration of Abiraterone acetate to patients with metastatic CRPC, the median time to reach maximum plasma Abiraterone concentrations is 2 hours. Abiraterone accumulation is observed at steady-state, with a 2-fold higher exposure (steady-state AUC) compared to a single 1,000 mg dose of Abiraterone acetate.

At the dose of 1,000 mg daily in patients with metastatic CRPC, steady-state values (mean ± SD) of $C_{max}$ were 226 ± 178 ng/mL and of AUC were 993 ± 639 ng*hr/mL. No major deviation from dose proportionality was observed in the dose range of 250 mg to 1,000 mg. However, the exposure was not significantly increased when the dose was doubled from 1,000 to 2,000 mg (8% increase in the mean AUC).

Systemic exposure of Abiraterone is increased when Abiraterone acetate is administered with food. Abiraterone $C_{max}$ and $AUC_{0-\infty}$ were approximately 7-and 5-fold higher, respectively, when Abiraterone acetate was administered with a low-fat meal (7% fat, 300 calories) and approximately 17-and 10-fold higher, respectively, when Abiraterone acetate was administered with a high-fat (57% fat, 825 calories) meal. Given the normal variation in the content and composition of meals, taking Zytiga® with meals has the potential to result in increased and highly variable exposures. Therefore, no food should be consumed for at least two hours before the dose of Zytiga® is taken and for at least one hour after the dose of Zytiga® is taken. The tablets should be swallowed whole with water.

Abiraterone is highly bound (> 99%) to the human plasma proteins, albumin and alpha-1 acid glycoprotein. The apparent steady-state volume of distribution (mean ± SD) is 19,669 ± 13,358 L. *In vitro* studies show that at clinically relevant concentrations, Abiraterone acetate and Abiraterone are not substrates of P-glycoprotein (P-gp) and that Abiraterone acetate is an inhibitor of P-gp. No studies have been conducted with other transporter proteins.

Following oral administration of $^{14}$C-abiraterone acetate as capsules, Abiraterone acetate is hydrolyzed to Abiraterone (active metabolite). The conversion is likely through esterase activity (the esterases have not been identified) and is not CYP mediated. The two main circulating metabolites of Abiraterone in human plasma are Abiraterone sulphate (inactive) and N-oxide Abiraterone sulphate (inactive), which account for about 43% of exposure each. CYP3A4 and SULT2A1 are the enzymes involved in the formation of N-oxide Abiraterone sulphate and SULT2A1 is involved in the formation of Abiraterone sulphate.

In patients with metastatic CRPC, the mean terminal half-life of Abiraterone in plasma (mean ± SD) is 12 ± 5 hours. Following oral administration of $^{14}$C-abiraterone acetate, approximately 88% of the radioactive dose is recovered in feces and approximately 5% in urine. The major compounds present in feces are unchanged Abiraterone acetate and Abiraterone (approximately 55% and 22% of the administered dose, respectively).

The usual dose is 4 tablets (1,000 mg) taken together once a day. The tablets have to be swallowed with a glass of water on an empty stomach. The tablets have to be taken at least one hour before food, or at least 2 hours afterwards. Abiraterone has to be taken with a steroid called prednisolone to help reduce some of the side effects.

In clinical studies following the oral administration of Abiraterone acetate Abiraterone exhibited variable pharmacokinetics and an exceptionally large positive food effect. Abiraterone $C_{max}$ and $AUC_{0-\infty}$ (exposure) were increased up to 17- and 10-fold higher, respectively, when a single dose of Abiraterone acetate was administered. In order to control Abiraterone plasma concentrations Zytiga® must be taken on an empty stomach. No food should be consumed for at least two hours before the dose of Zytiga® is taken and for at least one hour after the dose of Zytiga® is taken. The administered dose is also very large with 1 g taken once daily. Improving the oral bioavailability of the compound in the fasted state would therefore deliver two advantages: the abandoning of the requirement of taking the drug on an empty stomach and significant dose reduction. Based on the extent of the food effect of the currently used formula total elimination of it would allow 10-fold reduction of the dose.

In order to overcome the problems associated with prior conventional Abiraterone acetate formulations and available drug delivery systems novel complex formula of Abiraterone acetate and complexing agents and pharmaceutically acceptable excipients characterized by increased apparent solubility, instantaneous dissolution, reduced food effect which allows significant dose reduction and the abandoning of the requirement of taking the drug on an empty stomach.

A variety of strategies have been used to attempt to overcome these issues, see for example CN101768199A, CN102558275A, WO2014083512A1, WO2014145813A1, CN102321142A, WO2014102833A2, WO2014009436A1, WO2014145813A1, WO2014009434A1, WO2009009132A1, WO2013164473A1, WO1995011914A1, CA2513746A1, WO2010078300A1, WO2014100418A2 and WO2014009437A1.

A polymorph form of Abiraterone acetate according to CN 102336801 A patent application is characterized by typical X-ray diffraction pattern at 5.76°, 11.98°, 12.50°, 14.74°, 15.02°, 15.86°, 17.14°, 18.30°, 18.82°, 19.02°, 19.70°, 21.58°, 21.78°, 22.38°, 22.98°, 23.34° and 27.48° 2Θ and infrared absorption spectrum at 2937.73 $cm^{-1}$, 2889.59 $cm^{-1}$, 2855.6 $cm^{-1}$, l479.66 $cm^{-1}$, 1437.34 $cm^{-1}$, 1372.01 $cm^{-1}$, 1245.41 $cm^{-1}$, l034.63 $cm^{-1}$, 962.33 $cm^{-1}$, 800.75 $cm^{-1}$ and 713.79 $cm^{-1}$.

Abiraterone acetate exhibits polymorphism, CN101768199 patent application discloses Abiraterone acetate A, B, C, D forms of Abiraterone acetate. Polymorph A is characterized by X-ray powder diffraction peaks at 2Θ values of 5.860°, 12.060°, 15.120°, 15.920°, 18.400°, 18.940°, 19.700°, 21.700°, 22.460°, 23.500°, 25.380°, 27.580°. Polymorph B is characterized by X-ray powder diffraction peaks at 2 Θ values of 5.940°, 9.640°, 12.140°, 14.880°, 15.120°, 16.000°, 17.640°, 18.460°, 21.840°, 22.500°, 23.100°. Polymorph C is characterized by X-ray powder diffraction peaks at 2Θ values of 5.960°, 9.580°, 12.140°, 12.680°, 14.920°, 15.940°, 17.280°, 18.360°, 19.000°, 19.860°, 21.820°, 22.040°, 22.400°, 23.160°, 23.460°, 23.760°, 25.420°, 26.900°, 27.520° and 29.460° and 30.000° corresponding characteristic diffraction peaks. The crystal form D is characterized by X-ray powder diffraction peaks at 2Θ values of 5.860°, 12.040°, 14.800°, 15.100°, 15.920°, 17.580°, 18.400°, 19.100°, 19.740°, 21.680°, 22.380°, 23.500°, 29.500°, 36.780°.

The α polymorph crystal of Abiraterone acetate according to CN 102558275 A patent application is characterized by infrared spectrum comprising characteristic absorption peaks at 3047 $cm^{-1}$, 2937 $cm^{-1}$, 2891 $cm^{-1}$, 2855 $cm^{-1}$, 1735 $cm^{-1}$, 1560 $cm^{-1}$, 1374 $cm^{-1}$, 1245 $cm^{-1}$ and l035 $cm^{-1}$.

## BRIEF DESCRIPTION OF THE INVENTION

1. A stable complex with improved physicochemical characteristics and enhanced biological performance comprising

   a) as active compound Abiraterone acetate; or a combination of active compounds including Abiraterone acetate;

   b) at least one complexing agent chosen from polyethylene glycol glycerides composed of mono-, di- and triglycerides and mono- and diesters of polyethylene glycol, hydroxypropylcellulose, poloxamers, vinylpyrrolidone/vinyl acetate copolymer, polyethylene glycol, poly(2-ethyl-2-oxazoline), polyvinylpyrrolidone, block copolymers based on ethylene oxide and propylene oxide, poly(maleic acid/methyl vinyl ether), polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer, polyoxyl 15

hydroxystearate, ethylene oxide/propylene oxide block copolymer, polyvinyl alcohol-polyethylene glycol graft copolymer and d-alpha tocopheryl polyethylene glycol 1000 succinate;

c) if desired, pharmaceutically acceptable excipients;

wherein said complex has a particle size, which is less than 600 nm, and possesses one or more among the following features:

- it is instantaneously redispersible in physiological relevant media;
- it has increased dissolution rate;
- it is stable in solid form and in colloid solution and/or dispersion;
- its apparent solubility in water is of at least 0.6 mg/mL;
- it shows X-ray amorphous character in the solid form;
- it has a PAMPA permeability of at least $0.5*10^{-6}$ cm/s when dispersed in distilled water, which does not decrease in time at least for 3 months;
- exhibits no positive food effect (fed/fased ratio is under 1.25) which allows significant dose reduction and the abandoning of the requirement of taking the drug on an empty stomach;
- the variability of exposure is significantly reduced when compared to Zytiga.

2. The complex according to Point 1, wherein said complex has a particle size in the range between 50 nm and 600 nm.

3. The complex according to Point 1 and 2, wherein said complex has a particle size in the range between 100 nm and 500 nm.

4. The complex according to Points 1 to 3, wherein

a) the complexing agent is selected from the group consisting of a polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer; and

b) the excipient is sodium deoxycholate.

5. The complex according to Points 1 to 4, wherein said complex is composed of

a) 5 to 40% by weight of Abiraterone acetate;

b) 5 to 80% by weight of a polyvinylcaprolactam-polyvinyl acetate-polyethylene-glycol graft copolymer;

c) 0.1 to 50 % by weight of sodium deoxycholate.

6. The complex according to Points 1 to 4, wherein said complex comprises as active agent Abiraterone acetate and one or more additional active agent, which is selected from the group of agents selected from the group of Rifampicin, Prednisone/Prednisolone, Dexamethasone, Ketoconazole, Testosterone Enanthate, Enzalutamide, Dextromethorphan hydrobromide, Dexamethasone, Exemestane, Goserelin, Degarelix, Veliparib, Dovitinib, Leuprolide, Alisertib, cabozantinib, Cabazitaxel, Dasatinib, Glucocorticoid, Docetaxel, Dutasteride, Hydroxychloroquine, Ipilimumab, Metformin, Sunitinib, Selinexor, Everolimus, Trastuzumab, Tamoxifen, and combinations thereof.

7. The stable complex according to Points 1 to 3 comprising

a) Abiraterone acetate; or a combination of active compounds including Abiraterone acetate;

b) as complexing agent polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer;

c) as excipient sodium deoxycholate.

8. The stable complex according to Points 1 to 3 comprising

a) Abiraterone acetate;

b) as complexing agent polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer;

c) as excipient sodium deoxycholate;

wherein said complex is characterized by infrared (ATR) spectrum shown in Figure 19 and Raman spectrum shown in Figure 20.

In an embodiment said complex is characterized by infrared (ATR) spectrum having main/characteristic absorption peaks at least at 569 $cm^{-1}$, 607 $cm^{-1}$, **713 $cm^{-1}$**, 797 $cm^{-1}$, 843 $cm^{-1}$, 942 $cm^{-1}$, 973 $cm^{-1}$, **1030 $cm^{-1}$, 1103 $cm^{-1}$**, 1148 $cm^{-1}$, 1195 $cm^{-1}$, 1241 $cm^{-1}$, 1333 $cm^{-1}$, 1371 $cm^{-1}$, 1421 $cm^{-1}$, 1441 $cm^{-1}$, 1477 $cm^{-1}$, 1336 $cm^{-1}$, **1734 $cm^{-1}$**, 2858 $cm^{-1}$, 2928 $cm^{-1}$ characteristic absorption peaks; and is characterized by Raman spectrum having main/characteristic absorption peaks at least at 239 $cm^{-1}$, **581 $cm^{-1}$**, 701 $cm^{-1}$, 797 $cm^{-1}$, 846 $cm^{-1}$, **1026 $cm^{-1}$**, 1088 $cm^{-1}$, 1196 $cm^{-1}$, 1264 $cm^{-1}$, **1445** $cm^{-1}$, 1584 $cm^{-1}$, 1600 $cm^{-1}$, 1735 $cm^{-1}$characteristic absorption peaks.

In an embodiment said complex is characterized by infrared (ATR) spectrum having main/characteristic absorption peaks at least at 713 $cm^{-1}$, 1030 $cm^{-1}$, 1103 $cm^{-1}$ and 1734 $cm^{-1}$ characteristic absorption peaks; and is characterized by Raman spectrum having main/characteristic absorption peaks at least at 581 $cm^{-1}$, 1026 $cm^{-1}$and 1445 characteristic absorption peaks.

9. A process for the preparation of a stable complex according to Points 1 to 8, said process comprising the step of mixing a solution of the active agent and at least one complexing agent and optionally one or more pharmaceutically acceptable excipient in a pharmaceutically acceptable solvent with an aqueous solution containing optionally least one pharmaceutically acceptable excipient.

10. The process according to Point 9, wherein said process is performed in a continuous flow instrument.

11. The process according to Point 9 and 10, wherein said continuous flow instrument is a microfluidic flow instrument.

12. The process according to Points 9 to 11, wherein said pharmaceutically acceptable solvent is chosen from methanol, ethanol, isopropanol, n-propanol, acetone, acetonitrile, dimethyl-sulfoxide, tetrahydrofuran, or combinations thereof, preferably said pharmaceutically acceptable solvent is tetrahydrofuran.

13. The process according to Points 9 to 11, wherein said solvents are miscible with each other and the aqueous solvent comprises 0.1 to 99.9% weight of the final solution.

14. A composition comprising the stable complex according to Points 1 to 7, together with a pharmaceutically acceptable carrier.

15. The pharmaceutical composition according to Point 14, wherein said composition is suitable for oral, pulmonary, rectal, colonic, parenteral, intracisternal, intravaginal, intraperitoneal, ocular, otic, local, buccal, nasal, or topical administration, preferable the composition is suitable for oral administration.

16. The complex according to Points 1 to 7 for use in the manufacture of a medicament for the treatment of a certain type of prostate cancer that has spread to other parts of the body and earlier stages of prostate cancer and advanced breast cancer.

17. The complex according to Point 16 for use for the treatment of a type of prostate cancer that has spread to other parts of the body and earlier stages of prostate cancer and advanced breast cancer.

## DESCRIPTION OF THE INVENTION

The present invention relates to a stable complex comprising as active compound Abiraterone acetate or a combination of active compounds including Abiraterone acetate; and at least one complexing agent chosen from polyvinylcaprolactam-polyvinyl acetate-polyethylene-glycol graft copolymers; poloxamers; polyvinylpyrrolidone; copolymers of vinylpyrrolidone and vinyl-acetate; and poly(maleic acid-co-methyl-vinyl-ether); said complex characterized in that it possesses at least one of the following properties:

a) the particle size is less than 600 nm;
b) is instantaneously redispersible in physiological relevant media;
c) has increased dissolution rate;
d) is stable in solid form and in colloid solution and/or dispersion;
e) apparent solubility in water of at least 0.6 mg/mL;
f) shows X-ray amorphous character in the solid form;
g) has a PAMPA permeability of at least $0.5*10^{-6}$ cm/s when dispersed in distilled water, which does not decrease in time at least for 3 months;
h) exhibits no positive food effect which allows significant dose reduction and the abandoning of the requirement of taking the drug on an empty stomach;
i) the variability of exposure is significantly reduced when compared to Zytiga.

The invention is a complex formula having increased apparent solubility and exhibits no positive food effect which allows significant dose reduction and the abandoning of the requirement of taking the drug on an empty stomach.

We have found that only the selected combinations of complexing agents and pharmaceutically acceptable excipients disclosed in the present invention result in a stable complex formulae having improved physicochemical characteristics and enhanced biological performance.

In an embodiment, said complexing agent is chosen from polyethylene glycol glycerides composed of mono-, di- and triglycerides and mono- and diesters of polyethylene glycol, hydroxypropylcellulose, poloxamers (copolymers of ethylene oxide and propylene oxide blocks), vinylpyrrolidone/vinyl acetate copolymer, polyethylene glycol, poly(2-ethyl-2-oxazoline), polyvinylpyrrolidone, block copolymers based on ethylene oxide and propylene oxide, poly(maleic acid/methyl vinyl ether), polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer, polyoxyl 15 hydroxystearate, ethylene oxide/propylene oxide block copolymer, polyvinyl alcohol-polyethylene glycol graft copolymer and d-alpha tocopheryl polyethylene glycol 1000 succinate.

In a preferred embodiment, said complexing agent is a polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer.

In an embodiment, said polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer is Soluplus.

In an embodiment, said complex further comprises sodium deoxycholate.

In a particularly preferred embodiment the complex according to the present invention comprises polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer and sodium deoxycholate, and

a) is characterized by infrared (ATR) spectrum shown in Figure 19 and Raman spectrum shown in Figure 20, or

b) characterized by infrared (ATR) spectrum having main/characteristic absorption peaks at least at 569 $cm^{-1}$, 607 $cm^{-1}$, **713 $cm^{-1}$**, 797 $cm^{-1}$, 843 $cm^{-1}$, 942 $cm^{-1}$, 973 $cm^{-1}$, **1030 $cm^{-1}$, 1103 $cm^{-1}$**, 1148 $cm^{-1}$, 1195 $cm^{-1}$, 1241 $cm^{-1}$, 1333 $cm^{-1}$, 1371 $cm^{-1}$, 1421 $cm^{-1}$, 1441 $cm^{-1}$, 1477 $cm^{-1}$, 1336 $cm^{-1}$, **1734 $cm^{-1}$**, 2858 $cm^{-1}$, 2928 $cm^{-1}$ characteristic absorption peaks; and is characterized by Raman spectrum having main/characteristic absorption peaks at least

at 239 $cm^{-1}$, **581 $cm^{-1}$**, 701 $cm^{-1}$, 797 $cm^{-1}$, 846 $cm^{-1}$, **1026 $cm^{-1}$**, 1088 $cm^{-1}$, 1196 $cm^{-1}$, 1264 $cm^{-1}$, **1445** $cm^{-1}$, 1584 $cm^{-1}$, 1600 $cm^{-1}$, 1735 $cm^{-1}$characteristic absorption peaks, or

c) is characterized by infrared (ATR) spectrum having main/characteristic absorption peaks at least at 713 $cm^{-1}$, 1030 $cm^{-1}$, 1103 $cm^{-1}$ and 1734 $cm^{-1}$ characteristic absorption peaks; and is characterized by Raman spectrum having main/characteristic absorption peaks at least at 581 $cm^{-1}$, 1026 $cm^{-1}$and 1445 characteristic absorption peaks.

In an embodiment, said complex has a controlled particle size in the range between 50 nm and 600 nm. In an embodiment, said particle size is between 100 nm and 500 nm.

In an embodiment, said complex further comprises one or more additional active agents.

In an embodiment, said additional active agent is chosen from agents useful in the treatment of a certain type of prostate cancer and might be used for earlier stages of prostate cancer and advanced breast cancer.

In an embodiment, said additional active agent is chosen from Rifampicin, Prednisone/Prednisolone, Dexamethasone, Ketoconazole, Testosterone Enanthate, Enzalutamide, Dextromethorphan hydrobromide, Dexamethasone, Exemestane, Goserelin, Degarelix, Veliparib, Dovitinib, Leuprolide, Alisertib, cabozantinib, Cabazitaxel, Dasatinib, Glucocorticoid, Docetaxel, Dutasteride, Hydroxychloroquine, Ipilimumab, Metformin, Sunitinib, Selinexor, Everolimus, Trastuzumab, Tamoxifen, and combinations thereof.

In an embodiment, said complex exhibits no positive food effect which allows significant dose reduction and the abandoning of the requirement of taking the drug on an empty stomach.

In an embodiment, said complex possesses at least two of the properties described in a) – h).

In an embodiment, said complex possesses at least three of the properties described in a) – h).

In an embodiment, said complex has an increased dissolution rate.

Further disclosed herein is a stable complex comprising an active compound Abiraterone acetate, at least one complexing agent chosen from polyvinylcaprolactam-polyvinyl acetate-polyethylene-glycol graft copolymers; poloxamers; polyvinylpyrrolidone; copolymers of vinylpyrrolidone and vinyl-acetate; and poly(maleic acid-co-methyl-vinyl-ether); and at least one pharmaceutically

acceptable excipient chosen from sodium-lauryl-sulfate, poloxamers and sodium deoxycholate; wherein said complex obtained via a mixing process.

In an embodiment, said complexing agents are a polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer.

In an embodiment, said polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer is Soluplus.

In an embodiment, said complex further comprises sodium deoxycholate.

In an embodiment, said complex is obtained via a continuous flow mixing process.

In an embodiment, a complex comprises complexing agents which are a polyvinylcaprolactam-polyvinyl acetate-polyethylene-glycol graft copolymer and pharmaceutically acceptable excipient which is sodium deoxycholate, in a total amount ranging from about 1.0 weight% to about 95.0 weight % based on the total weight of the complex.

In an embodiment, a complex comprises complexing agents which are a polyvinylcaprolactam-polyvinyl acetate-polyethylene-glycol graft copolymer and pharmaceutically acceptable excipient which is sodium deoxycholate, in a total amount ranging from about 5.0 weight% to about 95.0 weight % based on the total weight of the complex.

In an embodiment, said complexing agent which is a polyvinylcaprolactam-polyvinyl acetate-polyethylene-glycol graft copolymer and pharmaceutically acceptable excipient which is sodium deoxycholate comprise 10 weight% to about 95 weight% of the total weight of the complex.

Further disclosed herein is a process for the preparation of the complex, comprising the steps of mixing a solution of Abiraterone acetate, and at least one complexing agent and optionally one or more pharmaceutically acceptable excipients in a pharmaceutically acceptable solvent with an aqueous solution containing optionally least one pharmaceutically acceptable excipient.

In an embodiment, said process is performed in a continuous flow instrument.

In an embodiment, said continuous flow instrument is a microfluidic flow instrument.

In an embodiment, said pharmaceutically acceptable solvent is chosen from methanol, ethanol, isopropanol, n-propanol, acetone, acetonitrile, dimethyl-sulfoxide, tetrahydrofuran, or combinations thereof.

In an embodiment, said pharmaceutically acceptable solvent is tetrahydrofuran.

In an embodiment, said pharmaceutically acceptable solvent and said aqueous solvent are miscible with each other.

In an embodiment, said aqueous solvent comprises 0.1 to 99.9% weight of the final solution.

In an embodiment, said aqueous solvent comprises 50 to 90% weight of the final solution.

In an embodiment, said aqueous solvent comprises 50 to 80% weight of the final solution.

In an embodiment, said aqueous solvent comprises 50 to 70% weight of the final solution.

In an embodiment, said aqueous solvent comprises 50 to 60% weight of the final solution.

In an embodiment, said aqueous solvent comprises 50 % weight of the final solution.

In an embodiment, said aqueous solvent comprises 10 to 40 % weight of the final solution.

In an embodiment, said aqueous solvent comprises 10 to 30 % weight of the final solution.

In an embodiment, said aqueous solvent comprises 10 to 20 % weight of the final solution.

In an embodiment, said aqueous solvent comprises 10 % weight of the final solution.

In an embodiment, a pharmaceutical composition comprises the complex together with pharmaceutically acceptable carrier.

In an embodiment, said composition is suitable for oral, pulmonary, rectal, colonic, parenteral, intracisternal, intravaginal, intraperitoneal, ocular, otic, local, buccal, nasal, or topical administration.

In an embodiment, said composition is suitable for oral administration.

In an embodiment, said complex is for use in the manufacture of a medicament for the treatment of a certain type of prostate cancer that has spread to other parts of the body and earlier stages of prostate cancer and advanced breast cancer.

In an embodiment, said complex is used for treatment of a certain type of prostate cancer that has spread to other parts of the body and earlier stages of prostate cancer and advanced breast cancer.

In an embodiment, a method for reducing the therapeutically effective dosage of Abiraterone acetate compared to Zytiga® tablets comprises oral administration of a pharmaceutical composition as described herein.

Further disclosed herein is a stable complex comprising

a) 5 – 40% by weight of Abiraterone acetate;

b) 5 – 80% by weight of a polyvinylcaprolactam-polyvinyl acetate-polyethylene-glycol graft copolymer;

c) 0.1 – 50 % by weight of sodium deoxycholate;

wherein said complex has a controlled particle size in the range between 50 nm and 600 nm; and wherein said complex is not obtained via a milling process or by high pressure homogenization process, encapsulation process and solid dispersion process, but it is obtained by a mixing process, preferable continuous flow mixing process.

In an embodiment, said particle size is between 100 nm and 500 nm.

In an embodiment, said polyvinylcaprolactam-polyvinyl acetate-polyethylene-glycol graft copolymer is Soluplus.

In an embodiment, said complex exhibits no positive food effect based on *in-vivo* dog and clinical studies.

In an embodiment, said complex exhibits no positive food effect which allows significant dose reduction and the abandoning of the requirement of taking the drug on an empty stomach.

In an embodiment, said complex is instantaneously redispersable in physiological relevant media.

In an embodiment, said complex is stable in solid form and in colloid solution and/or dispersion.

In an embodiment, said complex has apparent solubility in water of at least 0.6 mg/mL.

In an embodiment, said complex shows X-ray amorphous character in the solid form.

In an embodiment, said complex has a PAMPA permeability of at least $0.5*10^{-6}$ cm/s when dispersed in distilled water, which does not decrease in time at least for 3 months.

The complexing agents and pharmaceutically acceptable excipients of the Abiraterone acetate complex formulae of the invention are selected from the group of pharmaceutically acceptable nonionic, anionic, cationic, ionic polymers, surfactants and other types of excipients. The complexing agents themselves or together with the pharmaceutically accepted excipients have the function to form a complex structure with an active pharmaceutical ingredient through non-covalent secondary interactions. The secondary interactions can form through electrostatic interactions such as ionic interactions, H-bonding, dipole-dipole interactions, dipole-induced dipole interactions, London dispersion forces, π–π interactions, and hydrophobic interactions. The complexing agents, pharmaceutically accepted excipients and active ingredients are selected from the group of complexing agents, pharmaceutically accepted excipients and active ingredients which are able to form such complex structures through non-covalent secondary interactions.

In some embodiments, the compositions may additionally include one or more pharmaceutically acceptable excipients, auxiliary materials, carriers, active agents or combinations thereof. In some embodiments, active agents may include agents useful for the treatment of a certain type of prostate cancer that has spread to other parts of the body and earlier stages of prostate cancer and advanced breast cancer.

Another aspect of the invention is the complex formulae of the Abiraterone acetate with complexing agents and pharmaceutically acceptable excipients in which the complexing agents and pharmaceutically acceptable excipients preferably are associated or interacted with the Abiraterone acetate especially as the results of the mixing process, preferably continuous flow mixing process. In some embodiment, the structure of the complex Abiraterone acetate formula is different from the core-shell type milled particle, precipitated encapsulated particles, micelles and solid dispersions.

The pharmaceutical composition of the invention can be formulated: (a) for administration selected from the group consisting of oral, pulmonary, rectal, colonic, parenteral, intracisternal, intravaginal, intraperitoneal, ocular, otic, local, buccal, nasal, and topical administration; (b) into a dosage form selected from the group consisting of liquid dispersions, gels, aerosols, ointments, creams, lyophilized formulations, tablets, capsules; (c) into a dosage form selected from the group consisting of controlled release formulations, fast melt formulations, delayed release formulations, extended release formulations, pulsatile release formulations, and mixed immediate release and controlled release formulations; or (d) any combination of (a), (b), and (c).

The compositions can be formulated by adding different types of pharmaceutically acceptable excipients for oral administration in solid, liquid, local (powders, ointments or drops), or topical administration, and the like.

A preferred dosage form of the invention is a solid dosage form, although any pharmaceutically acceptable dosage form can be utilized.

Solid dosage forms for oral administration include, but are not limited to, capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active agent is admixed with at least one of the following excipients: (a) one or more inert excipients (or carriers), such as sodium citrate or dicalcium phosphate; (b) fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, microcrystalline cellulose and silicic acid; (c) binders, such as cellulose derivatives, alginates, gelatin, polyvinylpyrrolidone, sucrose and acacia; (d) humectants, such as glycerol; (e) disintegrating agents, such as crospovidon, sodium starch glycolate, effervescent compositions, croscarmellose sodium,, calcium carbonate, potato or tapioca starch, alginic acid, certain complex silicates and sodium carbonate; (f) solution retarders, such as acrylates, cellulose derivatives, paraffin; (g) absorption accelerators, such as quaternary ammonium compounds; (h) wetting agents, such as polysorbates, cetyl alcohol and glycerol monostearate; (i) adsorbents, such as kaolin and bentonite; and (j) lubricants, such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, or mixtures thereof. For capsules, tablets, and pills, the dosage forms may also comprise buffering agents.

Besides such inert diluents, the composition can also include adjuvants, such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

Advantages of the complex Abiraterone acetate formulae of the invention include, but are not limited to (1) physical and chemical stability, (2) instantaneous redispersibility, (3) stability in colloid solution or dispersion in the therapeutic time window, (4) increased apparent solubility compared to the conventional Abiraterone acetate formulation, (5) increased permeability, (6) increased oral bioavailability in fasted state, (7) no positive food effect and (8) good processability.

Beneficial features of the present invention are as follows: the good/instantaneous redispersibility of solid complex formulae of Abiraterone acetate in water, biologically relevant media, e.g. SGF, FessiF and FassiF media and gastro intestinal fluids and adequate stability in colloid solutions and/or dispersion in the therapeutic time window.

One of the preferred characteristics of the complex Abiraterone acetate formulae of the present invention is their increased apparent solubility and permeability. In some embodiments, the apparent solubility and permeability of the complex Abiraterone acetate formulae is at least 0.6 mg/mL and $0.5*10^{-6}$ cm/s, respectively.

Another preferred characteristic of the complex Abiraterone acetate formulae of the present invention relates to the enhanced pharmacokinetic performance of the complex Abiraterone acetate formulae. It exhibits no positive food effect which allows significant dose reduction and the abandoning of the requirement of taking the drug on an empty stomach.

## BRIEF DESCRIPTION OF THE DRAWINGS

**Figure 1** shows the complexing agent screening for formula selection in order to select the formulae having instantaneous redispersibility.

**Figure 2** shows comparative PAMPA assays of complex Abiraterone acetate formulations consisting of different pharmaceutically acceptable excipients.

**Figure 3** shows comparative redispersibility, stability tests and PAMPA assays of complex Abiraterone acetate formulations containing Soluplus and SDC in different ratios.

**Figure 4** shows comparative PAMPA assays of complex Abiraterone acetate formulations containing Soluplus and SDC in different ratios.

**Figure 5** shows the composition of the solution used for the production of the colloid solutions of Abiraterone acetate complex formulation of the present invention.

**Figure 6** shows effect of the flow rate ratio on the appearance and stability of the redispersed formulae.

**Figure 7** shows the stability of the redispersed complex Abiraterone acetate formulation prepared with different flow rate ratios.

**Figure 8** shows the particle size distribution of the as-synthetized colloid solution and redispersed solid complex of the selected formula.

**Figure 9** shows stability of the redispersed complex Abiraterone acetate formulation prepared with intensified process flow rates.

**Figure 10** shows the effect of the production temperature on the quality of complex Abiraterone acetate formulation.

**Figure 11** shows dissolution profile of wet milled Abiraterone acetate and complex Abiraterone acetate in FaSSIF medium.

**Figure 12** shows dissolution profile of wet milled Abiraterone acetate and complex Abiraterone acetate in FeSSIF medium.

**Figure 13** shows PAMPA permeability of extruded Abiraterone acetate formulation and complex Abiraterone formulation of the present invention.

**Figure 14** shows the stability of the colloid solution in simulated fasted and fed state (GI tract simulation).

**Figure 15** shows dissolution profile of crystalline Abiraterone acetate, physical mixture, Zytiga and complex Abiraterone acetate in FaSSIF medium.

**Figure 16** shows dissolution profile of crystalline Abiraterone acetate, physical mixture, Zytiga and complex Abiraterone acetate in FeSSIF medium.

**Figure 17** shows the stability of the solid form detected as the PAMPA permeability measured after redispersion in distilled water after storage at different conditions.

**Figure 18** shows scanning electron microscope (SEM) images about the complexes of Abiraterone acetate according to the present invention (B: the complex of the present invention containing Abiraterone acetate, polyvinylcaprolactam-polyvinyl acetate-polyethylene-glycol graft copolymer (Soluplus) and sodium deoxycholate and the placebo samples prepared in the absence of Abiraterone acetate (A).

**Figure 19** shows ATR spectra of crystalline Abiraterone acetate (A), complex Abiraterone acetate (B), placebo sample (C), polyvinylcaprolactam-polyvinyl acetate-polyethylene-glycol graft copolymer (Soluplus) (D) and sodium deoxycholate (E).

**Figure 20** shows Raman spectra of crystalline Abiraterone acetate (A), complex Abiraterone acetate (B), placebo sample (C), polyvinylcaprolactam-polyvinyl acetate-polyethylene-glycol graft copolymer (Soluplus) (D) and sodium deoxycholate (E).

**Figure 21** shows powder X-ray diffractograms of crystalline Abiraterone acetate, place sample and complex Abiraterone acetate formulation.

**Figure 22** shows pH of reconstituted solutions of complex Abiraterone acetate formulation.

**Figure 23** shows water content of PiB formulations right after the production.

**Figure 24** shows Abiraterone acetate content of the PIB formulations after reconstitution.

**Figure 25** shows Composition of the complex Abiraterone tablets.

**Figure 26** shows plasma concentration of Abiraterone following the oral administration of Zytiga to beagle dogs. N=4, dose: 50 mg.

**Figure 27** shows plasma concentration of Abiraterone following the oral administration of the Complex Abiraterone acetate formulation to beagle dogs. N=4, dose: 50 mg.

**Figure 28** shows pharmacokinetic parameters following the oral administration of Zytiga (a) of the Complex Abiraterone acetate forula (b) to beagle dogs. N=4, dose: 50 mg.

**Figure 29** shows plasma concentration of Abiraterone following the oral administration of 200 mg complex Abiraterone acetate formulation of the present invention to 10 healthy male volunteers in the fasted and in the fed state.

**Figure 30** shows pharmacokinetic parameters following the oral administration of 1000 mg Zytiga (*EMEA Assessment Report For Zytiga (abiraterone),* Acharya et al., 2012 and Attard et al., 2008.) or 200 mg complex Abiraterone acetate formulation to 10 healthy male volunteers in the fasted and in the fed state.

**EXAMPLES**

Several pharmaceutically acceptable complexing agents and pharmaceutically acceptable excipients and their combinations were tested in order to select the formulae having instantaneous redispersibility. One of the examples that displayed an acceptable level of redispersibility was selected for further analysis (Figure 1).

PAMPA permeability of the selected formulations was measured in order to select the complex Abiraterone acetate formulation having the best *in vitro* performance (Figure 2). PAMPA permeability measurements were performed as described by *M. Kansi et al.* (Journal of medicinal

chemistry, 41, (1998) pp 1007) with modifications based on *S. Bendels et al* (Pharmaceutical research, 23 (2006) pp 2525). Permeability was measured in a 96-well plate assay across an artificial membrane composed of dodecane with 20% soy lecithin supported by a PVDF membrane (Millipore, USA). The receiver compartment was phosphate buffered saline (pH 7.0) supplemented with 1% sodium dodecyl sulfate. The assay was performed at room temperature; incubation time was 1-24 hours. The concentration in the receiver compartment was determined by UV-VIS spectrophotometry (Thermo Scientific Genesys S10).

Polyvinylcaprolactam-polyvinyl acetate-polyethylene-glycol graft copolymer (Soluplus) as complexing agent and sodium deoxycholate (SDC) as pharmaceutically accepted excipient were selected to form complex Abiraterone acetate formulation having improved material characteristics. Based on the *in-vitro* properties (redispersibility profile, stability of the redispersed solution and PAMPA permeability) (Figure 3 and Figure 4) the optimal weight ratio of Abiraterone acetate, polyvinylcaprolactam-polyvinyl acetate-polyethylene-glycol graft copolymer (Soluplus) and sodium deoxycholate (SDC) in the complex formulation of the present invention was found to be 1:4:0.6.

The technological approach applied to the manufacture powder of the complex Abiraterone acetate formulation of the present invention relied on freeze-drying or spray-drying of the colloid solution of complex Abiraterone acetate formulation containing selected complexation agent(s), pharmaceutically acceptable excipient(s) and the active drug substance. The colloid solution of complex Abiraterone acetate formulation of the present invention was prepared by continuous flow mixing of two solutions. One of the solutions contained the Abiraterone acetate and the complexation agent(s). The second solution was water and contains the pharmaceutically acceptable excipient(s). The colloid solution was solidified right after the preparation. Properties of the produced colloid solution could be modified during the process by precise control and optimization of various transformation parameters (e.g. temperature, flow rate and concentration).

Colloid solutions of Abiraterone acetate complex formulation of the present invention were prepared by continuous mixing process using Solution 1/a,b,c containing Abiraterone acatetae and Soluplus® and Solution 2/a,b,c containing sodium deoxycholate (SDC) as shown in Figure 5. The optimized Abiraterone acetate : excipients ratio of the complex Abiraterone acetate formulation (1:4:0.6) was kept constant. Different flow rate ratios were tested in order to determine the optimal manufacturing condition. The total flow rate of the production (sum of

the Solvent 1 and Solvent 2 flow rates) and the amount of the colloid solution collected were kept constant at 50.0 mL/min and 25.0 mL, respectively. The appearance of the produced colloid solution and the stability of the redispersed complex Abiraterone acetate formulations were used to determine the optimal parameters of the production. Figure 6 summarizes the results.

The stability of the redispersed freeze-dried samples was monitored. Solid formulations of complex Abiraterone acetate were redispersed in purified water or in biorelevant media using 1 mg/mL concentration for the Abiraterone acetate. The stability of redispersed formulations was monitored by filtering it with 0.45 μm pore size filter at different time points. The Abiraterone acetate contents of the filtrates were determined by UV-VIS spectrophotometry (VWR UV-3100 PC) (Figure 7). Flow rate ratio of 1 : 4 was found to be optimal for the production of complex Abiraterone acetate formulation of the present invention.

A colloid solution of Abiraterone acetate complex formula with the optimal ratio of the complexing agent and pharmaceutically acceptable excipient of the present invention was prepared by continuous flow mixing in a flow instrument. As a starting solution, 1000 mg Abiraterone acetate and 4000 mg polyvinylcaprolactam-polyvinyl acetate-polyethylene-glycol graft copolymer (Soluplus) dissolved in 100 mL tetrahydrofuran was used. The prepared solution was passed into the instrument with 10 mL/min flow rate. Meanwhile, aqueous solvent containing 750 mg sodium deoxycholate in 500 mL water was passed into the instrument with 40 mL/min flow rate, where Abiraterone acetate formed complex Abiraterone acetate composition. The colloid solution of the complex Abiraterone acetate is continuously produced at atmospheric pressure. The produced colloid solution was frozen on dry-ice and then it was lyophilized using a freeze drier equipped with -110°C ice condenser, with a vacuum pump. For the process monitoring particle size and size distribution of the complex Abiraterone acetate formula was used. Particle size and size distribution of the colloid solution right after the production and the reconstituted solid complex Abiraterone acetate formula are seen in Figure 8 It was found to be D(50) = 310 nm for the produced colloid solution and D(50) = 158 nm for the redispersed particles, respectively.

Process intensification was performed in order to increase the efficiency of the production. The flow rate ratio was increased from 1:4 to 10:40. The produced colloid solution of the complex Abiraterone acetate formulation of the present invention was solid formulated using freeze-drying method as described above. The samples were reconstituted using purified water. The physical stability of redispersed solution was also monitored in time by the determination of the

Abiraterone acetate content of the redispersed solution after filtration (Figure 9). Process intensification did not have effect on the stability of the redispersed solution.

The effect of the production temperature on the product quality was investigated. A colloid solution of complex Abiraterone acetate formulation of the present invention was prepared using the intensified and optimized parameter sets described above at 20-, 30- and 40 °C temperatures. The colloid solutions produced were then freeze-dried. The freeze-dried samples were redispersed in purified water and their stability was monitored in time as previously described (Figure 10). Optimal production temperature was found to be 30 °C.

**Comparative formulation studies**

Crystalline Abiraterone acetate was wet milled in the presence of polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer (Soluplus) and Sodium deoxycholate in order to produce nanosized Abiraterone acetate particles. The milling process was carried out using a Fritsch Pulverisette 6 instrument. Volume of $Si_2N_3$ milling vessel was 250 mL. 25 milling balls with 10 mm diameter was used. Milling speed was set to be 500 rpm. 5x1 h milling time was applied.

Milled suspension contained 0.447 g Abiraterone acetate, 1.178 g Soluplus and 0.267 g Sodium deoxycholate in 12.5 mL MilliQ water. The wet milling process resulted in a foam-like suspension which was freeze-dried to obtain solid powder.

Dissolution profile of wet milled Abiraterone was compared with the dissolution of crystalline Abiraterone acetate and complex Abiraterone acetate of the present invention at 37 °C. 10 mg Abiraterone acetate equivalent samples were dispersed in 20 mL FaSSIF (fasted) and FeSSIF (fed) media and were filtered by 20 nm disposable syringe filter. The active content in the filtrate was measured by UV-Vis spectrophotometry.

Abiraterone acetate dissolution from the complex Abiraterone acetate formulation of the present invention is 3-fold higher in FeSSIF and 9-fold higher in FaSSIF compared to the dissolved amount of Abiraterone acetate from the wet milled samples (Figure 11 and Figure 12).

Pharmaceutical formulation of Abiraterone acetate was prepared by extrusion technique using polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer (Soluplus) and Sodium deoxycholate as pharmaceutically acceptable excipients. The extrusion was carried out using HAAKE™ MiniLab II Micro Compounder (Thermo Scientific) instrument.

In a premixing step, dry powders (17.9 w/w% Abireterone-acetate, 71.4 w/w% Soluplus, 10.7 w/w% SDC) were mixed in a mortar then 8 g powder mixture was fed into the extruder. The extrusion was performed at 130 $^0$C with a screw rate of 20 rpm. PAMPA permeability of the extruded Abiraterone acetate formulation was compared to the PAMPA permeability of complex Abiraterone acetate formulation of the present invention in water, FaSSIF and FeSSIF media. PAMPA permeability of complex Abiraterone acetate was 2-fold higher in FeSSIF medium than the permeability of the extruded formulation (Figure 13).

**Comparative solubility tests**

The apparent solubility of complex Abiraterone acetate formula and unformulated compounds was measured by UV-VIS spectroscopy at room temperature. The samples were dispersed in distillated water and the resulting dispersions were filtered by 100 nm disposable syringe filter. The active content in the filtrate was measured by UV-Vis spectrophotometry and the solubility was calculated. The filtrate may contain Abiraterone acetate complex particles which could not be filtrated out using 100 nm pore size filter.

Solubility of complex Abiraterone acetate formula and unformulated compound was 0.6 mg/mL and < 0.004 mg/mL, respectively.

**Comparative *in-vitro* PAMPA assays**

PAMPA permeability of complex Abiraterone acetate formula was above $0.5*10^{-6}$ cm/s, while it was below $0.1*10^{-6}$ cm/s for the unformulated compound.

**Stability of the colloid solution in the GI tract**

A simulated passage through the GI tract was performed in order to detect any instability of the colloid solution at pH values and bile acid concentrations representative of the GI tract in the fasted and in the fed conditions. No significant change in light scattering of the colloid solution was observed in the simulation indicating that the complex Abiraterone acetate formulation is stable under these conditions in the time window of the absorption process in both the fasted and in the fed conditions (Figure 14).

**Comparative dissolution tests**

Dissolution of crystalline Abiraterone acetate, physical mixture of the composition of the present invention and complex Abiraterone acetate formulation of the present invention was measured by UV-VIS spectroscopy at 37 °C. 10 mg Abiraterone acetate equivalent samples were dispersed in 20 mL FaSSIF and FeSSIF media and were filtered by 100 nm (crystalline Abiraterone acetate, Zytiga and the physical mixture) or a 20 nm (Abiraterone acetate complex) disposable syringe filter. The active content in the filtrate was measured by UV-Vis spectrophotometry.

Dissolution of Abiraterone acetate from the complex Abiraterone acetate formulation of the present invention outperformed the dissolution of Abiraterone acetate from the crystalline Abiraterone, physical mixture and Zytiga in each tested condition (Figure 15 and Figure 16). In FaSSIF condition, more than 35 % of the Abiraterone acetate dissolved from the complex Abiraterone acetate formulation within 0.5 h, while it was less than 4 % for Zytiga in 4 h. In FeSSIF condition Abiraterone dissolution from the complex Abiraterone acetate formulation of the present invention exceeded 90% within 0.5 h, while the dissolution of Abiraterone acetate from Zytiga was less than 35 % in 4 h.

**Stability of the solid form**

PAMPA permeability of the solid (Formulation 1) is measured after storage at different conditions. 3 month storage at 4 °C, RT or 40 °C 75% relative humidity showed no significant decrease in the measured PAMPA permeability under any of the conditions tested (Figure 17).

**Structural analysis**

Morphology of complex Abiraterone acetate formulation was investigated using FEI Quanta 3D scanning electron microscope. The morphology of the complex of the present invention was compared to the placebo samples (prepared in the absence of Abiraterone acetate), prepared as described above. Complexes of Abiraterone acetate of the present invention consists of spherical particles (Figure 18 B). In the lack of the active compound, the complexing agent(s) and pharmaceutically acceptable excipient(s) do not form spherical particles (Figure 18 A).

Structural analysis was performed by using Bruker Vertex 70 FT-IR spectrometer with Bruker Platinum diamond ATR unit and HORIBA JobinYvon LabRAM HR UV–VIS–NIR equipped with Olympus BXFM free-space microscope using a 785 nm (NIR) diode laser.

In an embodiment, said complex is characterized by infrared (ATR) spectrum having main/characteristic absorption peaks at least at 569 $cm^{-1}$, 607 $cm^{-1}$, **713 $cm^{-1}$**, 797 $cm^{-1}$, 843 $cm^{-1}$, 942 $cm^{-1}$, 973 $cm^{-1}$, **1030 $cm^{-1}$, 1103 $cm^{-1}$**, 1148 $cm^{-1}$, 1195 $cm^{-1}$, 1241 $cm^{-1}$, 1333 $cm^{-1}$, 1371 $cm^{-1}$, 1421 $cm^{-1}$, 1441 $cm^{-1}$, 1477 $cm^{-1}$, 1336 $cm^{-1}$, **1734 $cm^{-1}$**, 2858 $cm^{-1}$, 2928 $cm^{-1}$ characteristic absorption peaks (Figure 19).

In a preferred embodiment, said complex is characterized by infrared (ATR) spectrum having main/characteristic absorption peaks at least at **713 $cm^{-1}$, 1030 $cm^{-1}$, 1103 $cm^{-1}$1734 $cm^{-}$** characteristic absorption peaks (Figure 19).

In an embodiment, said complex is further characterized by Raman spectrum having main/characteristic absorption peaks at 239 $cm^{-1}$, **581 $cm^{-1}$**, 701 $cm^{-1}$ , 797 $cm^{-1}$, 846 $cm^{-1}$, **1026 $cm^{-1}$**, 1088 $cm^{-1}$, 1196 $cm^{-1}$, 1264 $cm^{-1}$, **1445** $cm^{-1}$, 1584 $cm^{-1}$, 1600 $cm^{-1}$, 1735 $cm^{-1}$ (Figure 20).

In a preferred embodiment, said complex is further characterized by Raman spectrum having main/characteristic absorption peaks at **581 $cm^{-1}$, 1026 $cm^{-1}$**, and **1445** $cm^{-1}$ (Figure 20).

The structure of the complex Abiraterone acetate of the present invention was investigated by powder X-ray diffraction (XRD) analysis (Philips PW1050/1870 RTG powder-diffractometer). The measurements showed that the complex Abiraterone acetate composition was XRD amorphous (see in Figure 21). Characteristic reflections on the diffractogram of complex Abiraterone acetate and placebo sample are be attributed to sample holder.

**Powder in a bottle formulation**

50 mg dose strength powder in a bottle (PIB) formulation of complex Abiraterone acetate of the present invention was prepared. Following production parameters were used for the manufacturing process:

| | |
|---|---|
| Solvent 1: | Tetrahydrofuran |
| $C_{Abiraterone\ acetate}$: | 10 mg/mL |
| $C_{Soluplus®}$: | 40 mg/mL |
| Solvent 2: | Purified water |
| $C_{Sodium\ deoxycholate}$: | 3.5 mg/mL |
| Flow $rate_{Solution\ 1}$: | 10.0 mL/min |
| Flow $rate_{Solution\ 2}$: | 40.0 mL/min |
| Temperature: | 30 °C |
| Filling volume: | 25 mL |

| | |
|---|---|
| Freezing time: | 30 min in dry-ice/Acetone bath at least |
| Freeze-drying time: | 36 h at least |

The Abiraterone acetate content of the produced colloid was investigated right after the production and after filtration with 0.45 μm pore size filter. The active content of the colloid solution was 2.007 mg/mL, while the Abiraterone acetate content of the filtrate was found to be 2.026 mg/mL. The nominal active content of the solution mixture is 2.000 mg/mL.

*Determination of mass uniformity of PiB formulation:* 25 mL aliquots of produced solution mixture were filled into 200 mL amber glass pharmaceutical bottles. The weight of the PiB formulation was checked after the freeze-drying process. The average mass of the freeze-dried powders in the bottles was 0.2773 mg ± 0.0015 mg.

*Determination of content uniformity of PiB formulation:* Content uniformity of the freeze-dried PiB formulations was investigated. The freeze-dried powder was dissolved in methanol. The Abiraterone acetate content was measured by HPLC method. Each samples tested met AV NMT 15 criterion.

*Determination of stability of PiB formulation in solid and reconstituted solution*: Abiraterone acetate complex PiB formulations were reconstituted with 50 mL purified water right after the production and 2 weeks storage at 40 $^{0}$C. The stability of reconstituted colloid solutions were monitored in time determining the active content of the colloid solution after filtration with 0.45 μm pore size filter. The Abiraterone acetate contents of the filtrate were in a good agreement right after the production and 2 weeks storage. Both reconstitutions resulted in homogenous opalescent colloid solutions which were practically free of visible particles.

The reconstituted colloid solution was ready for administration within 10 minutes. The reconstituted solution was stable for at least 4 hour at room temperature.

*Determination of pH of reconstituted PiB formulations*: pH of the reconstituted PiB formulations of complex Abiraterone acetate of the present invention was investigated. The pH of each reconstituted solution was within the pH range recommended by the ICH guidelines for the products intended for oral administration (Figure 22).

*Determination of water content of PiB formulation*: Karl Fischer titration was used to determine the water content of the PiB formulations of complex Abiraterone acetate of the present invention right after the production (Figure 23).

The water content of the formulation met the acceptance criteria specified in the relevant ICH guidelines in each case.

*Reconstitution and Administration for 50 mg Dose:* Reconstitution of the PiB formulations of complex Abiraterone acetate of the present invention using 50 mL Ph.Eur water yielded an opalescent solution within 10 minutes. This solution had to be administered orally. Another 190 mL of Ph.Eur water should be added to the bottle making the total of orally administered volume 240 mL.

*Reconstitution and Administration for 100 mg Dose:* Reconstitution of the PiB formulations of complex Abiraterone acetate of the present invention using 50 mL of Ph.Eur water yielded an opalescent solution. This liquid had to be administered orally. Another 70 mL of Ph.Eur water should be added to the bottle and administered orally. The administration should be repeated using a second bottle of 50 mg strength PiB formulation. The total of orally administered volume will be 240 mL.

*Reconstitution and Administration for 200 mg Dose:* Reconstitution of the PiB formulations of complex Abiraterone acetate of the present invention using 50 mL of Ph.Eur water yielded an opalescent solution. This liquid has to be administered orally. Another 10 mL of Ph.Eur water should be added to the bottle and administered orally. The administration should be repeated four times using another three bottles of 50 mg strength PiB formulation. The total of orally administered volume will be 240 mL.

The reconstitution of the PiB formulations of the complex Abiraterone acetate of the present invention was tested. Different amount of Ph.Eur water was added to the PiB formulations in order to reconstitute the freeze-dried powder. The Abiraterone acetate content of the reconstituted colloid solutions was measured. Then the bottles were rinsed once adding 10 mL of Ph.Eur water. The Abiraterone acetate content of rising liquid was also measured. Finally the

bottles were rinsed with methanol to dissolve completely the remaining Abiraterone acetate. The Abiraterone acetate content was also determined in this case (Figure 24). More than 98 % of the Abiraterone acetate content was in the reconstituted volume. After one rising step less than 0.7 % Abiraterone acetate remained in the bottles.

**Enteric coated tablet containing complex Abiraterone acetate**

Freeze dried complex Abiraterone acetate formulation of the present invention was dry granulated via slugging or roll compaction in order to obtain powder with sufficient flowability. The particle size of the granulated complex Abiraterone acetate formulation was between 160-320 μm. The granulated complex Abiraterone acetate formulation was then blended with lactose-monohydrate, microcrystalline cellulose as fillers, crosscarmellose sodium as disintegrant and sodium-deoxycholate as absorption supporting agent (Figure 25).

The powder mixture containing granulated complex Abiraterone acetate formulation of the present invention was compressed into tablets with 50 mg dose strength. Disintegration time of the tablets containing complex Abiraterone acetate formulation in simulated intestinal fluid was less than 5 minutes. The cores of tablets containing complex Abiraterone acetate formulation were coated with anionic copolymer based on methacrylic acid and ethyl acrylate.

***In-vivo* pharmacokinetics**

***In-vivo* PK test in animals**

The administration of 50 mg Zytiga to beagle dogs in the fasted and in the fed (high fat) state absorption was rapid in both cases, however, plasma concentrations, $C_{max}$ and $AUC_{inf}$ values were over 5-fold lower in the fasted state than in the fed (high fat) state (Figure 26 and Figure 27). Following oral administration of the complex Abiraterone acetate formulation to fasted and fed (high fat) beagle dogs the maximal plasma Abiraterone concentrations were detected at 0.5 hour indicating immediate absorption of the active ingredient from the formula. No significant differences were observed in the plasma concentrations when the compound was administered in the fasted or in the fed (high fat) state (Figure 27). $AUC_{inf}$ and $C_{max}$ values calculated from the curves showed significantly higher exposure for the complex Abiraterone acetate formulation of the present invention than for Zytiga both in the fasted and in the fed state along with total elimination of the positive food effect Zytiga exhibits (Figure 28).

***Pharmacokinetics in healthy man***

Ten healthy male volunteers between the ages of 45 and 65 were enrolled in a clinical pharmacokinetic study where 200 mg of the complex abiraterone formulation was administered orally in the fasted and in the fed state. Maximal plasma Abiraterone concentrations were detected at 0.5 hour indicating immediate absorption of the Abiraterone acetate from the complex Abiraterone formulation of the present invention. No significant increase was observed in the plasma concentrations in the fed state when compared to the fasted state, actually, there plasma concentration were lower in the fed state at early time points, while were practically identical after the 4 hour time point (Figure 29). $AUC_{inf}$ and $C_{max}$ values calculated from the curves and variability of exposure and food effect was calculated form these pharmacokinetic parameters and compared to published clinical pharmacokinetic data for 1000 mg Zytiga (Figure 30). AUC in the fasted state for the 200 mg dose of the complex Abiraterone Acetate formulation of the present invention was 80% of the 1000 mg dose for Zytiga, therefore, significant dose reduction is possible using the complex Abiraterone acetate formulation of the present invention. Also, the very large positive food effect was eliminated which shows that the requirement for Zytiga to be taken for an empty stomach was eliminated. The variability of exposure was also significantly reduced. The elimination half life was identical to data published for Zytiga (*EMEA Assessment Report For Zytiga (abiraterone)*).

WHAT IS CLAIMED IS

1. A stable complex with improved physicochemical characteristics and enhanced biological performance comprising

   a) as active compound Abiraterone acetate; or a combination of active compounds including Abiraterone acetate;

   b) at least one complexing agent chosen from polyethylene glycol glycerides composed of mono-, di- and triglycerides and mono- and diesters of polyethylene glycol, hydroxypropylcellulose, poloxamers, vinylpyrrolidone/vinyl acetate copolymer, polyethylene glycol, poly(2-ethyl-2-oxazoline), polyvinylpyrrolidone, block copolymers based on ethylene oxide and propylene oxide, poly(maleic acid/methyl vinyl ether), polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer, polyoxyl 15 hydroxystearate, polyvinyl alcohol-polyethylene glycol graft copolymer and d-alpha tocopheryl polyethylene glycol 1000 succinate;

   c) sodium deoxycholate as pharmaceutically acceptable excipient;

wherein said complex consists of spherical particles, and wherein said complex has a particle size, which is less than 600 nm, and possesses the following features:

- it is instantaneously redispersible in physiological relevant media;
- it has increased dissolution rate;
- it is stable in solid form and in colloid solution and/or dispersion;
- its apparent solubility in water is of at least 0.6 mg/mL;
- it shows X-ray amorphous character in the solid form;
- it has a PAMPA permeability of at least $0.5*10^{-6}$ cm/s when dispersed in distilled water, which does not decrease in time at least for 3 months;
- exhibits no positive food effect which allows significant dose reduction and the abandoning of the requirement of taking the drug on an empty stomach;
- the variability of exposure is significantly reduced when compared to Zytiga.

2. The complex as claimed in Claim 1, wherein said complex has a particle size in the range between 50 nm and 600 nm.

3. The complex as claimed in Claim 1 and 2, wherein said complex has a particle size in the range between 100 nm and 500 nm.

4. The complex as claimed in Claim 1 to 3, wherein

   a) the complexing agent is selected from the group consisting of a polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer; and

   b) the excipient is sodium deoxycholate.

5. The complex as claimed in Claim 1 to 4, wherein said complex is composed of

   a) 5 to 40% by weight of Abiraterone acetate;

   b) 5 to 80% by weight of a polyvinylcaprolactam-polyvinyl acetate-polyethylene-glycol graft copolymer;

   c) 0.1 to 50 % by weight of sodium deoxycholate.

6. The complex as claimed in Claim 1 to 4, wherein said complex comprises as active agent Abiraterone acetate and one or more additional active agent, which is selected from the group of agents selected from the group of Rifampicin, Prednisone/Prednisolone, Dexamethasone, Ketoconazole, Testosterone Enanthate, Enzalutamide, Dextromethorphan hydrobromide, Dexamethasone, Exemestane, Goserelin, Degarelix, Veliparib, Dovitinib, Leuprolide, Alisertib, cabozantinib, Cabazitaxel, Dasatinib, Glucocorticoid, Docetaxel, Dutasteride, Hydroxychloroquine, Ipilimumab, Metformin, Sunitinib, Selinexor, Everolimus, Trastuzumab, Tamoxifen, and combinations thereof.

7. The stable complex as claimed in Claims 1 to 3 comprising

   a) Abiraterone acetate; or a combination of active compounds including Abiraterone acetate;

   b) as complexing agent polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer;

   c) as excipient sodium deoxycholate.

8. The stable complex as claimed in Claims 1 to 3 comprising

   a) Abiraterone acetate;

   b) as complexing agent polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer;

   c) as excipient sodium deoxycholate;

wherein said complex is characterized by infrared (ATR) spectrum having main/characteristic absorption peaks at least at 569 $cm^{-1}$, 607 $cm^{-1}$, **713 $cm^{-1}$**, 797 $cm^{-1}$, 843 $cm^{-1}$, 942 $cm^{-1}$, 973 $cm^{-1}$, **1030 $cm^{-1}$, 1103 $cm^{-1}$**, 1148 $cm^{-1}$, 1195 $cm^{-1}$, 1241 $cm^{-1}$, 1333 $cm^{-1}$, 1371 $cm^{-1}$, 1421 $cm^{-1}$, 1441 $cm^{-1}$, 1477 $cm^{-1}$, 1336 $cm^{-1}$, **1734 $cm^{-1}$**, 2858 $cm^{-1}$, 2928 $cm^{-1}$ characteristic absorption peaks; and is characterized by Raman spectrum having main/characteristic absorption peaks at least at 239 $cm^{-1}$, **581 $cm^{-1}$**, 701 $cm^{-1}$ , 797 $cm^{-1}$, 846 $cm^{-1}$, **1026 $cm^{-1}$**, 1088 $cm^{-1}$, 1196 $cm^{-1}$, 1264 $cm^{-1}$, **1445** $cm^{-1}$, 1584 $cm^{-1}$, 1600 $cm^{-1}$, 1735 $cm^{-1}$characteristic absorption peaks.

9. A process for the preparation of a stable complex as claimed in Claims 1 to 8, said process comprising the step of mixing a solution of the active agent and at least one complexing agent and optionally one or more pharmaceutically acceptable excipient in a pharmaceutically acceptable solvent with an aqueous solution containing optionally least one pharmaceutically acceptable excipient.

10. The process as claimed in Claim 9, wherein said process is performed in a continuous flow instrument.

11. The process as claimed in Claim 9 and 10, wherein said continuous flow instrument is a microfluidic flow instrument.

12. The process as claimed in Claim 9 to 11, wherein said pharmaceutically acceptable solvent is chosen from methanol, ethanol, isopropanol, n-propanol, acetone, acetonitrile, dimethyl-sulfoxide, tetrahydrofuran, or combinations thereof, preferably said pharmaceutically acceptable solvent is tetrahydrofuran.

13. The process as claimed in Claim 9 to 11, wherein said solvents are miscible with each other and the aqueous solvent comprises 0.1 to 99.9% weight of the final solution.

14. A composition comprising the stable complex as claimed in Claims 1 to 7, together with a pharmaceutically acceptable carrier.

15. The pharmaceutical composition as claimed in Claim 14, wherein said composition is suitable for oral, pulmonary, rectal, colonic, parenteral, intracisternal, intravaginal, intraperitoneal, ocular, otic, local, buccal, nasal, or topical administration, preferable the composition is suitable for oral administration.

16. The complex as claimed in Claims 1 to 7 for use in the manufacture of a medicament for the treatment of a certain type of prostate cancer that has spread to other parts of the body and earlier stages of prostate cancer and advanced breast cancer.

17. The complex as claimed in Claim 16 for use in the treatment of a type of prostate cancer that has spread to other parts of the body and earlier stages of prostate cancer and advanced breast cancer.