PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

ABIRATERONE 500 TEVA film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 500 mg of abiraterone acetate.

Excipient with known effect:

Contains sugar (lactose monohydrate) 90 mg per tablet.

For the full list of excipients, see **section 6.1**.

3. PHARMACEUTICAL FORM

Film-coated tablets

ABIRATERONE 500 TEVA: Yellow, oblong film-coated tablet, debossed with “A436” on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ABIRATERONE 500 TEVA is indicated with low-dose corticosteroids (prednisone or prednisolone) in adult males for the treatment of:

- high-risk metastatic hormone treatment naïve prostate cancer (mHNPC) or newly diagnosed high-risk metastatic hormone sensitive prostate cancer (mHSPC) in combination with androgen deprivation therapy (LHRH agonist or surgical castration).

  High-risk is defined as having at least 2 of the following 3 risk factors:

  (1) Gleason score of ≥ 8;

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(2) presence of 3 or more bone lesions;

(3) presence of measurable visceral (excluding lymph node disease) metastasis.

- metastatic castration resistant prostate cancer with bone metastases who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated.
- metastatic advanced prostate cancer (castration resistant prostate cancer) who have received prior chemotherapy containing docetaxel.

4.2 Posology and method of administration

This medicine should be prescribed by a medical practitioner experienced in chemotherapy.

Posology

The recommended dose of ABIRATERONE 500 TEVA is 1 g (two 500 mg tablets) as a single daily dose that **must not be taken with food**. ABIRATERONE 500 TEVA must be taken on an empty stomach, at least two hours after a meal (see Method of administration below). Taking ABIRATERONE 500 TEVA with food increases systemic exposure to abiraterone (see **section 4.5** and 5.**2**).

Patients should be maintained on ABIRATERONE 500 TEVA until radiographic progression and symptomatic / clinical progression and until PSA progression (confirmed 25 % increase over the patient's baseline / nadir).

Dosage of prednisone or prednisolone

For metastatic hormone naïve prostate cancer (mHNPC) or hormone sensitive prostate cancer (mHSPC), ABIRATERONE 500 TEVA is used with 5 mg prednisone or prednisolone once daily.

For metastatic castration-resistant prostate cancer (mCRPC), ABIRATERONE 500 TEVA is used with 10 mg prednisone or prednisolone daily.

Recommended monitoring

Serum transaminases and bilirubin should be measured prior to starting treatment with ABIRATERONE 500 TEVA, every two weeks for the first three months of treatment and monthly thereafter. Blood pressure, serum potassium and fluid retention should be monitored monthly (see **section 4.4**).

In the event of a missed daily dose of either ABIRATERONE 500 TEVA, prednisone or prednisolone, treatment should be resumed the following day with the usual daily dose.

Hepatic impairment:

No dose adjustment is necessary for patients with pre-existing mild hepatic impairment, Child-Pugh class A. There are no data on the clinical safety and efficacy of multiple doses of ABIRATERONE 500 TEVA when administered to patients with moderate or severe hepatic impairment (Child Pugh Class B or C). No dose adjustment can be predicted. ABIRATERONE 500 TEVA should not be used in patients with moderate to severe hepatic impairment (see **section 4.3**).

For patients who develop hepatotoxicity during treatment with ABIRATERONE 500 TEVA (alanine aminotransferase (ALT) or aspartate aminotransferase (AST) increases above 5 times the upper limit of normal or bilirubin increases above 3 times the upper limit of normal), treatment should be withheld immediately until liver function tests normalise (see **section 4.4**). Re-treatment following return of liver function tests to the patient's baseline may be given at a reduced dose of 500 mg (two tablets) once daily. For patients being re-treated, serum transaminases and bilirubin should be monitored at a minimum of every two weeks for three months and monthly thereafter. If hepatotoxicity recurs at the reduced dose of 500 mg daily, treatment should be discontinued. Reduced doses should not be taken with food.

If patients develop severe hepatotoxicity (ALT or AST 20 times the upper limit of normal) anytime

while on therapy, ABIRATERONE 500 TEVA should be discontinued and patients should not be re-treated with ABIRATERONE 500 TEVA.

Renal impairment:

No dose adjustment is necessary for patients with renal impairment (see **section 5.2**).

Paediatric population:

There is no relevant use of ABIRATERONE 500 TEVA in paediatric patients, as prostate cancer is not present in the paediatric population.

Method of administration

ABIRATERONE 500 TEVA is for oral use.

ABIRATERONE 500 TEVA must be taken on an empty stomach, at least one hour before or at least two hours after a meal. The tablets should be swallowed whole with water.

Precautions to be taken before handling or administering ABIRATERONE 500 TEVA.

Based on its mechanism of action, ABIRATERONE 500 TEVA may harm a developing foetus; therefore, women (including healthcare professionals), who are pregnant or women who may be pregnant should not handle ABIRATERONE 500 TEVA tablets without protection, e.g. gloves (see **section 4.6** and **6.6**).

For concomitant use with prednisolone, the Professional Information for prednisolone should be consulted.

4.3 Contraindications

ABIRATERONE 500 TEVA is contraindicated in:

- Patients with hypersensitivity to abiraterone acetate, or to any of the excipients of ABIRATERONE 500 TEVA listed in **section 6.1**.
- Pregnancy and lactation (see **section 4.6**).

- Moderate (Child-Pugh B) to severe (Child-Pugh C) hepatic impairment (see **sections 4.2, 4.4** and **5.2**).
- Concomitant administration with rifampicin (see **section 4.5**).
- Women should not use ABIRATERONE 500 TEVA (see **section 4.6**).
- ABIRATERONE 500 TEVA with prednisone or prednisolone is contraindicated in combination with Ra-223.

4.4 Special warnings and precautions for use

Hypertension, hypokalaemia, fluid retention and cardiac failure due to mineralocorticoid excess

ABIRATERONE 500 TEVA may cause hypertension, hypokalaemia and fluid retention (see **section 4.8**) as a consequence of increased mineralocorticoid levels resulting from CYP17 inhibition (see **section 5.1**). Co-administration of a corticosteroid suppresses adrenocorticotropic hormone (ACTH) drive, resulting in a reduction in incidence and severity of these adverse reactions. Caution is required in treating patients whose underlying medical conditions might be compromised by increases in blood pressure, hypokalaemia (e.g., those on digoxin), or fluid retention (e.g., those with heart failure, severe or unstable angina pectoris, recent myocardial infarction or ventricular dysrhythmia and those with severe renal impairment).

ABIRATERONE 500 TEVA should be used with caution in patients with a history of cardiovascular disease. The safety in patients with left ventricular ejection fraction (LVEF) < 50 % or NYHA Class II, III or IV heart failure has not been established (see **sections 4.8** and **5.1).**

Before treating patients with a significant risk for congestive heart failure (e.g., a history of cardiac failure, uncontrolled hypertension, or cardiac events such as ischaemic heart disease), consider obtaining an assessment of cardiac function (e.g. echocardiogram). Before treatment with ABIRATERONE 500 TEVA, cardiac failure should be treated and cardiac function optimised. Hypertension, hypokalaemia and fluid retention should be corrected and controlled. During

treatment, blood pressure, serum potassium, fluid retention (weight gain, peripheral oedema), and other signs and symptoms of congestive heart failure should be monitored every 2 weeks for 3 months, then monthly thereafter and abnormalities corrected. QT prolongation has been observed in patients experiencing hypokalaemia in association with ABIRATERONE 500 TEVA treatment. Assess cardiac function as clinically indicated, institute appropriate management and consider discontinuation of this treatment if there is a clinically significant decrease in cardiac function.

Hepatotoxicity and hepatic impairment

Marked increases in liver enzymes leading to treatment discontinuation or dose modification occurred in controlled clinical studies (see **section 4.8**). Serum transaminase levels should be measured prior to starting treatment with ABIRATERONE 500 TEVA, every two weeks for the first three months of treatment, and monthly thereafter. If clinical symptoms or signs suggestive of hepatotoxicity develop, serum transaminases should be measured immediately. If at any time the ALT or AST rises above 5 times the ULN or bilirubin rises above 3 times the upper limit of normal, treatment should be interrupted immediately and liver function closely monitored.

Re-treatment with ABIRATERONE 500 TEVA may take place only after return of liver function tests to the patient's baseline and at a reduced dose level (see **section 4.2**).

If patients develop severe hepatotoxicity (ALT or AST 20 times the ULN) anytime while on therapy, treatment with ABIRATERONE 500 TEVA should be discontinued and patients should not be re-treated with ABIRATERONE 500 TEVA.

There are no data on the clinical safety and efficacy of multiple doses of abiraterone acetate when administered to patients with moderate or severe hepatic impairment (Child-Pugh Class B or C). ABIRATERONE 500 TEVA should not be used in patients with moderate to severe hepatic impairment (see **sections 4.2, 4.3** and **5.2**).

There have been post-marketing reports of acute liver failure and hepatitis fulminant, some with fatal outcome (see **section 4.8**).

Risk of Non-Alcoholic Fatty Liver Disease (NAFLD):

Literature showed that testosterone deficiency was associated with higher serum and hepatic levels of triglycerides and higher serum levels of low-density lipoprotein (LDL) in body, with significant increases in fasting plasma glucose and insulin levels. Patients who receive androgen deprivation therapy (ADT), as with ZYBERA treatment, are at a greater risk of being diagnosed with NAFLD than those who aren't on ADT. Moreover, ADT is associated with significant increase in incidences of other liver diseases such as cirrhosis, liver necrosis, and any liver disease. A significant correlation between the number of ADT doses and the indicdence of NAFLD and other liver diseases was noted.

Based on the reviewed available data, it was noted that normal androgen levels prevent hepatic fat accumulation, whereas androgen deficiency induce hepatic steatosis. Considering the plausible mechanism of action and the consequences of increased metabolic syndromes, the risk of NAFLD pose a public health concern and necessitate risk minimisation measures.

Interactions with other medicines

Strong inducers of CYP3A4 during treatment are to be avoided unless there is no therapeutic alternative, due to risk of decreased exposure to abiraterone (see **section 4.5**).

Corticosteroid withdrawal and coverage of stress situations

Caution is advised and monitoring for adrenocortical insufficiency should occur if patients are withdrawn from prednisone or prednisolone. If ABIRATERONE 500 TEVA is continued after corticosteroids are withdrawn, patients should be monitored for symptoms of mineralocorticoid excess (see information above).

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In patients on prednisone or prednisolone who are subjected to unusual stress, an increased dose of corticosteroids may be indicated before, during and after the stressful situation.

Bone density

Decreased bone density may occur in men with metastatic advanced prostate cancer. The use of ABIRATERONE 500 TEVA in combination with a glucocorticoid could increase this effect.

Prior use of ketoconazole

Lower rates of response might be expected in patients previously treated with ketoconazole for prostate cancer.

Use with chemotherapy

The safety and efficacy of concomitant use of ABIRATERONE 500 TEVA with cytotoxic chemotherapy has not been established.

Use in combination with radium 223 dichloride

It has been reported in a randomised clinical trial in patients with asymptomatic or mildly symptomatic bone-predominant metastatic castration resistant prostate cancer, at the time of unblinding, the addition of radium 223 dichloride to ABIRATERONE 500 TEVA plus prednisone/prednisolone showed an increase in mortality and an increased rate of fracture. Radium 223 dichloride is not recommended for use in combination with ABIRATERONE 500 TEVA plus prednisone/prednisolone outside of clinical trials.

Treatment with ABIRATERONE 500 TEVA and prednisone/prednisolone in combination with Ra-223 is contraindicated (see **section 4.3**) due to an increased risk of fractures and a trend for increased mortality among asymptomatic or mildly symptomatic prostate cancer patients as observed in clinical trials.

It is recommended that subsequent treatment with Ra-223 is not initiated for at least 5 days after the

last administration of ABIRATERONE 500 TEVA in combination with prednisone/prednisolone.

Hypoglycaemia

Cases of hypoglycaemia have been reported when ABIRATERONE 500 TEVA plus prednisone / prednisolone was administered to patients with pre-existing diabetes receiving pioglitazone or repaglinide (see **section 4.5**). Blood glucose should be monitored in patients with diabetes.

Hyperglycaemia

The use of glucocorticoids could increase hyperglycaemia, therefore blood sugar should be measured frequently in patients with diabetes.

Vaccination with live attentuated bacterial or viral vaccines

Prostate cancer patients on treatment should receive guidance on age and indication appropriate vaccinations, in particular live attentuated bacterial or viral vaccines. Patients should also be advised to take extra precaution should they come into contact with someone who has received a live vaccine.

Tuberculosis and/or HIV

Prostate cancer patients with tuberculosis and/or HIV, who are not well-controlled on treatment should be monitored closely.

Potential risks

Anaemia and sexual dysfunction may occur in men with metastatic prostate cancer including those undergoing treatment with ABIRATERONE 500 TEVA.

Skeletal muscle effects

Cases of myopathy and rhabdomyolysis have been reported in patients treated with ABIRATERONE 500 TEVA. Most cases developed within the first 6 months of treatment and

recovered after ABIRATERONE 500 TEVA withdrawal. Caution is recommended in patients concomitantly treated with medicines known to be associated with myopathy/rhabdomyolysis.

Interactions with other medicines

Strong inducers of CYP3A4 during treatment are to be avoided unless there is no therapeutic alternative, due to risk of decreased exposure to ABIRATERONE 500 TEVA (see **section 4.5**).

Intolerance to excipients

ABIRATERONE 500 TEVA contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take ABIRATERONE 500 TEVA.

ABIRATERONE 500 TEVA also contains less than 1 mmol (or 23 mg) sodium per dose that is to say it is essentially 'sodium-free'.

4.5 Interaction with other medicines and other forms of interaction

Effect of food on ABIRATERONE 500 TEVA

Administration of ABIRATERONE 500 TEVA with food significantly increases the absorption of abiraterone as in ABIRATERONE 500 TEVA. The efficacy and safety when given with food have not been established therefore ABIRATERONE 500 TEVA **must not be taken with food** (see **sections 4.2** and **5.2**).

Interactions with other medicines

Potential for other medicines to affect abiraterone exposures

In a clinical pharmacokinetic interaction study of healthy subjects pretreated with a strong CYP3A4 inducer rifampicin, 600 mg daily for 6 days followed by a single dose of abiraterone acetate 1 000 mg, the mean plasma AUC_{∞} of abiraterone was decreased by 55 %.

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Strong inducers of CYP3A4 (e.g., phenytoin, carbamazepine, rifampicin, rifabutin, rifapentine, phenobarbitone, St John's wort [*Hypericum perforatum*]) during treatment are to be avoided.

In a separate clinical pharmacokinetic interaction study of healthy subjects, co-administration of ketoconazole, a strong inhibitor of CYP3A4, had no clinically meaningful effect on the pharmacokinetics of abiraterone as in ABIRATERONE 500 TEVA.

Potential for ABIRATERONE 500 TEVA to affect exposures to other medicines

ABIRATERONE 500 TEVA is an inhibitor of the hepatic drug-metabolising enzymes CYP2D6 and CYP2C8.

In a study to determine the effects of abiraterone acetate (plus prednisone) on a single dose of the CYP2D6 substrate dextromethorphan, the systemic exposure (AUC) of dextromethorphan was increased approximately 200 % . The AUC_{24} for dextrorphan, the active metabolite of dextromethorphan, increased approximately 33 %.

Caution is advised when administering with medicines activated by or metabolised by CYP2D6, particularly with medicines that have a narrow therapeutic index. Dose reduction of medicines with a narrow therapeutic index that are metabolised by CYP2D6 should be considered. Examples of medicines metabolised by CYP2D6 include metoprolol, paroxetine, propranolol, desipramine, venlafaxine, haloperidol, risperidone, propafenone, flecainide, codeine, oxycodone and tramadol (the latter three medicines requiring CYP2D6 to form their active analgesic metabolites).

In the same study to determine the effects of ABIRATERONE 500 TEVA (plus prednisone) on a single dose of the CYP1A2 substrate theophylline, no increase in systemic exposure of theophylline was observed).

In a CYP2C8 interaction trial in healthy subjects, the AUC of pioglitazone was increased by 46 %

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and the AUCs for M-III and M-IV, the active metabolites of pioglitazone, each decreased by 10 % when pioglitazone was given together with a single dose of 1 000 mg abiraterone acetate as in ABIRATERONE 500 TEVA. Patients should be monitored for signs of toxicity related to a CYP2C8 substrate with a narrow therapeutic index if used concomitantly.

In vitro, the major metabolites abiraterone sulphate and N-oxide abiraterone sulphate were shown to inhibit the hepatic uptake transporter OATP1B1 and as a consequence it may increase the concentrations of medicines eliminated by OATP1B1. There are no clinical data available to confirm transporter based interaction.

Use of ABIRATERONE 500 TEVA with medicines known to prolong QT interval

Since androgen deprivation treatment may prolong the QT interval, caution is advised when administering ABIRATERONE 500 TEVA with medicines known to prolong the QT interval or medicines able to induce torsades de pointes such as class IA (e.g. quinidine, disopyramide) or class III (e.g. amiodarone, sotalol, dofetilide, ibutilide) anti-dysrhythmic medicines, methadone, moxifloxacin, antipsychotics, etc.

Concomitant use with Spironolactone

Spironolactone binds to the androgen receptor and may increase prostate specific antigen (PSA) levels. Use with ABIRATERONE 500 TEVA is not recommended (see **section 5.1).**

Concomitant use with eplenerone

There is no clinical study data related to concomitant use of eplenerone with ABIRATERONE 500 TEVA.

4.6 Fertility, pregnancy and lactation

Women should not use ABIRATERONE 500 TEVA.

Women of childbearing potential

There are no human data on the use of ABIRATERONE 500 TEVA in pregnancy and ABIRATERONE 500 TEVA is not for use in women of childbearing potential. Maternal use of a CYP17 inhibitor is expected to produce changes in hormone levels that could affect development of the foetus. Women of child-bearing potential should handle ABIRATERONE 500 TEVA tablets with gloves (see **section 6.6**).

Contraception in males and females

It is not known whether abiraterone as in ABIRATERONE 500 TEVA or its metabolites are present in semen. A condom is required if the patient is engaged in sexual activity with a pregnant woman. If the patient is engaged in sex with a woman of childbearing potential, a condom is required along with another effective contraceptive method until one week after last dose of ABIRATERONE 500 TEVA.

Pregnancy

ABIRATERONE 500 TEVA is contraindicated in women who are or may potentially be pregnant (see **section 4.3**).

Pregnant women should handle ABIRATERONE 500 TEVA tablets with gloves (see **section 6.6**).

Breastfeeding

ABIRATERONE 500 TEVA is not for use in women. It is not known if either abiraterone acetate as in ABIRATERONE 500 TEVA or its metabolites are excreted in human breast milk.

Fertility

Abiraterone as contained in ABIRATERONE 500 TEVA affected fertility in male and female rats, but these effects were fully reversible in 4 to 16 weeks after ABIRATERONE 500 TEVA was stopped.

It is recommended to store semen before starting treatment with ABIRATERONE 500 TEVA in patients who might want to father a child.

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4.7 Effects on ability to drive and use machines

ABIRATERONE 500 TEVA has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

a. Summary of the safety profile

The most frequent adverse reactions seen with ABIRATERONE 500 TEVA are peripheral oedema, hypokalaemia, hypertension, urinary tract infection, haematuria, increased aspartate aminotransferase, increased alanine aminotransferase, dyspepsia and fractures.

Other important adverse reactions include, cardiac disorders, hepatotoxicity, and allergic alveolitis.

b. Tabulated list of adverse reactions

Adverse reactions identified in clinical studies and post-marketing		
(MedDRA) System Organ Class	**Adverse reaction and frequency**	
Infections and infestations	*Frequent*	urinary tract infection, sepsis
Immune system disorders	*Unknown frequency*	anaphylactic reactions
Endocrine disorders	*Less frequent*	adrenal insufficiency
Metabolism and nutrition disorders	*Frequent*	hypokalemia, hypertriglyceridaemia
Cardiac disorders	*Frequent*	cardiac failure*, angina pectoris, atrial fibrillation, tachycardia
	Less frequent	dysrhythmias

	Unknown frequency	myocardial infarction, QT prolongation
Vascular disorders	*Frequent*	hypertension
Respiratory, thoracic and mediastinal disorders	*Less frequent*	allergic alveolitis[a]
Gastrointestinal disorders	*Frequent*	diarrhoea, dyspepsia
Hepato-biliary disorders	*Frequent*	increased alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST)[b]
	Less frequent	hepatitis fulminant, acute hepatic failure
	Unknown frequency:	Non-alcoholic fatty liver disease (NAFLD), cirrhosis, liver necrosis and any liver diseases.
Skin and subcutaneous tissue disorders	*Frequent*	rash
Musculoskeletal and connective tissue disorders	*Less frequent*	myopathy, rhabdomyolysis
Renal and urinary disorders	*Frequent*	haematuria

General disorders and administration site conditions	*Frequent*	peripheral oedema
Injury, poisoning and procedural complications	*Frequent*	fractures**

* Cardiac failure also includes congestive heart failure, left ventricular dysfunction and decreased ejection fraction.

** Fractures includes osteoporosis and all fractures with the exception of pathological fractures

[a] Spontaneous reports from post-marketing experience

[b] Alanine aminotransferase increased and/or aspartate aminotransferase increased includes ALT increased, AST increased, and hepatic function abnormal.

c. Description of selected adverse reactions

Cardiovascular reactions

Phase 3 studies conducted with ABIRATERONE 500 TEVA excluded patients with uncontrolled hypertension, clinically significant heart disease as evidenced by myocardial infarction, or arterial thrombotic events in the past 6 months, severe or unstable angina, or NYHA Class III or IV heart failure (study 301) or Class II to IV heart failure (studies 3011 and 302) or cardiac ejection fraction measurement of < 50 %. All patients enrolled (both active and placebo-treated patients) were concomitantly treated with androgen deprivation therapy, predominantly with the use of LHRH analogues, which has been associated with diabetes, myocardial infarction, cerebrovascular accident and sudden cardiac death. The incidence of cardiovascular adverse reactions in the Phase 3 studies in patients taking abiraterone acetate versus patients taking placebo were as follows: atrial fibrillation 2,6 % vs. 2,0 %, tachycardia 1,9 % vs. 1,0 %, angina pectoris 1,7 % vs. 0,8 %, cardiac failure 0,7 % vs. 0,2 %, and dysrhythmia 0,7 % vs. 0,5 %.

Hepatotoxicity

Hepatotoxicity with elevated ALT, AST and total bilirubin has been reported in patients treated with abiraterone acetate. Across Phase 3 clinical studies, hepatotoxicity grades 3 and 4 (e.g., ALT or AST increases of > 5 x ULN or bilirubinincreases > 1,5 x ULN) were reported in approximately 6 % of patients who received abiraterone acetate, typically during the first 3 months after starting treatment. In Study 3011, grade 3 or 4 hepatotoxicity was observed in 8.4 % of patients treated with ABIRATERONE 500 TEVA. Ten patients who received ABIRATERONE 500 TEVA were discontinued because of hepatotoxicity; two had Grade 2 hepatotoxicity, six had Grade 3 hepatotoxicity, and two had Grade 4 hepatotoxicity. No patient died of hepatotoxicity in Study 3011. In the Phase 3 clinical studies, patients whose baseline ALT or AST were elevated were more likely to experience liver function test elevations than those beginning with normal values. When elevations of either ALT or AST > 5 x ULN, or elevations in bilirubin > 3 x ULN were observed, abiraterone acetate was withheld or discontinued. In two instances marked increases in liver function tests occurred (see section 4.4). These two patients with normal baseline hepatic function, experienced ALT or AST elevations 15 to 40 x ULN and bilirubin elevations 2 to 6 x ULN. Upon discontinuation of treatment, both patients had normalisation of their liver function tests and one patient was re-treated without recurrence of the elevations. In study 302, Grade 3 or 4 ALT or AST elevations were observed in 35 (6,5 %) patients treated with abiraterone acetate. Aminotransferase elevations resolved in all but 3 patients (2 with new multiple liver metastases and 1 with AST elevation approximately 3 weeks after the last dose of abiraterone acetate). In Phase 3 clinical studies, treatment discontinuations due to ALT and AST increases or abnormal hepatic function were reported in 1,1 % of patients treated with abiraterone acetate and 0,6 % of patients treated with placebo; no deaths were reported due to hepatotoxicity events.

In clinical trials, the risk for hepatotoxicity was mitigated by exclusion of patients with baseline hepatitis or significant abnormalities of liver function tests. In the 3011 trial, patients with baseline ALT and AST > 2,5 X ULN, bilirubin > 1,5 X ULN or those with active or symptomatic viral hepatitis or chronic liver disease; ascites or bleeding disorders secondary to hepatic dysfunction were

excluded. In the 301 trial, patients with baseline ALT and AST ≥ 2,5 x ULN in the absence of liver metastases and > 5 x ULN in the presence of liver metastases were excluded. In the 302 trial, patients with liver metastases were not eligible and patients with baseline ALT and AST ≥ 2,5 x ULN were excluded. Abnormal liver function tests developing in patients participating in clinical trials were vigorously managed by requiring treatment interruption and permitting re-treatment only after return of liver function tests to the patient's baseline (see section 4.2). Patients with elevations of ALT or AST > 20 x ULN were not re-treated. The safety of re-treatment in such patients is unknown. The mechanism for hepatotoxicity is not understood.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

Side effects may be precipitated and exacerbated.

There is no specific antidote. In the event of an overdose, administration of ABIRATERONE 500 TEVA should be withheld and general supportive measures undertaken, including monitoring for dysrhythmias, hypokalaemia and for signs and symptoms of fluid retention. Liver function also should be assessed. In case of overdose, side effects may be exacerbated and exaggerated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A.21.12 Hormone inhibitors

Pharmacotherapeutic group: endocrine therapy, other hormone antagonists and related agents, ATC code: L02BX03

Mechanism of action

Abiraterone acetate is converted *in vivo* to abiraterone, an androgen biosynthesis inhibitor. Abiraterone selectively inhibits the enzyme 17α-hydroxylase/C17,20-lyase (CYP17). This enzyme is expressed in and is required for androgen biosynthesis in testicular, adrenal and prostatic tumour tissues. CYP17 catalyses the conversion of pregnenolone and progesterone into testosterone precursors, DHEA and androstenedione, respectively, by 17α- hydroxylation and cleavage of the C17,20 bond. CYP17 inhibition also results in increased mineralocorticoid production by the adrenals (see section 4.4).

Androgen-sensitive prostatic carcinoma responds to treatment that decreases androgen levels. Androgen deprivation therapies, such as treatment with Luteinizing Hormone Releasing Hormone (LHRH) analogues or orchiectomy, decrease androgen production in the testes but do not affect androgen production by the adrenals or in the tumour. Treatment with abiraterone acetate decreases serum testosterone to undetectable levels (using commercial assays) when given with LHRH analogues (or orchiectomy).

Pharmacodynamic effects

Prostate specific antigen (PSA) serves as a biomarker in patients with prostate cancer. In a phase 3 clinical study of patients who failed prior chemotherapy with taxanes, 38 % of patients treated with abiraterone acetate, versus 10 % of patients treated with placebo, had at least a 50 % decline from baseline in PSA levels.

5.2 Pharmacokinetic properties

Following administration of abiraterone acetate, the pharmacokinetics of abiraterone and abiraterone acetate have been studied in healthy subjects, patients with metastatic advanced prostate cancer and subjects without cancer with hepatic or renal impairment. Abiraterone acetate is rapidly converted *in vivo* to abiraterone, an androgen biosynthesis inhibitor (see **section 5.1**).

Absorption

Following oral administration of abiraterone acetate in the fasting state, the time to reach maximum plasma abiraterone concentration is approximately 2 hours.

Administration of abiraterone acetate with food, compared with administration in a fasted state, results in up to a 17-fold increase in mean systemic exposure of abiraterone, depending on the fat content of the meal. Given the normal variation in the content and composition of meals, taking abiraterone acetate with meals has the potential to result in highly variable exposures. Therefore, **abiraterone acetate must not be taken with food.**

Abiraterone acetate should be taken at least two hours after eating and no food should be eaten for at least one hour after taking the tablet. The tablets should be swallowed whole with water (see **section 4.2**).

Distribution

The plasma protein binding of ^{14}C-abiraterone in human plasma is 99,8 %. The apparent volume of distribution is approximately 5 630 L, suggesting that abiraterone extensively distributes to peripheral tissues.

Biotransformation

Following oral administration of ^{14}C-abiraterone acetate as capsules, abiraterone acetate is hydrolysed to abiraterone, which then undergoes metabolism including sulphation, hydroxylation and oxidation primarily in the liver. The majority of circulating radioactivity (approximately 92 %) is found in the form of metabolites of abiraterone. Of 15 detectable metabolites, 2 main metabolites, abiraterone sulphate and N-oxide abiraterone sulphate, each represents approximately 43 % of total radioactivity.

Elimination

The mean half-life of abiraterone in plasma is approximately 15 hours based on data from healthy subjects. Following oral administration of ^{14}C-abiraterone acetate 1 000 mg, approximately 88 % of the radioactive dose is recovered in faeces and approximately 5 % in urine. The major compounds present in faeces are unchanged abiraterone acetate and abiraterone (approximately 55 % and 22 % of the administered dose, respectively).

Pharmacokinetics in special patient groups

Hepatic impairment

The pharmacokinetics of abiraterone acetate was examined in subjects with pre-existing mild or moderate hepatic impairment (Child-Pugh Class A and B, respectively) and in healthy control subjects. Systemic exposure to abiraterone after a single oral 1 000 mg dose increased by approximately 11 % and 260 % in subjects with mild and moderate preexisting hepatic impairment, respectively. The mean half-life of abiraterone is prolonged to approximately 18 hours in subjects with mild hepatic impairment and to approximately 19 hours in subjects with moderate hepatic impairment.

There are no data on the clinical safety and efficacy of multiple doses of abiraterone when administered to patients with moderate or severe hepatic impairment (Child Pugh Class B or C). No dose adjustment can be predicted. Abiraterone acetate should not be used in patients with moderate to severe hepatic impairment (see section 4.3).

For patients who develop hepatotoxicity during treatment, suspension of treatment and dose adjustment may be required (see **sections 4.2** and **4.4**).

Renal impairment

The pharmacokinetics of abiraterone acetate was compared in patients with end-stage renal disease on a stable haemodialysis schedule versus matched control subjects with normal renal

function. Systemic exposure to abiraterone after a single oral 1 000 mg dose did not increase in subjects with end-stage renal disease on dialysis. Administration of ABIRATERONE 500 TEVA in patients with renal impairment, including severe renal impairment, does not require dose reduction (see **section 4.2**).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Croscarmellose sodium

Lactose monohydrate

Microcrystalline cellulose

Povidone

Silica, colloidal anhydrous

Sodium laurilsulfate

Magnesium stearate

Tablet coating for ABIRATERONE 500 TEVA

Opadry II 85F32410 yellow consisting of:

Iron Oxide Yellow (E172)

Polyvinyl alcohol (part hydrolysed)

Macrogol 4000/PEG (E1521)

Talc

Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

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2 years

6.4 Special precautions for storage

Store at or below 25 °C.

Store in the original package until required for use.

6.5 Nature and contents of container

ABIRATERONE 500 TEVA is packaged in PVC/ACLAR/PVC – aluminium blister pack. The blisters strips are further packed into carton boxes with a leaflet included.

Pack size is 60 tablets.

6.6 Special precautions for disposal and other handling

Based on its mechanism of action, ABIRATERONE 500 TEVA tablets may harm a developing foetus. Women who are pregnant or women who may be pregnant should not handle ABIRATERONE 500 TEVA tablets if broken, crushed, or damaged without protection, e.g., gloves (see **section 4.4**).

Any unused medicine should be returned to the pharmacy to be correctly disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Teva Pharmaceuticals (Pty) Ltd

Maxwell Office Park

Magwa Crescent West

Waterfall City, Midrand

2090

South Africa

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8. REGISTRATION NUMBER

57/21.12/0329

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

30 June 2026

10. DATE OF REVISION OF THE TEXT

This submission has been effected according to SAHPRA recommendations, and the Professional Information is free of typographical and grammatical errors.	*Arlene Anderson (B.Pharm)*