1.3.1.1 Approved Professional Information

SCHEDULING STATUS **S4**

1 NAME OF THE MEDICINE

Abizista 250 mg, 250 mg film-coated tablets

Abizista 500 mg, 500 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

ABIZISTA 250 mg: Each film-coated tablet contains 250 mg abiraterone acetate.

ABIZISTA 500 mg: Each film-coated tablet contains 500 mg abiraterone acetate.

Contains sugar (lactose monohydrate).

ABIZISTA 250 mg: Each film-coated tablet contains 34 mg lactose monohydrate.

ABIZISTA 500 mg: Each film-coated tablet contains 68 mg lactose monohydrate.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film coated tablet.

250 mg: White to off-white, oval-shaped film-coated tablets, debossed with “250” on one side.

500 mg: Purple, oval-shaped film-coated tablets, debossed with “500” on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

ABIZISTA 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;

(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

Posology

The recommended dose of ABIZISTA is 1 g as a single daily dose that must not be taken with food (see Method of administration below). Taking ABIZISTA with food increases systemic exposure to abiraterone acetate (see sections 4.5 and 5.2).

Patients should be maintained on ABIZISTA 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), ABIZISTA is used with 5 mg prednisone or prednisolone once daily.

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

Recommended monitoring

Serum transaminases and bilirubin should be measured prior to starting treatment with ABIZISTA, 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 ABIZISTA, prednisone or prednisolone, treatment should be resumed the following day with the usual daily dose.

Special populations

Hepatic impairment

No dose adjustment is necessary for patients with pre-existing mild hepatic impairment, Child-Pugh class A. Safety and efficacy of multiple doses of abiraterone acetate in patients with moderate or severe hepatic impairment (Child Pugh Class B or C) has not been established. No dose adjustment can be predicted. ABIZISTA 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 acetate (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). Retreatment following return of liver function tests to the patient's baseline may be given at a reduced dose of 500 mg 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 (see previous).

If patients develop severe hepatotoxicity (ALT or AST 20 times the upper limit of normal) anytime while on therapy, ABIZISTA should be discontinued and patients should not be retreated with ABIZISTA.

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 acetate in paediatric patients, as prostate cancer is not present in the paediatric population. Safety and efficacy for use of abiraterone acetate in children has not been established.

Method of administration

ABIZISTA 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 ABIZISTA

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

4.3 Contraindications

ABIZISTA is contraindicated in:

- Patients with hypersensitivity to abiraterone acetate or to any of the excipients listed in section 6.1.
- Pregnancy and Lactation (see section 4.6).
- Moderate to severe hepatic impairment (see sections 4.2, 4.4 and 5.2).
- Women.
- Concomitant administration with rifampicin (see section 4.5).
- ABIZISTA with prednisone or prednisolone in combination with Ra-223.

4.4 Special warnings and precautions for use

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

ABIZISTA 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 cardiac glycosides), 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).

ABIZISTA should be used with caution in patients with a history of cardiovascular disease. Safety in patients with uncontrolled hypertension, clinically significant heart disease as evidenced by myocardial infarction, recent arterial thrombotic events, severe or unstable angina, atrial fibrillation, cardiac dysrhythmia requiring medical therapy, left ventricular ejection fraction (LVEF) < 50 % or NYHA Class II to 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 ABIZISTA, 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 acetate 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 (see section 4.2).

Hepatotoxicity and hepatic impairment

Studies have documented increases in liver enzymes leading to abiraterone acetate as in ABIZISTA discontinuation or dose modification (see section 4.8). Serum transaminase levels should be measured prior to starting treatment, 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, treatment should be interrupted immediately and liver function closely monitored. Re-treatment 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 should be discontinued and patients should not be re-treated.

Safety and efficacy of ABIZISTA in patients with active or symptomatic viral hepatitis has not been established.

Safety and efficacy of multiple doses of abiraterone acetate in patients with moderate or severe hepatic impairment (Child Pugh Class B or C) has not been established. ABIZISTA should not be used in patients with moderate to severe hepatic impairment (see sections 4.2, 4.3 and 5.2).

Spontaneous reports have documented of acute liver failure and fulminant hepatitis, some with fatal outcome (see section 4.8).

Corticosteroid withdrawal and coverage of stress situations

Caution is advised and monitoring for adrenocortical insufficiency should occur if patients need to be withdrawn from prednisone or prednisolone. If ABIZISTA is continued after corticosteroids are withdrawn, patients should be monitored for symptoms of mineralocorticoid excess (see previous).

In patients on prednisone or prednisolone who are subjected to unusual stress, increased dosage 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 ABIZISTA 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.

Hyperglycaemia

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

Hypoglycaemia

Hypoglycaemia has been documented when abiraterone acetate plus prednisone/prednisolone was administered to patients with pre-existing diabetes receiving pioglitazone or repaglinide (see section 4.5); therefore, blood sugar should be monitored in patients with diabetes.

Use with chemotherapy

The safety and efficacy of concomitant use of ABIZISTA with cytotoxic chemotherapy has not been established (see section 5.1).

Potential risks

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

Skeletal muscle effects

Myopathy and rhabdomyolysis have been documented in patients treated with abiraterone acetate. Most cases developed within the first 6 months of treatment and recovered after abiraterone acetate withdrawal. Caution is recommended in patients concomitantly treated with medicines known to be associated with myopathy/rhabdomyolysis.

Interactions with other medicinal products

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).

Combination of abiraterone acetate and prednisone/prednisolone with Ra-223

Treatment with abiraterone acetate 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 ABIZISTA in combination with prednisone/prednisolone.

Intolerance to excipients

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine. This medicine contains less than 1 mmol (21,24 mg) sodium per dose of four ABIZISTA 250 mg tablets or per dose of two ABIZISTA 500 mg tablets, that is to say essentially ‘sodium-free’. This should be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of food on ABIZISTA

Administration of ABIZISTA with food significantly increases the absorption of abiraterone acetate. The efficacy and safety of abiraterone acetate given with food have not been established. ABIZISTA must not be taken with food (see sections 4.2 and 5.2).

Interactions with other medicines

Potential for other medicines to affect ABIZISTA exposures

Studies documented that pre-treatment with a strong CYP3A4 inducer (rifampicin, 600 mg daily for 6 days) followed by a single dose of abiraterone acetate 1 000 mg, resulted in mean plasma AUC∞ of abiraterone acetate was decreased by 55 % (see section 4.3).

Other strong inducers of CYP3A4 (e.g. phenytoin, carbamazepine, rifabutin, rifapentine, phenobarbitone) during treatment with abiraterone acetate are to be avoided.

Studies documented that co-administration of ketoconazole, a strong inhibitor of CYP3A4, had no clinically meaningful effect on the pharmacokinetics of abiraterone acetate.

Potential for ABIZISTA to affect exposures to other medicines

Abiraterone acetate is an inhibitor of the hepatic medicine-metabolising enzymes CYP2D6 and CYP2C8. Studies documented the effect of abiraterone acetate (plus prednisone) on a single dose of the CYP2D6 substrate dextromethorphan, as increase in the systemic exposure (AUC) of dextromethorphan by approximately 200 %. The AUC24 for dextrorphan, the active metabolite of dextromethorphan, increased approximately 33 %.

Caution is advised when ABIZISTA is administered with medicines activated by or metabolised by CYP2D6, particularly with medicines that have a narrow therapeutic index. Dose reduction of narrow therapeutic index medicines metabolised by CYP2D6 should be considered (e.g.paroxetine, propafenone, flecainide and haloperidol).

Studies documented the effect on abiraterone acetate (plus prednisone) on a single dose of the CYP1A2 substrate theophylline, as no increase in systemic exposure of theophylline.

Studies documented the AUC of pioglitazone was increased by 46 % 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. Patients should be monitored for signs of toxicity related to CYP2C8 substrate with a narrow therapeutic index if used concomitantly with ABIZISTA.

Concomitant use with Spironolactone
Spironolactone binds to the androgen receptor and may increase prostate specific antigen (PSA) levels. Use with ABIZISTA is not recommended.

Concomitant use with eplenerone
The safety and efficacy related to concomitant use of eplenerone with abiraterone acetate has not been established.

4.6 Fertility, pregnancy and lactation

Women should not use ABIZISTA.

Women of childbearing potential

Safety and efficacy for use of abiraterone acetate in pregnancy has not been established and ABIZISTA should not be used 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.

Contraception in males and females

It is not known whether abiraterone acetate 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 the last dose of ABIZISTA.

Pregnancy

ABIZISTA is contraindicated in women who are or may potentially be pregnant (see section 4.3). Pregnant women or women of child-bearing potential should handle ABIZISTA uncoated tablets with gloves.

Breastfeeding

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

Fertility

Studies documented in both male and female rats, abiraterone acetate reduced fertility, which was reversible in 4 to 16 weeks after was abiraterone acetate discontinuation. It is recommended to store semen before starting treatment with ABIZISTA in patients who might want to father a child.

4.7 Effects on ability to drive and use machines

ABIZISTA has no or negligible influence on the ability to drive or use machines.

4.8 Undesirable effects

Summary of the safety profile

The most frequent adverse reactions are peripheral oedema, hypokalaemia, hypertension, urinary tract infection, and increased alanine aminotransferase and/or increased aspartate aminotransferase. Other important adverse reactions include, cardiac disorders, hepatotoxicity, fractures, and allergic alveolitis. Hypertension, hypokalaemia and fluid retention may occur as a pharmacodynamic consequence of the mechanism of action of abiraterone acetate. Concomitant use of a corticosteroid reduces the incidence and severity of these adverse reactions (see section 4.4).

Tabulated summary of adverse reactions

Adverse events are listed below by system organ class and frequency. Frequencies are defined as: Frequent, Less Frequent and Frequency unknown. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

SOC category	**Frequency**	**Side effect**
Infections and infestations	Frequent	urinary tract infection
		sepsis
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	dysrhythmia
	Frequency unknown[b]	myocardial infarction, QT prolongation
Vascular disorders	Frequent	hypertension
Respiratory, thoracic and mediastinal disorders	Frequency unknown[b]	allergic alveolitis

SOC category	**Frequency**	**Side effect**
Gastrointestinal disorders	Frequent	diarrhoea
		dyspepsia
Hepatobiliary disorders	Frequent	increased alanine aminotransferase (ALT) and/or increased aspartate aminotransferase[a] (AST)
	Frequency unknown[b]	Fulminant hepatitis, Acute hepatic failure
Skin and subcutaneous tissue disorders	Frequent	rash
Musculoskeletal and connective tissue disorders	Less frequent	myopathy, rhabdomyolysis
	Frequent	fractures**
Immune system disorders	Frequency unknown	Anaphylactic reactions
Renal and urinary disorders	Frequent	Haematuria
General disorders and administration site conditions	Frequent	peripheral oedema

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

** Fractures include osteoporosis and all fractures with the exception of pathological fracture.

[a] Increased alanine aminotransferase and/or increased aspartate aminotransferase includes increased ALT, increased AST, and abnormal hepatic function**.**

[b] Analyses of spontaneous case reports documented from abiraterone acetate use.

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. Health care providers are asked to report any

suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

There is no specific antidote. In the event of an overdose, administration of ABIZISTA should be stopped and general supportive measures undertaken, including monitoring for dysrrhythmias. Liver function should also be assessed. In cases of overdose, side effects may be exacerbated and exaggerated.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: 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 luteinising hormone-releasing hormone (LHRH) agonists 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 agonists (or orchiectomy).

Pharmacodynamic effects

Prostate specific antigen (PSA) serves as a biomarker in patients with prostate cancer. Studies documented that 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

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 ABIZISTA. 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 g, 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).

Patients with 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 g dose increased by approximately 11 % and 260 % in subjects with mild and moderate pre-existing 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. No dose adjustment is necessary for patients with pre- existing mild 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 with abiraterone acetate, suspension of treatment and dose adjustment may be required (see sections 4.2 and 4.4).

Patients with 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 g dose did not increase in subjects with end-stage renal disease on dialysis. Administration of abiraterone acetate 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

Croscarmellose sodium

Type A Sodium laurilsulfate

Povidone K 30 (E1201)

Cellulose Microcrystalline 102 (E460)

Lactose monohydrate

Silica Colloidal anhydrous (E551)

Magnesium stearate (E470b)

Water, purified

Coating:

Poly(vinyl alcohol) (E1203)

Titanium dioxide (E171)

Macrogol 3350 (E1521)

Talc (E553b)

Iron oxide red (E172) or Iron oxide black (E172)

Water, purified

6.2 Incompatibilities

Not known.

6.3 Shelf life

The shelf life is 18 months. Store at or below 25 °C.

6.4 Special precautions for storage

This medicine does not require any special storage conditions.

6.5 Nature and contents of container

AluminiumOPA/Alu/PVC blisters or Aluminium-PVC/PE/PVDC blisters.

6.6 Special precaution for disposal

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Eurolab (Pty) Ltd

Woodmead Office Park,

3 Stirrup Lane

Van Reenens Avenue,

Woodmead,

2144

8 REGISTATRATION NUMBER

To be allocated

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

To be allocated

10 DATE OF REVISION OF THE TEXT