Proprietary name:	ABIKEM
Dosage form:	Tablets
Active Ingredient:	Abiraterone acetate
Strength per dosage unit:	250 mg per tablet

1.3.1.1 PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

ABIKEM Tablets

Abiraterone acetate

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 250 mg of abiraterone acetate.

Contains sugar.

Excipient(s) with known effect:

Each tablet contains 150 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

White to off white oval shaped tablets debossed with "A" on one side “250” on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ABIKEM is indicated with prednisone or prednisolone for:

- For the treatment of metastatic castration-resistant prostate cancer (CRPC) in adult men with bone metastases who are asymptomatic or mildy symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated.

- The treatment of metastatic advanced prostate cancer (castration resistant prostate cancer) in adult patients who have received prior chemotherapy containing docetaxel.

4.2 Posology and method of administration

ABIKEM should be prescribed by an appropriate healthcare professional.

Posology

The recommended dose is 1,000 mg (four 250 mg tablets) as a single daily dose that must not be taken with food .

Taking ABIKEM tablets with food increases systemic exposure to abiraterone (see *sections 4.5 and 5.2*).

Patients should be maintained on ABIKEM until radiographic progression and symptomatic/clinical progression and until prostate specific antigen (PSA) progression (confirmed 25 % increase over the patient's baseline/nadir).

ABIKEM is used with low dose prednisone or prednisolone. The recommended dose of prednisone or prednisolone is 10 mg daily.

Serum transaminases and bilirubin should be measured, prior to starting treatment with ABIKEM, 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 ABIKEM, 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.

There are no data on the clinical safety and efficacy of multiple doses of abiraterone acetate as in ABIKEM when administered to patients with moderate or severe hepatic impairment (Child-Pugh Class B or C). No dose adjustment can be predicted.

ABIKEM should not be used in patients with moderate to severe hepatic impairment (see section 4.3).

For patients who develop hepatotoxicity during treatment (alanine aminotransferase [ALT] increases or aspartate aminotransferase [AST] increases above 5 times the upper limit of normal [ULN]) or bilirubin increases aboves 3 times the upper limit of normal, treatment should be withheld immediately until liver functions normalises (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 ULN) anytime while on therapy, treatment should be discontinued and patients should not be re-treated with ABIKEM.

Renal impairment

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

Paediatric population

There is no relevant use of ABIKEM in the paediatric population.

Method of administration

ABIKEM is for oral use. ABIKEM should be taken at least 2 hours after eating and no eating for at least 1 hour after taking ABIKEM. ABIKEM should be swallowed whole with water.

Precautions to be taken before handling or administering ABIKEM

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

4.3 Contraindications

- Hypersensitivity to the abiraterone acetate or to any of the excipients in ABIKEM listed in section 6.1.
- Pregnancy and lactation (see section 4.6).
- Moderate to severe hepatic impairment [Child-Pugh Class B or C (see sections 4.2, 4.4 and 5.2)].
- Women should not use ABIKEM
- Concomitant administration with rifampicin
- ABIKEM 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

ABIKEM 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).

ABIKEM should be used with caution in patients with a history of cardiovascular disease. Safety of ABIKEM in patients with left ventricular ejection fraction (LVEF) < 50 % or NYHA Class III or IV heart failure 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 ABIKEM, 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 ABIKEM treatment. Assess cardiac function as clinically indicated, institute appropriate management and consider discontinuation of ABIKEM if there is a clinically significant decrease in cardiac function (see section 4.2).

Hepatotoxicity and hepatic impairment

Marked increases in liver enzymes leading to ABIKEM discontinuation or dose modification occurred in controlled clinical studies (see section 4.8). Serum transaminase levels should be measured prior to starting treatment with ABIKEM, 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 ULN, treatment with ABIKEM 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, ABIKEM treatment should be discontinued and patients should not be re-treated with ABIKEM.

Patients with active or symptomatic viral hepatitis were excluded from clinical trials; thus, there are no data to support the use of ABIKEM in this population. 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). ABIKEM 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 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 are withdrawn from prednisone or prednisolone. If ABIKEM is continued after corticosteroids are withdrawn, patients should be monitored for symptoms of mineralocorticoid excess (see information

above). 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 ABIKEM 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.

Use with chemotherapy

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

Skeletal muscle effects

Cases of myopathy and rhabdomyolysis have been reported in patients treated with ABIKEM. Most cases developed within the first 6 months of treatment and recovered after ABIKEM 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 (see section 4.5).

Combination of abiraterone and prednisone/prednisolone with Ra-223

Treatment with abiraterone 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 ABIKEM in combination with prednisone/prednisolone.

Excipient

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicines and other forms of interaction

Effect of food on abiraterone acetate

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

Medicines that Inhibit or Induce CYP3A4 Enzymes

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 %.

Strong inducers of CYP3A4 (e.g., phenytoin, carbamazepine, rifampicin, rifabutin, rifapentine, phenobarbitone, St John's wort [Hypericum perforatum]) during treatment with ABIKEM 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 ABIKEM.

Effects of Abiraterone on Medicine Metabolising Enzymes

Abiraterone as in ABIKEM is an inhibitor of the hepatic medicine 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 ABIKEM is administered 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, propranolol, desipramine, venlafaxine, haloperidol, risperidone, propafenone, flecainide, codeine, oxycodone and tramadol (the latter three medicines requiring CYP2D6 to form their active analgesic metabolites).

In CYP2C8 interaction study in healthy subjects, 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 ABIKEM.

In the same study to determine the effects of ABIKEM (plus prednisone) on a single dose of the CYP1 A2 substrate theophylline, no increase in systemic exposure of theophylline was observed).

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 with medicines known to prolong QT interval

Since androgen deprivation treatment may prolong the QT interval, caution is advised when administering ABIKEM 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) antidysrhythmic medicines, methadone, moxifloxacin, antipsychotics, etc.

Use with Spironolactone

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

4.6 Fertility, pregnancy and lactation

Women of child-bearing age

ABIKEM is not for use in women and thus is not recommended in women of child-bearing age. Maternal use of a CYP17 inhibitor is expected to produce changes in hormorne levels that could affect development of the foetus.

Contraception in males and females

It is known whether abiraterone as in ABIKEM or its metabolites are present in semen. A condom is required if the patient is engaged in sexual activity with pregnant women. If the patient is engaged in sexual acivity with a woman of child bearing age, a condom is required along with other effective contraceptive method until one week after the last dose of ABIKEM.

Pregnancy

ABIKEM is not for use in women, thus contraindicated during pregnancy.

Breast-feeding

ABIKEM is not for use in women, thus contraindicated during lactation.

Fertility

ABIKEM affected fertility of male or female rats, but these are reversible in 4 to 6 weeks after ABIKEM was stopped. It is recommended to store semen before starting treatment with ABIKEM in patients who might want to father a child.

4.7 Effects on ability to drive and use machines

ABIKEM has no or negligigle influence on the ability to drive or use machines.

4.8 Undesirable effects

Summary of the safety profile

Adverse reactions that were observed were fluid retention (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.

Concomitant use of a corticosteroid reduces the incidence and severity of these adverse reactions (see section 4.4).

The frequencies of adverse events are ranked according to the following: Frequent, Less frequent, and frequency unknown and listed in table below.

System Organ Class	**Adverse reaction and frequency**
Infections and infestations	Frequent: urinary tract infection, sepsis
Endocrine disorders	Less frequent: adrenal insufficiency
Metabolism and nutrition disorders	Frequent: hypokalaemia, hypertriglyceridaemia
Cardiac disorders	Frequent: cardiac failure*, angina pectoris, atrial fibrillation, tachycardia Less frequent: other dysrhythmias Frequency unknown: myocardial infarction, QT prolongation (see sections 4.4 and 4.5)
Vascular disorders	Frequent: hypertension
Respiratory, thoracic and mediastinal disorders	Less frequent: allergic alveolitis[a]
Gastrointestinal disorders	Frequent: diarrhoea, dyspepsia
Hepatobiliary disorders	Frequent: increased alanine aminotransferase and/or increased aspartate aminotransferase[b] Less frequent: hepatitis fulminant, acute hepatic failure
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 ejection fraction decreased ** Fractures includes osteoporosis and all fractures with the exception of pathological fractures [a] Spontaneous reports from post-marketing experience [b] Increased Alanine aminotransferase and/or increased aspartate aminotransferase includes increased ALT, increased AST, and abnormal hepatic function.	

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 professionals 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 Alternatively all adverse events can be reported to Alkem Laboratories vial the e-mail: pharmacist.rsa@Alkem.com.

4.9 Overdose

Human experience of overdose with ABIKEM is limited.

There is no specific antidote. In the event of an overdose, administration of ABIKEM 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

Pharmacotherapeutic Classification: A 21.12 Hormone inhibitors.

Mechanism of action

Abiraterone acetate (ABIKEM) is converted *in vivo* to abiraterone, an androgen biosynthesis inhibitor. Specifically, abiraterone selectively inhibits the enzyme 17α-hydroxylase and 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 LHRH analogues or orchiectomy, decrease androgen production in the testes but do not affect androgen production by the adrenals or in the tumour.

Receptors and pharmacodynamics targets

Treatment with ABIKEM decreases serum testosterone to undetectable levels (using commercial assays) when given with LHRH analogues (or orchiectomy).

ABIKEM decreases serum testosterone and other androgens to levels lower than those achieved by the use of LHRH analogues alone or by orchiectomy. This results from the selective inhibition of the CYP17 enzyme required for androgen biosynthesis. PSA serves as a biomarker in patients with prostate cancer.

Clinical efficacy and safety

The test product ABIKEM is bioequivalent to the reference innovator with regard to rate of absorption and extent of absorption under fed and fasting conditions. Both products were well tolerated by the patients

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, resulted in an 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 ABIKEM with meals has the potential to result in highly variable exposures. Therefore, ABIKEM must not be taken with food. It should be taken at least two hours after eating and no food should be eaten for at least one hour after taking ABIKEM. 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 litres, suggesting that abiraterone extensively distributes to peripheral tissues.

Biotransformation

Following oral administration of ^{14}C-abiraterone acetate, 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 40 % of total radioactivity.

Elimination

The mean half-life of abiraterone in plasma is approximately 15 hours in healthy subjects. Following oral administration of ^{14}C-abiraterone acetate 1000 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).

Special Populations

Hepatic impairment

Systemic exposure to abiraterone after a single oral 1,000 mg dose increased in subjects with mild and moderate pre-existing hepatic impairment. 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 in patients with moderate to 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 sections 4.2, 4.3 and 4.4).

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

Renal impairment

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 in patients with renal impairment, including severe renal impairment, does not require dose reduction (see section 4.2). However, there is no clinical experience in patients with prostate cancer and severe renal impairment. Caution is advised in these patients.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone, and sodium lauryl sulphate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store at or below 25 °C. Protect from moisture.

Keep bottle tightly until required for use.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

HDPE bottle pack comprises of round wide mouth white high density polyethylene (HDPE) bottle with white Child Resistance Closure with heat seal and pulp liner for induction seal. The HDPE bottle pack may either be placed in an outer cardboard carton or provided without a carton based on commercial requirement.

Pack sizes: 1 bottle of 120 tablets

6.6 Special precautions for disposal and other handling

Women who are or may be pregnant shuld not handle the product without protection, such as gloves.

Any unused or expired product should be returned to the pharmacy and not be dumped in any drains.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Ascend Laboratories (Pty) Ltd.

R21 Corporate Park

121 Sovereign Drive, Block A, Office 202

Irene Ext.30, Centurion, 0157

8 REGISTRATION NUMBER(S)

To be allocated by authority.

9 DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION

10 DATE OF REVISION OF THE TEXT