**PACKAGE INSERT**
**(For the use of a Registered Medical Practitioner or a Hospital)**

## 1. NAME OF THE MEDICINAL PRODUCT

ABYTONE (Abiraterone Acetate Tablets 250 mg)

## 2. QUALITATIVE AND QUATITATIVE COMPOSITION

Each tablet contains

Abiraterone acetate 250 mg

For a full list of excipients, see Section 6.1.

## 3. PHARMACEUTICAL FORM

Tablet

White to off-white, oval-shaped tablets debossed with A on one side and 250 on other side.

## 4. CLINICAL PARTICULARS

### 4.1 Indications

Abiraterone Acetate is indicated with prednisone or prednisolone for

• the treatment of metastatic castration resistant prostate cancer (mCRPC) in adult men who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated.

• the treatment of mCRPC in adult men whose disease has progressed on or after a docetaxel-based chemotherapy regimen.

Abiraterone Acetate is also indicated in combination with prednisone or prednisolone and androgen deprivation therapy (ADT) for the treatment of patients with newly diagnosed high risk metastatic hormone sensitive prostate cancer (mHSPC) who may have received up to 3 months of prior ADT.

### 4.2 Posology and method of administration

Posology

The recommended dose is 1000 mg (four 250 mg tablets) as a single daily dose that must not be taken with food (see information on the method of administration). Taking the tablets with food increases systemic exposure to abiraterone (see sections 4.5 and 5.2).

*Dosage of prednisone or presnisolone*

For mCRPC, Abiraterone Acetate is used with 10 mg prednisone or prednisolone daily.

For mHSPC, Abiraterone Acetate is used with 5 mg prednisone or prednisolone daily.

Medical castration with LHRH analogue should be continued during treatment in patients not surgically castrated.

*Recommended monitoring*

Serum transaminases should be measured prior to starting treatment, every two weeks for the first three months of treatment and monthly thereafter. Blood pressure, serum potassium and fluid retention should be monitored monthly. However, patients with a significant risk or congestive heart failure should be monitored every 2 weeks for the first three months of treatment and monthly thereafter (see section 4.4).

In patients with pre-existing hypokalaemia or those that develop hypokalaemia whilst being treated with Abiraterone Acetate, consider maintaining the patient's potassium level at ≥ 4.0mM.

For patients who develop Grade ≥ 3 toxicities including hypertension, hypokalaemia, oedema and other non-mineralocorticoid toxicities, treatment should be with held and appropriate medical management should be instituted. Treatment with Abiraterone Acetate should not be reinitiated until symptoms of the toxicity have resolved to Grade 1 or baseline.

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

*Hepatotoxicity*

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]), treatment should be withheld immediately (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 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.

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

*Hepatic impairment*

No dose adjustment is necessary for patients with pre-existing mild hepatic impairment, Child-Pugh Class A.

Moderate hepatic impairment (Child-Pugh Class B) has been shown to increase the systemic exposure to abiraterone by approximately four-fold following single oral doses of abiraterone acetate 1000 mg (see section 5.2). 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). No dose adjustment can be predicted. The use of Abiraterone Acetate should be cautiously assessed in patients with moderate hepatic impairment, in whom the benefit clearly should outweigh the possible risk. Abiraterone Acetate should not be used in patients with severe hepatic impairment.

*Renal impairment*

No dose adjustment is necessary for patients with renal impairment (see section 5.2). However, there is no clinical experience in patients with prostate cancer and severe renal impairment. Caution is advised in these patients.

Paediatric population

There is no relevant use of this medicinal product in the paediatric population, as prostate cancer is not present in children and adolescents.

Method of administration

Abiraterone Acetate is for oral use.

The tablets should be taken at least two hours after eating and no food should be eaten for at least one hour after taking the tablets. These should be swallowed whole with water.

**4.3 Contraindications**

• Hypersensitivity to the active substance or to any of the excipients.

• Women who are or may potentially be pregnant.

• Severe hepatic impairment [(Child-Pugh Class C)].

• Abiraterone Acetate with prednisone or prednisolone is contraindicated in combination with Ra-223.

**4.4 Special warnings and precautions for use**

Hypertension, hypokalaemia and fluid retention due to mineralocorticoid excess

Abiraterone Acetate may cause hypertension, hypokalaemia and fluid retention as a consequence of increased mineralocorticoid levels resulting from CYP17 inhibition. Co-administration of a corticosteroid suppresses adrenocorticotropic hormone (ACTH) drive, resulting in a reduction in the 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 or fluid retention, e.g., those with heart failure, recent myocardial infarction or ventricular arrhythmia. In postmarketing experience, QT prolongation and Torsades de Pointes have been observed in patients who develop hypokalemia or have underlying cardiovascular conditions while taking Abiraterone Acetate.

Abiraterone Acetate should be used with caution in patients with a history of cardiovascular disease. Before treatment with Abiraterone Acetate, hypertension must be controlled and hypokalemia must be corrected. Blood pressure, serum potassium and fluid retention should be monitored at least monthly.

Hepatotoxicity and hepatic impairment

Serum transaminase and bilirubin levels should be measured prior to starting treatment with Abiraterone Acetate, 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 upper limit of normal or the bilirubin rises above 3 times the upper limit of normal, treatment with Abiraterone Acetate should be interrupted immediately and liver function closely monitored.

Re-treatment with Abiraterone Acetate may only take place after the return of liver function tests to the patient’s baseline and at a reduced dose level.

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

There are no data on the clinical safety and efficacy of multiple doses of abiraterone acetate. No dose adjustment can be predicted. Abiraterone Acetate should be used with caution in patients with moderate hepatic impairment only if the benefit clearly outweighs the possible risk. Abiraterone Acetate should not be used in patients with severe hepatic impairment.

There have been rare post-marketing reports of acute liver failure and hepatitis fulminant, some with fatal outcome.

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 Abiraterone Acetate is continued after corticosteroids are withdrawn, patients should be monitored for symptoms of mineralocorticoid excess.

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

Hypoglycemia

Cases of hypoglycemia have been reported when Abiraterone Acetate was administered to patients with pre-existing diabetes receiving pioglitazone or repaglinide; therefore, blood sugar should be measured frequently in patients with diabetes.

Use with chemotherapy

The safety and efficacy of concomitant use of Abiraterone Acetate with cytotoxic chemotherapy has not been established.

Combination of abiraterone and prednisone/prednisolone with Ra-223

Treatment with abiraterone and prednisone/prednisolone in combination with Ra-223 is contraindicated 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 Acetate in combination with prednisone/prednisolone.

Bone density

Decreased bone density may occur in men with metastatic advanced prostate cancer (castration resistant prostate cancer). The use of Abiraterone Acetate 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.

Intolerance to excipients

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine. This medicinal product also contains more than 1 mmol (or 27.2 mg) sodium per dose of four tablets. To 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 abiraterone acetate

Administration of Abiraterone Acetate with food significantly increases the absorption of abiraterone acetate. The efficacy and safety of Abiraterone Acetate given with food has not been established. Abiraterone Acetate must not be taken with food.

Interactions with other drugs

Potential for other drugs to affect abiraterone exposures

Strong inducers of CYP3A4 (e.g., phenytoin, carbamazepine, rifampicin, rifabutin, rifapentine, phenobarbital) during treatment with Abiraterone Acetate are to be avoided or used with careful evaluation of clinical efficacy.

*Potential for Abiraterone Acetate to affect exposures to other drugs*

Abiraterone is an inhibitor of the hepatic drug-metabolizing enzymes CYP2D6 and CYP2C8.

Caution is advised when Abiraterone Acetate is administered with drugs activated by or metabolized by CYP2D6, particularly with drugs that have a narrow therapeutic index. Dose reduction of narrow therapeutic index drugs metabolized by CYP2D6 should be considered.

In a CYP2C8 drug-drug interaction trial 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 1000mg abiraterone acetate. Patients should be monitored for signs of toxicity related to a CYP2C8 substrate with a narrow therapeutic index if used concomitantly. Examples of medicinal products metabolized by CYP2C8 include pioglitazone and repaglinide

**4.6 Fertility, Pregnancy and Lactation**

Pregnancy

Abiraterone Acetate is contraindicated in women who are or may potentially be pregnant.

There are no human data on the use of Abiraterone Acetate in pregnancy and Abiraterone Acetate is not for use in women of child-bearing potential. Maternal use of a CYP17 inhibitor is expected to produce changes in hormone levels that could affect development of the fetus.

It is not known if abiraterone 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 child-bearing potential, a condom is required along with another effective contraceptive method.

To avoid inadvertent exposure, women who are pregnant or women who may be pregnant should not handle Abiraterone Acetate 250 mg uncoated tablets without protection, e.g., gloves.

Breast-feeding

Abiraterone Acetate is not for use in women.

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

**4.7 Effects on Ability to Drive and Use Machines**

No studies on the effects of Abiraterone Acetate on the ability to drive or use machines have been performed. It is not anticipated that Abiraterone Acetate will affect the ability to drive and use machines.

**4.8 Adverse Reactions**

Summary of the safety profile

In an analysis of adverse reactions with Abiraterone Acetate, adverse reactions that were observed in ≥10% of patients were peripheral oedema, hypokalaemia, hypertension urinary tract infection, and alanine aminotransferase increased and/or aspartate aminotransferase increased.

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

Abiraterone Acetate may cause hypertension, hypokalaemia and fluid retention as a pharmacodynamic consequence of its mechanism of action. Mineralocorticoid adverse reactions were seen more commonly in patients treated with abiraterone acetate than in patients. Mineralocorticoid reactions generally were able to be successfully managed medically. Concomitant use of a corticosteroid reduces the incidence and severity of these adverse reactions.

Tabulated list of adverse reactions

Adverse reactions identified and post-marketing experience are listed below by seriousness category.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

| **Table 1: Adverse reactions identified and post-marketing** | |
|---|---|
| **System Organ Class** | **Adverse reaction and frequency** |
| **Infections and infestations** | very common: urinary tract infection<br>common: sepsis |
| **Immune system disorders** | not known: anaphylactic reactions |
| **Endocrine disorders** | uncommon: adrenal insufficiency |
| **Metabolism and nutrition disorders** | very common: hypokalaemia<br>common: hypertriglyceridaemia |
| **Cardiac disorders** | common: cardiac failure*, angina pectoris, atrial fibrillation, tachycardia<br>uncommon: other arrhythmias<br>not known: myocardial infarction, QT prolongation (see sections 4.4 and 4.5) |
| **Vascular disorders** | very common: hypertension |
| **Respiratory, thoracic and mediastinal disorders** | rare: allergic alveolitis[a] |
| **Gastrointestinal disorders** | very common: diarrhoea<br>common: dyspepsia |
| **Hepatobiliary disorders** | very common: alanine aminotransferase increased and/or aspartate aminotransferase increased[b]<br>rare: hepatitis fulminant, acute hepatic failure |
| **Skin and subcutaneous tissue disorders** | common: rash |
| **Musculoskeletal and connective tissue disorders** | uncommon: myopathy, rhabdomyolysis |
| **Renal and urinary disorders** | common: haematuria |

| | |
|---|---|
| **General disorders and administration site conditions** | very common: oedema peripheral |
| **Injury, poisoning and procedural complications** | common: fractures** |
| * Cardiac failure also includes congestive heart failure, left ventricular dysfunction and ejection fraction decreased<br>** Fractures includes osteoporosis and all fractures with the exception of pathological fractures<br>[a] Spontaneous reports from post-marketing experience<br>[b] Alanine aminotransferase increased and/or aspartate aminotransferase increased includes ALT increased, AST increased, and hepatic function abnormal. | |

**4.9 Overdose**

Human experience of overdose with Abiraterone Acetate is limited.

There is no specific antidote. In the event of an overdose, administration of Abiraterone Acetate should be stopped and general supportive measures undertaken, including monitoring for arrhythmias. Liver function also should be assessed.

**5. PHARMACOLOGICAL PROPERTIES**

**5.1 Pharmacodynamic Properties**

**Pharmacotherapeutic group: Other hormone antagonists and related agents, ATC code: L02BX03**

Mechanism of action

Abiraterone acetate is converted in vivo to abiraterone, an androgen biosynthesis inhibitor. Specifically, 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 tumor tissues. It catalyzes 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.

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

Pharmacodynamic effects

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

**5.2 Pharmacokinetic properties**

**General introduction**

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.

Absorption

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

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 Abiraterone Acetate. The tablets should be swallowed whole with water.

Distribution and protein binding

The plasma protein binding of 14C-abiraterone in human plasma is 99.8%. The abiraterone extensively distributes to peripheral tissues.

Metabolism

Following oral administration of 14C-abiraterone acetate as capsules, abiraterone acetate is hydrolyzed to abiraterone, which then undergoes metabolism including sulphation, hydroxylation and oxidation primarily in the liver.

Elimination

Following oral administration of 14C-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).

Special populations

*Renal impairment*

Administration of Abiraterone Acetate in patients with renal impairment including severe renal impairment does not require dose reduction.

*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 acetate when administered to patients with moderate or severe hepatic impairment (Child Pugh Class B or C). No dosage adjustment can be predicted. Abiraterone Acetate should be used with caution in patients with moderate hepatic impairment, only if the benefit clearly outweighs the possible risk. Abiraterone Acetate should not be used in patients with severe hepatic impairment. For patients who develop hepatotoxicity during treatment with Abiraterone Acetate, suspension of treatment and dosage adjustment may be required.

*Effects on the QT interval*

In a cardiovascular safety study in patients with metastatic advanced prostate cancer there were no significant effects of abiraterone acetate on the cardiac QT/QTc interval.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

*Inter-granular Portion*

Microcrystalline Cellulose

Lactose Monohydrate

Povidone

Sodium Lauryl Sulfate

Croscarmellose Sodium (Part-1)

Purified water

*Extra-granular Portion*

Croscarmellose Sodium (Part-2)

Microcrystalline Cellulose (Part-2)

Colloidal Silicon Dioxide

Magnesium Stearate

**6.2 Shelf life**

24 months

**6.3 Special precautions for storage**

Store below 30° C. Protect from light. Keep out of reach of children.

**6.4 Nature and contents of container**

Abiraterone acetate tablets 250 mg are white to off-white, oval-shaped tablets debossed with A on one side and 250 on other side. Abiraterone acetate tablets 250 mg are available 120 Tablets packed in 150ml HDPE Round Opaque white/off-white bottles with 38 mm childresistance closure with heat seal and pulp liner for induction seal. Bottles are packed in a carton with a package insert.

Bottles of 120 tablets.

**6.5 Instructions for Use and Handling and Disposal**

Method of administration

ABYTONE is for oral use.

The abiraterone acetate tablets should be taken at least two hours after eating and no food should be eaten for at least one hour after taking the abiraterone acetate tablets. The tablets should be swallowed whole with water.

Instructions for Use and Handling and Disposal

Based on its mechanism of action, ABYTONE may harm a developing fetus. Therefore, women who are pregnant or women who may be pregnant should not handle ABYTONE without gloves.

Any unused product or waste material should be disposed of in accordance with local requirements.

**7. NAME AND ADDRESS OF MANUFACTURER**

Aizant Drug Research Solutions (P) Ltd.,

Sy. No.172&173, Apparel Park Road, Dulapally Village,

Dundigal Gandimaisamma Mandal, Medchal-Malkajgiri District,

Hyderabad,500 100, Telangana, India.

**8. PRODUCT REGISTRATION HOLDER**

Accord Healthcare Sdn Bhd

26-6, Menara 1MK, Kompleks One Mont' Kiara

No. 1, Jalan Kiara, Mont' Kiara,

50480 Kuala Lumpur, Malaysia

**9. DATE OF REVISION OF PACKAGE INSERT**

January 2022

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