SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Xbira 500 mg
(Abiraterone Acetate Film-Coated Tablets USP 500 mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains 500 mg of Abiraterone acetate.

Excipients with known effect:

Each film coated tablet contains 245.00 mg of lactose monohydrate and 12.472 mg of sodium.

3. PHARMACEUTICAL FORM

Film-coated tablets

Purple colored, oval shaped, biconvex bevel edge film coated tablet, debossed with "A" on one side and "500" on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Xbira 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 (see section 5.1).

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

Xbira 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 (two 500 mg tablets or 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 acetate (see sections 4.5 and 5.2).

Dosage of prednisone or prednisolone

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

For mHSPC, Xbira 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 Xbira, 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 withheld and appropriate medical management should be instituted. Treatment with Xbira 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 Xbira, 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 (one 500 mg tablet or two 250 mg 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 acetate 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 Xbira should be cautiously assessed in patients with moderate hepatic impairment, in whom the benefit clearly should outweigh the possible risk. Xbira should not be used in patients with severe hepatic impairment (see sections 4.3, 4.4 and 5.2).

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 (see section 4.4).

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

Xbira is for oral use.

The tablets must be taken as a single dose once daily on an empty stomach. Xbira must be taken at least two hours after eating and food must not be eaten for at least one hour after taking Xbira. Xbira tablets must be swallowed whole with water.

4.3 Contraindications

- Hypersensitivity to the active substances or to the excipients. (see 6.1)
- Women who are or may potentially be pregnant (see 4.6).
- Severe hepatic impairment [(Child-Pugh Class C) (see 4.2, 4.4 and 5.2)].
- Xbira 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 (see 4.8) as a consequence of increased mineralocorticoid levels resulting from CYP17 inhibition (see 5.1-Mechanism of action). 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. The safety of abiraterone acetate in patients with left ventricular ejection fraction (LVEF) <50% or New York Heart Association (NYHA) Class III or IV heart failure (in Study 301) or NYHA Class II to IV heart failure (in Studies 3011 and 302) was not

established (see 4.8). 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

Marked increases in liver enzymes leading to drug discontinuation or dosage modification occurred in controlled clinical studies (see 4.8. 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 (see 4.2).

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 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 be used with caution in patients with moderate hepatic impairment only if the benefit clearly outweighs the possible risk (see 4.2 and 5.2–Special populations). Abiraterone acetate should not be used in patients with severe hepatic impairment (see 4.2 and 5.2–Special populations).

There have been rare post-marketing reports of acute liver failure and hepatitis fulminant, some with fatal outcome (see 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 abiraterone acetate is continued after corticosteroids are withdrawn, patients should be monitored for symptoms of mineralocorticoid excess (see 4.4-Hypertension, hypokalemia and fluid retention due to 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 acetate and prednisone/prednisolone with Ra-223

Treatment with abiraterone acetate and prednisone/prednisolone in combination with Ra-223 is contraindicated (see 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 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, total lactase deficiency or glucose-galactose malabsorption should not take this medicine. This medicinal product contains 12.472 mg sodium per tablet. As per maximum daily dose which is 2 tablets of 500 mg, the sodium content per dose of 2 tablets is 24.944 mg, which is equivalent to 1.25% of the WHO recommended maximum daily intake of 2g sodium for an adult.

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. The efficacy and safety of abiraterone acetate given with food has not been established. **Abiraterone acetate must not be taken with food** (see 4.2 and 5.2-Absorption).

Interactions with other drugs

Potential for other drugs to affect abiraterone acetate 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 acetate was decreased by 55%.

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.

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 acetate.

Potential for abiraterone acetate to affect exposures to other drugs

Abiraterone acetate is an inhibitor of the hepatic drug-metabolizing enzymes CYP2D6 and CYP2C8. In a clinical 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 by approximately 200%. The AUC24 for dextrorphan, the active metabolite of dextromethorphan, increased approximately 33%.

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

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 1000 mg abiraterone acetate. Patients should be monitored for signs of toxicity related to a CYP2C8 substrate with a narrow therapeutic index if used concomitantly with abiraterone acetate. 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 (see 4.3).

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 (see 5.1-Mechanism of action).

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

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 Undesirable effects

Throughout this section, adverse reactions are presented. Adverse reactions are adverse events that were considered to be reasonably associated with the use of abiraterone acetate based on the comprehensive assessment of the available adverse event information. A causal relationship with abiraterone acetate cannot be reliably established in individual cases. Further, because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

In an analysis of adverse reaction of composite Phase 3 studies with abiraterone acetate, adverse reactions that were observed in ≥10% of patients were hypertension, peripheral edema, hypokalemia, urinary tract infection, and aspartate aminotransferase increased and/or alanine aminotransferase increased.
Abiraterone acetate may cause hypertension, hypokalemia and fluid retention as a pharmacodynamic consequence of its mechanism of action. In Phase 3 studies anticipated mineralocorticoid effects were seen more commonly in patients treated with abiraterone acetate versus patients treated with placebo: hypokalemia 18% versus 8%, hypertension 22% versus 16% and fluid retention (peripheral edema) 23% versus 17%, respectively. In patients treated with abiraterone acetate, grades 3 and 4 hypokalemia were observed in 6% and 2% of patients, grades 3 and 4 hypertension were observed in 8% and 5% of patients, and grades 3 and 4 fluid retention edema were observed in 1% and 1% of patients, respectively. Mineralocorticoid effects generally were able to be successfully managed medically. Concomitant use of a corticosteroid reduces the incidence and severity of these adverse reactions (see 4.4-Hypertension, hypokalemia and fluid retention due to mineralocorticoid excess).

In studies of patients with metastatic advanced prostate cancer who were using a LHRH agonist, or were previously treated with orchiectomy, abiraterone acetate was administered

at a dose of 1000 mg daily in combination with low dose prednisone or prednisolone (5 or 10 mg daily).

Adverse reactions that occurred at a rate of ≥ 1% (all grades) are shown in Table 1[a]:

Table 1a: Adverse Reactions Due to abiraterone acetate in ≥1% of Patients in a Clinical Studies[a]

	Abiraterone acetate 1000 mg daily with prednisone or prednisolone n = 2659[b]		
System Organ Class Adverse Reaction	All grades %	Grade 3 %	Grade 4 %
General Disorders and Administration Site Conditions			
Edema peripheral	20	<1	0
Metabolism and Nutrition Disorders			
Hypokalemia	20	5	<1
Hypertriglyceridemia	1	0	0
Infections and Infestations			
Urinary tract infection	10	2	<1
Hepatobiliary Disorders			
ALT increased and/or AST increased[c]	13	4	<1
Vascular Disorders			
Hypertension	21	6	0
Injury, Poisoning and Procedural Complications			
Fractures[d]	7	2	<1
Cardiac Disorders			
Cardiac failure[e]	1	<1	<1
Angina pectoris	2	<1	0
Arrhythmia	1	0	0
Atrial fibrillation	3	1	<1
Tachycardia	2	<1	0
Renal and Urinary Disorders			
Hematuria	7	1	0
Gastrointestinal Disorders			
Dyspepsia	6	0	0

[a] All patients were using an LHRH agonist or had undergone orchiectomy.
[b] n = patients assessed for safety.
[c] ALT increased and/or AST increased includes ALT increased, AST increased, and hepatic function abnormal.
[d] Fractures includes all fractures with the exception of pathological fractures.
[e] Cardiac failure also includes congestive heart failure, left ventricular dysfunction and ejection fraction decreased.
The adverse reaction, adrenal insufficiency, occurred in the Phase 3 clinical studies at a rate of 0.3% in patients taking abiraterone acetate and at a rate of 0.1% in patients taking placebo.

Cardiovascular effects

The three Phase 3 studies excluded patients with uncontrolled hypertension, clinically significant heart disease as evidenced by myocardial infarction, arterial thrombotic events in the past 6 months, severe or unstable angina, 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 agonists, 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 arrhythmia 0.7% vs. 0.5%.

Hepatotoxicity

Drug associated hepatotoxicity with elevated ALT, aspartate transaminase (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 > 5X ULN or bilirubin increases > 1.5XULN) 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 acetate. Ten patients who received - abiraterone acetate 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 was elevated were more likely to experience liver function test elevations than those beginning with normal values. When elevations of either ALT or AST > 5X ULN, or elevations in bilirubin >3X ULN were observed, abiraterone acetate was withheld or discontinued. In two instances marked increases in liver function tests occurred (see 4.4-Hepatotoxicity and Hepatic impairment). These two patients with normal baseline hepatic function, experienced ALT or AST elevations 15 to 40 XULN and bilirubin elevations 2 to 6X ULN. Upon discontinuation of abiraterone acetate, both patients had normalisation of their liver function tests and one patient was re-treated with abiraterone acetate 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 event.

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 > 2.5X ULN, bilirubin >1.5X 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 ≥ 2.5X ULN in the absence of liver metastases and > 5X 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 ≥ 2.5x 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 4.2). Patients with elevations of ALT or AST > 20X ULN were not re-treated. The safety of re-treatment in such patients is unknown. The mechanism for hepatotoxicity associated with abiraterone acetate is not understood.

Post-marketing experience

Adverse reactions identified during the post-marketing experience based on spontaneous reports with abiraterone acetate are described below. The frequencies are provided according to the following convention:

Uncommon ≥ 1/1000 and < 1/100, Rare ≥1/10000 and <1/1000, Very Rare <1/10000

System Organ Class: Respiratory, thoracic and mediastinal disorders
Rare: Allergic alveolitis
System Organ Class: Musculoskeletal and connective tissue disorders
Uncommon: Rhabdomyolysis, Myopathy
System Organ Class: Hepatobiliary disorders
Rare: Hepatitis fulminant, Acute hepatic failure
System Organ Class: Cardiac disorders
Very rare: QT prolongation and Torsades de Pointes (observed in patients who developed hypokalemia or had underlying cardiovascular conditions).
System Organ Class: Immune System Disorders – Hypersensitivity
Very rare: Anaphylactic reaction (severe allergic reactions that include, but are not limited to difficulty swallowing or breathing, swollen face, lips, tongue or throat, or an itchy rash (urticaria)).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the local reporting system.

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 acetate 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 (see 4.4-Hypertension, hypokalemia and fluid retention due to mineralocorticoid excess).
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. 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.

Use of Spironolactone

Patients in pivotal clinical trials with abiraterone acetate were not allowed to use spironolactone as spironolactone binds to the androgen receptor and may increase PSA levels.

5.2 Pharmacokinetic properties

General introduction

Following administration of abiraterone acetate, the pharmacokinetics of abiraterone acetate has 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 5.1-Mechanism of action).

Absorption

Following oral administration of abiraterone acetate in the fasting state, the time to reach maximum plasma abiraterone acetate 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 acetate, 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 tablets must be taken as a single dose once daily on an empty stomach. Abiraterone acetate must be taken at least two hours after eating and food must not be eaten for at least one hour after taking abiraterone acetate. The tablets must be swallowed whole with water (see 4.2).

Distribution and protein binding

The plasma protein binding of 14c-abiraterone acetate in human plasma is 99.8%. The apparent volume of distribution is approximately 5630 L, suggesting that abiraterone acetate 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. 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 acetate in plasma is approximately 15 hours based on data from healthy subjects. 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

The pharmacokinetics of abiraterone acetate was compared in patients with end-stage renal disease on a stable hemodialysis schedule, versus matched control subjects with normal renal function. Systemic exposure to abiraterone acetate after a single oral 1000 mg dose did not increase in patients 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 4.2).

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 acetate after a single oral 1,000 mg dose increased by approximately 11% and 260% in subjects with mild and moderate pre-existing hepatic impairment, respectively. The mean half-life of abiraterone acetate 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 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 (see 4.2 and 4.4-Hepatotoxicity and Hepatic impairment). 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 (see 4.2 and 4.4- Hepatotoxicity and Hepatic impairment).

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

Tablet core
Lactose monohydrate,
Croscarmellose sodium,
Hypromellose,
Sodium lauryl sulfate,
Colloidal silicon dioxide,
Silicified microcrystalline cellulose,
Magnesium stearate

Tablet film-coat

Polyvinyl alcohol,
Titanium dioxide,
Macrogol / PEG,
Talc,
Iron oxide red,
Ferrosoferric oxide/black iron oxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

18 months.

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

Xbira is proposed for marketing in blister pack. Blister pack comprises of plain clear Polyvinyl chloride/Polyethylene/Polyvinylidene chloride film and Plain Aluminium hard foil coated with heat seal lacquer. The blisters are packed in a carton box along with the patient's information leaflet

Pack size: Box containing 5 blisters of 12 tablets each.

6.6 Special precautions for disposal and other handling

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

7. Manufactured and Released by:

Aizant Drug Research Solutions Private Limited.
Block A and B, Survey No 172/173, Apparel
Park Road, Dulapally, Dundigal Gandimaisamma
Medchal Malkhajgiri, Hyderabad, 500100, India

8. Product registration holder

Cipla Malaysia Sdn Bhd
Suite 1101, Amcorp Tower, Amcorp Trade Centre,
18 Persiaran Barat, 46050, Petaling Jaya, Selangor, Malaysia

9. Date of Revision of the text

17 July 2025