XBIRA Tablets (Abiraterone Acetate)

For the use of oncologists only

1.Qualitative and Quantitative Composition

Each 500 mg film coated tablet contains:

Abiraterone Acetate IP ..... 500 mg

Colour: Titanium Dioxide IP

Each 250 mg uncoated tablet contains:

Abiraterone Acetate IP ..... 250 mg

2.Dosage Form & Strength

250 mg / 500 mg tablets for oral use.

3.Clinical Particulars

3.1 Therapeutic Indications

Abiraterone acetate tablets is indicated:

- in combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer (mCRPC) who have received prior chemotherapy containing docetaxel.
- for the treatment of mCRPC in adult men who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated, with prednisone or prednisolone.

3.2 Posology and Method of Administration

The recommended dose is 1,000 mg (two 500 mg tablets or four 250 mg tablets) as a single daily dose with prednisone 5 mg orally twice daily, that must not be taken with food. Taking the tablets with food increases systemic exposure to abiraterone. **Abiraterone** must be taken on an empty stomach. No food should be consumed for at least one hour before the dose of **Abiraterone** is taken and for at least two hours after the dose of **Abiraterone** is taken. The tablets should be swallowed whole with water. Do not crush or chew tablets.

Dosage of prednisone or prednisolone

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

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 for congestive heart failure should be monitored every 2 weeks for the first three months of treatment and monthly thereafter.

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

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 abiraterone 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, 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. Re-treatment following return of liver function tests to the patient's baseline may be given at a reduced dose of 500 mg (one 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 ULN) 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 1,000 mg. 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 should be cautiously assessed in patients with moderate hepatic impairment, in whom the benefit clearly should outweigh the possible risk. Abiraterone should not be used in patients with severe hepatic impairment.

Renal impairment

No dose adjustment is necessary for patients with renal impairment.

However, there is no clinical experience in patients with prostate cancer and severe renal impairment. Caution is advised in these patients.

Dose Modification Guidelines for Strong CYP3A4 Inducers:

Avoid concomitant strong CYP3A4 inducers (e.g. phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital) during abiraterone acetate treatment. If a strong CYP3A4 inducer must

be co-administered, increase the abiraterone acetate dosing frequency to twice a day only during the co-administration period (e.g. from 1,000 mg once daily to 1,000 mg twice a day). Reduce the dose back to the previous dose and frequency, if the concomitant strong CYP3A4 inducer is discontinued

Paediatric Population

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

Important Administration Instructions

Patients receiving **abiraterone** should also receive a gonadotropin-releasing hormone (GnRH) analog concurrently or should have had bilateral orchiectomy

Method of Administration

Abiraterone is for oral use.

The tablets should be taken at least one hour before or at least two hours after eating. These should be swallowed whole with water.

3.3 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 with prednisone or prednisolone is contraindicated in combination with Ra-223.

3.4 Special Warnings and Precautions for Use

Hypertension, Hypokalaemia, Fluid Retention and Cardiac Failure Due to Mineralocorticoid Excess

Abiraterone 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 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 arrhythmia and those with severe renal impairment).

Abiraterone should be used with caution in patients with a history of cardiovascular disease. The Phase 3 studies conducted with Abiraterone excluded patients with uncontrolled hypertension, clinically significant heart disease as evidenced by myocardial infarction, or arterial thrombotic events in the past 6 months, severe or unstable angina, or New York Heart Association Class (NYHA) III or IV heart failure (study 301) or Class II to IV heart failure (302) or cardiac ejection fraction measurement of < 50%. In study 302, patients with atrial fibrillation, or other cardiac arrhythmia requiring medical therapy were excluded. Safety in patients with left ventricular ejection fraction (LVEF) <50% or NYHA Class III or IV heart failure (in study 301) or NYHA Class II to IV heart failure (in study 302) was not established.

Before treating patients with a significant risk for congestive heart failure (e.g. a history of cardiac failure, uncontrolled hypertension, or cardiac events such as ischaemic heart disease), consider

obtaining an assessment of cardiac function (e.g. echocardiogram). Before treatment with Abiraterone, 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 treatment. Assess cardiac function as clinically indicated, institute appropriate management and consider discontinuation of this treatment if there is a clinically significant decrease in cardiac function.

Hepatotoxicity and Hepatic Impairment

Marked increases in liver enzymes leading to treatment discontinuation or dose modification occurred in controlled clinical studies. 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.

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.

Patients with active or symptomatic viral hepatitis were excluded from clinical trials; thus, there are no data to support the use of Abiraterone 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). The use of Abiraterone should be cautiously assessed in patients with moderate hepatic impairment, in whom the benefit clearly should outweigh the possible risk. Abiraterone 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 are withdrawn from prednisone or prednisolone. If Abiraterone 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, an increased dose of corticosteroids maybe indicated before, during and after the stressful situation.

Embryo-Fetal Toxicity

The safety and efficacy of abiraterone have not been established in females. Based on animal reproductive studies and mechanism of action, abiraterone can cause fetal harm and loss of pregnancy when administered to a pregnant female. In animal reproduction studies, oral administration of abiraterone acetate to pregnant rats during organogenesis caused adverse developmental effects at maternal exposures approximately ≥ 0.03 times the human exposure (AUC) at the recommended dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with abiraterone and for 3 weeks after the last dose of

abiraterone. Abiraterone should not be handled by females who are or may become pregnant.

Bone Density

Decreased bone density may occur in men with metastatic advanced prostate cancer. The use of Abiraterone 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

Cases of hypoglycaemia have been reported when Abiraterone plus prednisone/prednisolone was administered to patients with pre-existing diabetes receiving pioglitazone or repaglinide; therefore, blood sugar should be monitored in patients with diabetes.

Use with Chemotherapy

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

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 sodium in the tablets. To be taken into consideration by patients on a controlled sodium diet.

Potential Risks

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

Skeletal Muscle Effects

Cases of myopathy and rhabdomyolysis have been reported in patients treated with Abiraterone. Most cases developed within the first 6 months of treatment and recovered after Abiraterone withdrawal. Caution is recommended in patients concomitantly treated with medicinal products known to be associated with myopathy/rhabdomyolysis.

QT Prolongation

In a multicentre, open-label, single-arm trial, 33 patients with metastatic CRPC received abiraterone acetate orally at a dose of 1,000 mg once daily at least 1 hour before or 2 hours after a meal in combination with prednisone 5 mg orally twice daily. Assessments up to day 2 of cycle 2 showed no large changes in the QTc interval (i.e. >20 ms) from baseline. However, small increases in the QTc interval (i.e. <10 ms) due to abiraterone acetate cannot be excluded due to study design limitations.

QT prolongation has been observed in patients experiencing hypokalaemia in association with abiraterone acetate treatment.

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.

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 in combination with prednisone/prednisolone.

3.5 Drug Interactions

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 medicinal product must not be taken with food.

Interactions with other medicinal products

Potential for other medicinal products to affect abiraterone exposures

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

Strong inducers of CYP3A4 (e.g., phenytoin, carbamazepine, rifampicin, rifabutin, rifapentine, phenobarbital, St John's wort [Hypericum perforatum]) during treatment are to be avoided, unless there is no therapeutic alternative.

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.

Potential to affect exposures to other medicinal products

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

In a study to determine the effects of abiraterone acetate (plus prednisone) on a single dose of the CYP2D6 substrate dextromethorphan, the systemic exposure (AUC) of dextromethorphan was increased approximately 2.9-fold. The AUC_{24} for dextrorphan, the active metabolite of dextromethorphan, increased approximately 33%.

Caution is advised when administering with medicinal products activated by or metabolised by CYP2D6, particularly with medicinal products that have a narrow therapeutic index. Dose reduction of medicinal products with a narrow therapeutic index that are metabolised by CYP2D6 should be

considered. Examples of medicinal products metabolised by CYP2D6include metoprolol, propranolol, desipramine, venlafaxine, haloperidol, risperidone, propafenone, flecainide, codeine, oxycodone and tramadol (the latter three medicinal products requiring CYP2D6 to form their active analgesic metabolites).

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 1,000 mg 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 metabolised by CYP2C8 include pioglitazone and repaglinide.

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 medicinal products eliminated by OATP1B1. There are no clinical data available to confirm transporter-based interaction.

Use with products known to prolong QT interval

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

Use with Spironolactone

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

3.6 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Patients with Renal Impairment

No dosage adjustment is necessary for patients with renal impairment. However, there is no clinical experience in patients with prostate cancer and severe renal impairment. Caution is advised in these patients.

Patients with Hepatic Impairment

The pharmacokinetics of abiraterone were examined in subjects with baseline mild (N=8) or moderate (N=8) hepatic impairment (Child-Pugh Class A and B, respectively) and in 8 healthy control subjects with normal hepatic function. The systemic exposure (AUC) of abiraterone after a single oral 1,000 mg dose of abiraterone acetate increased by approximately 1.1-fold and 3.6-fold in subjects with mild and moderate baseline hepatic impairment, respectively compared to subjects with normal hepatic function.

In another trial, the pharmacokinetics of abiraterone were examined in subjects with baseline severe (N=8) hepatic impairment (Child-Pugh Class C) and in 8 healthy control subjects with normal hepatic function. The systemic exposure (AUC) of abiraterone increased by approximately 7-fold and the fraction of free drug increased 2-fold in subjects with severe baseline hepatic impairment

compared to subjects with normal hepatic function.

No dosage adjustment is necessary for patients with baseline mild hepatic impairment. In patients with baseline moderate hepatic impairment (Child-Pugh Class B), reduce the recommended dose of **XBIRA** to 250 mg once daily. Do not use **XBIRA** in patients with baseline severe hepatic impairment (Child-Pugh Class C). If elevations in ALT or AST >5X ULN or total bilirubin >3X ULN occur in patients with baseline moderate hepatic impairment, discontinue **XBIRA** treatment.

For patients who develop hepatotoxicity during treatment, interruption of treatment and dosage adjustment may be required.

Pregnant Women

Abiraterone is not for use in women and is contraindicated in women who are or may potentially be pregnant.

Lactating Women

Abiraterone is not for use in women. The safety and efficacy of abiraterone have not been established in females. There is no information available on the presence of abiraterone acetate in human milk, or on the effects on the breastfed child or milk production.

Pediatric Use

Safety and effectiveness of **ABIRATERONE** in pediatric patients have not been established.

Geriatric Use

Of the total number of patients receiving abiraterone acetate in Phase 3 trials, 73% of patients were 65 years and over and 30% were 75 years and over. No overall differences in safety or effectiveness were observed between these elderly patients and younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Women of Childbearing Potential

There are no human data on the use of Abiraterone in pregnancy and this medicinal product is not for use in women of childbearing potential.

Contraception in Males and Females

It is not known whether 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 childbearing potential, a condom is required along with another effective contraceptive method. Studies in animals have shown reproductive toxicity.

Fertility

Abiraterone affected fertility in male and female rats, but these effects were fully reversible.

3.7 Effects on ability to drive and use machines

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

3.8 Undesirable Effects

Summary of the safety profile

In an analysis of adverse reactions of composite Phase 3 studies with abiraterone, 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 may cause hypertension, hypokalaemia and fluid retention as a pharmacodynamic consequence of its mechanism of action. In Phase 3 studies, anticipated mineralocorticoid adverse reactions were seen more commonly inpatients treated with abiraterone acetate than in patients treated with placebo: hypokalaemia 18% vs.8%, hypertension22% vs. 16% and fluid retention (peripheral oedema) 23% vs. 17%, respectively. In patients treated with abiraterone acetate versus patients treated with placebo: CTCAE (version 4.0) Grades 3 and 4 hypokalaemia were observed in 6%versus 1%, CTCAE (version 4.0) Grades 3 and 4 hypertension were observed in 7% versus 5%, and fluid retention (peripheral oedema) Grades 3 and 4 were observed in 1% versus 1% of patients, respectively. Mineralocorticoid reactions generally were able to be successfully managed medically. Concomitant use of a corticosteroid reduces the incidence and severity of these adverse reactions (see section 3.4).

Tabulated list of adverse reactions

In studies of patients with metastatic advanced prostate cancer who were using an LHRH analogue, or were previously treated with orchiectomy, abiraterone was administered at a dose of 1,000 mg daily in combination with low dose prednisone or prednisolone (either 5 or 10 mg daily depending on the indication).

Adverse reactions observed during clinical studies and post-marketing experience are listed below by frequency category. Frequency categories are defined as follows: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000) and not known (frequency cannot be estimated from the available data).

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

Table 1: Adverse reactions identified in clinical studies and post-marketing		
System Organ Class	**Adverse reaction and frequency**	
Infections and infestations	very common: urinary tract infection common: sepsis	
Immune system disorders	not known: anaphylactic reactions	
Endocrine disorders	uncommon: adrenal insufficiency	
Metabolism and nutrition disorders	very common: hypokalaemia common: hyper triglyceridaemia	
Cardiac disorders	common: cardiac failure*, angina pectoris, atrial fibrillation, tachycardia uncommon: other arrhythmias not known: myocardial infarction, QT prolongation	

Vascular disorders	very common: hypertension	
Respiratory, thoracic and mediastinal disorders	rare: allergic alveolitis[a]	
Gastrointestinal disorders	very common: diarrhoea common: dyspepsia	
Hepatobiliary disorders	very common: alanine aminotransferase increased and/or aspartate aminotransferase increased[b] 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 ** Fractures includes osteoporosis and all fractures with the exception of pathological fractures a Spontaneous report from post-marketing experience b Alanine aminotransferase increased and/or aspartate aminotransferase increased includes ALT increased, AST increased, and hepatic function abnormal.		

The following CTCAE (version 4.0) Grade 3 adverse reactions occurred in patients treated with abiraterone acetate: hypokalaemia 5%; urinary tract infection 2%; alanine aminotransferase increased and/or aspartate aminotransferase increased 4%; hypertension 6%; fractures 2%; peripheral oedema, cardiac failure, and atrial fibrillation 1% each. CTCAE (version 4.0) Grade 3 hypertriglyceridaemia and angina pectoris occurred in < 1% of patients. CTCAE (version 4.0) Grade 4 urinary tract infection, alanine aminotransferase increased and/or aspartate aminotransferase increased, hypokalemia, cardiac failure, atrial fibrillation, and fractures occurred in < 1% of patients.

Hypertension was observed in 11.8% and 20.2 % of population in 301 and 302 studies respectively, and hypokalemia was observed in 19.2% and 14.9% of population in 301 and 302 respectively.

The incidence and severity of adverse events was higher in the subgroup of patients with baseline ECOG2 performance status grade and also in elderly patients (≥75 years).

Description of selected adverse reactions

Cardiovascular Reactions

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

patients taking placebo were as follows: atrial fibrillation 2.6% vs. 2.0%, tachycardia 1.9% vs. 1.0%, angina pectoris 1.7% vs. 0.8%, cardiac failure 0.7% vs. 0.2%, and arrhythmia 0.7% vs. 0.5%.

Hepatotoxicity

Hepatotoxicity with elevated ALT, AST and total bilirubin has been reported in patients treated with abiraterone acetate. Across Phase 3 clinical studies, hepatotoxicity grades 3 and 4 (e.g., ALT or AST increases of > 5 x ULN or bilirubin increases > 1.5 x ULN) were reported in approximately 6% of patients who received abiraterone acetate, typically during the first 3 months after starting treatment. In the Phase 3 clinical studies, patients whose baseline ALT or AST were elevated were more likely to experience liver function test elevations than those beginning with normal values. When elevations of either ALT or AST> 5 x ULN, or elevations in bilirubin > 3 x ULN were observed, abiraterone acetate was withheld or discontinued. In two instances marked increases in liver function tests occurred (see section 3.4). These two patients with normal baseline hepatic function, experienced ALT or AST elevations 15 to 40 x ULN and bilirubin elevations 2 to 6 x ULN. Upon discontinuation of treatment, both patients had normalisation of their liver function tests and one patient was re-treated without recurrence of the elevations. In study 302, Grade 3 or 4 ALT or AST elevations were observed in 35 (6.5%) patients treated with abiraterone acetate. Aminotransferase elevations resolved in all but 3 patients (2 with new multiple liver metastases and 1 with AST elevation approximately 3 weeks after the last dose of abiraterone acetate). In Phase 3 clinical studies, treatment discontinuations due to ALT and AST increases or abnormal hepatic function were reported in1.1% of patients treated with abiraterone acetate and 0.6% of patients treated with placebo; no deaths were reported due to hepatotoxicity events.

In clinical trials, the risk for hepatotoxicity was mitigated by exclusion of patients with baseline hepatitis or significant abnormalities of liver function tests. In the 301 trial, patients with baseline ALT and AST ≥ 2.5 x ULN in the absence of liver metastases and > 5 x ULN in the presence of liver metastases were excluded. In the 302 trial, patients with liver metastases were not eligible and patients with baseline ALT and AST ≥ 2.5 x ULN were excluded. Abnormal liver function tests developing in patients participating in clinical trials were vigorously managed by requiring treatment interruption and permitting re-treatment only after return of liver function tests to the patient's baseline (see section 3.2).Patients with elevations of ALT or AST > 20 x ULN were not re-treated. The safety of re-treatment in such patients is unknown. The mechanism for hepatotoxicity is not understood.

Postmarketing Experience

The following additional adverse reactions have been identified during post approval use of abiraterone acetate. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Respiratory, Thoracic and Mediastinal Disorders: non-infectious pneumonitis.

Musculoskeletal and Connective Tissue Disorders: myopathy, including rhabdomyolysis.

Hepatobiliary Disorders: fulminant hepatitis, including acute hepatic failure and death.

Cardiac Disorders: QT prolongation and Torsades de Pointes (observed in patients who developed hypokalemia or had underlying cardiovascular conditions).

Immune System Disorders: Hypersensitivity: anaphylactic reactions (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)).

3.9 Overdose

Human experience of overdose with abiraterone is limited.

There is no specific antidote. In the event of an overdose, administration should be withheld and general supportive measures undertaken, including monitoring for arrhythmias, hypokalaemia and for signs and symptoms of fluid retention. Liver function also should be assessed.

Reporting of suspected adverse reactions

Health care professionals, patients/consumers are advised to closely monitor the possibility of the above ADRs associated with the use of the above drugs. If such reactions are encountered, please report to the Hetero either by filling of Suspect Adverse Drug Reactions Reporting Form (form.heteroworld.com) or by Hetero Helpline No.1800-120-8689 and for all India safety cases and complaints, please write to drugsafetyindia@heterodrugs.com.

4.Pharmacological Properties

4.1Mechanism 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 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.

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

4.2 Pharmacodynamic Properties

Abiraterone 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. 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.

Cardiac Electrophysiology

In a multi-center, open-label, single-arm trial, 33 patients with metastatic CRPC received Abiraterone orally at a dose of 1,000 mg once daily at least 1 hour before or 2 hours after a meal in combination with prednisone 5 mg orally twice daily.

Assessments up to Cycle 2 Day 2 showed no large changes in the QTc interval (i.e., >20 ms) from baseline. However, small increases in the QTc interval (i.e., <10 ms) due to abiraterone acetate cannot be excluded due to study design limitations

4.3 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.

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 10-fold (AUC) and up to a 17-fold (C_{max}) 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 with meals has the potential to result in highly variable exposures. Therefore, abiraterone must not be taken with food. It should be taken at least one hour before or at least two hours after eating. The tablets should be swallowed whole with water.

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 14C-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 approximately43% of total radioactivity.

Elimination

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

Hepatic Impairment

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

In another trial, the pharmacokinetics of abiraterone were examined in subjects with pre-existing severe (n = 8) hepatic impairment (Child-Pugh Class C) and in 8 healthy control subjects with normal hepatic function. The AUC to abiraterone increased by approximately 600% and the fraction of free drug increased by 80% in subjects with severe hepatic impairment compared to subjects with normal hepatic function.

No dose adjustment is necessary for patients with pre-existing mild hepatic impairment.

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.

For patients who develop hepatotoxicity during treatment, suspension of treatment and dose adjustment may be required.

Renal Impairment

The pharmacokinetics of abiraterone acetate was compared in patients with end-stage renal disease on a stable haemodialysis schedule versus matched control subjects with normal renal function. Systemic exposure to abiraterone after a single oral 1,000 mg dose did not increase in subjects with end-stage renal disease on dialysis. Administration inpatients with renal impairment, including severe renal impairment, does not require dose reduction. However, there is no clinical experience in patients with prostate cancer and severe renal impairment. Caution is advised in these patients.

Drug Interactions

In vitro studies with human hepatic microsomes showed that abiraterone has the potential to inhibit CYP1A2, CYP2D6, CYP2C8 and to a lesser extent CYP2C9, CYP2C19 and CYP3A4/5.

In an in vivo drug-drug interaction trial, the Cmax and AUC of dextromethorphan (CYP2D6 substrate) were increased 2.8- and 2.9-fold, respectively when dextromethorphan 30 mg was given with abiraterone acetate 1,000 mg daily (plus prednisone 5 mg twice daily). The AUC for dextrorphan, the active metabolite of dextromethorphan, increased approximately 1.3-fold.

In a clinical study to determine the effects of abiraterone acetate 1,000 mg daily (plus prednisone 5 mg twice daily) on a single 100 mg dose of the CYP1A2 substrate theophylline, no increase in systemic exposure of theophylline was observed.

Abiraterone is a substrate of CYP3A4, in vitro. In a clinical pharmacokinetic interaction study of healthy subjects pretreated with a strong CYP3A4 inducer (rifampin, 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%.

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.

In a CYP2C8 drug-drug interaction trial in healthy subjects, the AUC of pioglitazone was increased by 46% when pioglitazone was given together with a single dose of 1,000 mg abiraterone acetate.

In vitro, abiraterone and its major metabolites were shown to inhibit the hepatic uptake transporter OATP1B1. There are no clinical data available to confirm transporter based interaction.

5.Nonclinical Properties

5.1Animal Toxicology or Pharmacology

In all animal toxicity studies, circulating testosterone levels were significantly reduced. As a result, reduction in organ weights and morphological and/or histopathological changes in the reproductive organs, and the adrenal, pituitary and mammary glands were observed. All changes showed complete or partial reversibility. The changes in the reproductive organs and androgen-sensitive organs are consistent with the pharmacology of abiraterone. All treatment-related hormonal changes reversed or were shown to be resolving after a 4-week recovery period.

In fertility studies in both male and female rats, abiraterone acetate reduced fertility, which was completely reversible in 4to 16 weeks after abiraterone acetate was stopped.

In a developmental toxicity study in the rat, abiraterone acetate affected pregnancy including reduced foetal weight and survival. Effects on the external genitalia were observed though abiraterone acetate was not teratogenic.

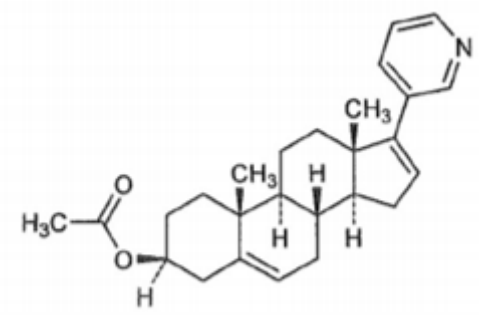
In these fertility and developmental toxicity studies performed in the rat, all effects were related to the pharmacological activity of abiraterone.

Aside from reproductive organ changes seen in all animal toxicology studies, non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential. Abiraterone acetate was not carcinogenic in a 6-month study in the transgenic (Tg.rasH2) mouse. In a 24-month carcinogenicity study in the rat, abiraterone acetate increased the incidence of interstitial cell neoplasms in the testes. This finding is considered related to the pharmacological action of abiraterone and rat specific. Abiraterone acetate was not carcinogenic in female rats.

The active substance, abiraterone, shows an environmental risk for the aquatic environment, especially to fish.

6.Description

Abiraterone acetate, the active ingredient of abiraterone tablet is the acetyl ester of abiraterone. Abiraterone is an inhibitor of CYP17 (17α-hydroxylase/C17,20-lyase). Abiraterone acetate is designated chemically as (3β)-17-(3-pyridinyl) androsta-5,16-dien-3-yl acetate and its structure is:



7.Pharmaceutical Particulars

7.1 Incompatibilities

Not applicable.

7.2 Shelf-life

2 years

7.3 Packing Information

500 mg tablets

60’s HDPE Container [150 cc HDPE Container (HW) with 38 mm Child Resistant Closure, Silica Gel Bags 1 gm and Absorbent Cotton]

250 mg tablets

120’s HDPE Container [150 cc HDPE Container (HW) with 38 mm Child Resistant Closure, Silica Gel Bags 1 gm and Absorbent Cotton]

7.4 Storage and handling instructions

Store protected from light and moisture, at a temperature not exceeding 30°C.

Keep out of reach of children.

8.Patient Counselling Information

Read this Patient Information that comes with **XBIRA** before you start taking it and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or your treatment.

What is XBIRA?

XBIRA is a prescription medicine that is used along with prednisone. **XBIRA** is used to treat men with castration-resistant prostate cancer (prostate cancer that is resistant to medical or surgical treatments that lower testosterone) that has spread to other parts of the body. **XBIRA** is not for use in women. It is not known if **XBIRA** is safe or effective in children.

Who should not take XBIRA?

Do not take **XBIRA** if you are pregnant or may become pregnant. **XBIRA** may harm your unborn baby. Women who are pregnant or who may become pregnant should not touch **XBIRA** without protection, such as gloves.

What should I tell my healthcare provider before taking XBIRA?

Before you take **XBIRA**, tell your healthcare provider if you:

• have heart problems

• have liver problems

• have diabetes

• have a history of adrenal problems

• have a history of pituitary problems

•are receiving any other treatment for prostate cancer

• are pregnant or plan to become pregnant. **XBIRA** can cause harm to your unborn baby and loss of pregnancy (miscarriage). Females who are or may become pregnant should not handle **XBIRA** uncoated tablets or other **XBIRA** tablets if broken, crushed, or damaged without protection, such as gloves.

• are breastfeeding or plan to breastfeed. It is not known if **XBIRA** passes into your breast milk. You and your healthcare provider should decide if you will take **XBIRA** or breastfeed. You should not do both. Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. **XBIRA** can interact with many other medicines.

You should not start or stop any medicine before you talk with the healthcare provider that prescribed **XBIRA**. Know the medicines you take. Keep a list of them with you to show to your healthcare provider and pharmacist when you get a new medicine.

How should I take **XBIRA**?

• Take **XBIRA** and prednisone exactly as your healthcare provider tells you.

• Take your prescribed dose of **XBIRA** 1 time a day.

• Your healthcare provider may change your dose if needed.

• Do not stop taking your prescribed dose of **XBIRA** or prednisone without talking with your healthcare provider first.

• Take **XBIRA** on an empty stomach. Do not take **XBIRA** with food. Taking **XBIRA** with food may cause more of the medicine to be absorbed by the body than is needed and this may cause side effects.

• Take **XBIRA** on an empty stomach at least one hour before or at least two hours after a meal.

• Swallow **XBIRA** tablets whole. Do not crush or chew tablets.

• Take **XBIRA** tablets with water.

• Men who are sexually active with a pregnant woman must use a condom during and for 1 week after treatment with **XBIRA**. If their female partner may become pregnant, a condom and another form of birth control must be used during and for 1 week after treatment with **XBIRA** Talk with your healthcare provider if you have questions about birth control.

• If you miss a dose of **XBIRA** or prednisone, take your prescribed dose the following day. If you miss more than 1 dose, tell your healthcare provider right away.

• Your healthcare provider will do blood tests to check for side effects.

What are the possible side effects of **XBIRA**?

XBIRA may cause serious side effects including:

• High blood pressure (hypertension), low blood potassium levels (hypokalemia) and fluid retention (edema). Tell your healthcare provider if you get any of the following symptoms:

◦ dizziness
◦ fast heartbeats
◦ feel faint or lightheaded o headache
◦ confusion
◦ muscle weakness
◦ pain in your legs
◦ swelling in your legs or feet

• Adrenal problems may happen if you stop taking prednisone, get an infection, or are under stress.

• Liver problems. You may develop changes in liver function blood test. Your healthcare provider will do blood tests to check your liver before treatment with **XBIRA** and during treatment with **XBIRA**. Liver failure may occur, which can lead to death. Tell your healthcare provider if you notice any of the following changes:

◦ yellowing of the skin or eyes
◦ darkening of the urine or severe nausea or vomiting

•Increased risk of bone fracture and death when **XBIRA** and prednisone or prednisolone, is used in combination with a type of radiation called radium Ra 223 dichloride. Tell your healthcare provider about any other treatments you are taking for prostate cancer.

• Severe low blood sugar (hypoglycemia). Severe low blood sugar with **XBIRA** can happen in people who have diabetes and take certain antidiabetic medicines. You and/or your healthcare provider should check your blood sugar levels regularly during treatment with **XBIRA** and after you stop treatment. Your healthcare provider may also need to change the dose of your antidiabetic medicines.

Signs and symptoms of low blood sugar may include.

◦ headache
◦ irritability
◦ drowsiness
◦ hunger
◦ weakness
◦ fast heartbeat
◦ dizziness
◦ sweating
◦ confusion
◦ feeling jittery

The most common side effects of **XBIRA** include:

◦ weakness

- joint swelling or pain
- swelling in your legs or feet
- hot flushes
- diarrhea
- vomiting
- cough
- high blood pressure
- shortness of breath
- urinary tract infection
- bruising
- low red blood cells (anemia) and low blood potassium levels
- high blood sugar levels, high blood cholesterol and triglycerides
- certain other abnormal blood tests

Tell your healthcare provider if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of XBIRA. For more information, ask your healthcare provider or pharmacist. Call your doctor for medical advice about side effects.

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.

Reporting of suspected adverse reactions

Health care professionals, patients/consumers are advised to closely monitor the possibility of the above ADRs associated with the use of the above drugs. If such reactions are encountered, please report to the Hetero either by filling of Suspect Adverse Drug Reactions Reporting Form **(form.heteroworld.com)** or by **Hetero Helpline No.1800-120-8689** and for all India safety cases and complaints, please write to drugsafetyindia@heterodrugs.com

How should I store XBIRA?

Store protected from light and moisture at a temperature not exceeding 30ºC. KEEP OUT OF REACH OF CHILDREN.

General information about XBIRA

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use **XBIRA** for a condition for which it was not prescribed. Do not give **XBIRA** to other people, even if they have the same symptoms that you have. It may harm them. This leaflet summarizes the most important information about **XBIRA**. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about **XBIRA** that is written for health professionals.

What are the ingredients of XBIRA?

Active ingredient: Abiraterone acetate

Inactive ingredients: Colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone, and sodium lauryl sulfate.

9.Details of Manufacturer

Hetero Labs Limited (Unit I)

Kalyanpur (Village), Chakkan Road,

Baddi (Tehsil), Solan (Dist.)

Himachal Pradesh – 173205

Marketed by CIPLA LTD.

Cipla House, Peninsula Business Park, Ganpatrao Kadam Marg, Lower Parel, Mumbai - 400 013 INDIA.

10.Details of Permission or Licence Number with Date

MNB/06/328, Dated: 21 Jan 2021

Date of Revision

11 August 2021