Ablax® 250

Abiraterone Acetate

FORMS AND PRESENTATION
Ablax® 250: Tablets. Jar of 120.

COMPOSITION
Ablax® 250: Each tablet contains Abiraterone acetate 250mg.
Excipients: microcrystalline cellulose, lactose, croscarmellose sodium, povidone, sodium lauryl sulfate, colloidal silicon dioxide, magnesium stearate.

PHARMACOLOGICAL PROPERTIES
Pharmacodynamic properties
Pharmacotherapeutic group: endocrine therapy, other hormone antagonists and related agents, ATC code: L02BX03.
Mechanism of action
Abiraterone acetate is converted in vivo to abiraterone, an androgen biosynthesis inhibitor. 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. CYP17 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 analogues 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 analogues (or orchiectomy).
Pharmacokinetic properties
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 (Cmax) 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 Ablax ® 250 with meals has the potential to result in highly variable exposures. Therefore, Ablax® 250 must not be taken with food. It should be taken at least two hours after eating and no food should be eaten for at least one hour after taking Ablax® 250. 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 ^{14}C-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 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).

INDICATIONS
Ablax® 250 is indicated with prednisone or prednisolone for:
• the treatment of newly diagnosed high risk metastatic hormone sensitive prostate cancer (mHSPC) in adult men in combination with androgen deprivation therapy (ADT)
• 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.

CONTRAINDICATIONS
- Hypersensitivity to the active substance or to any of the excipients listed.
- 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.

PRECAUTIONS
Hypertension hypokalaemia fluid retention and cardiac failure due to mineralocorticoid excess
Hypertension, hypokalaemia, fluid retention and cardiac failure due to mineralocorticoid excess Ablax® 250 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).
Ablax® 250 should be used with caution in patients with a history of cardiovascular disease.
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 Ablax® 250, cardiac failure should be treated, and cardiac function optimized. Hypertension, hypokalaemia and fluid retention should be corrected and controlled. During treatment, blood pressure, serum potassium, fluid retention (weight gain, peripheral oedema), and other signs and symptoms of congestive heart failure should be monitored every 2 weeks for 3 months, then monthly thereafter and abnormalities corrected. QT prolongation has been observed in patients experiencing hypokalaemia in association with Abiraterone acetate tablets 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 acetate tablets 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 Ablax® 250 should be cautiously assessed in patients with moderate hepatic impairment, in whom the benefit clearly should outweigh the possible risk. Ablax® 250 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 Ablax® 250 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 may be indicated before, during and after the stressful situation.
Bone density
Decreased bone density may occur in men with metastatic advanced prostate cancer. The use of Ablax® 250 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 acetate 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 acetate 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 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.
Potential risks
Anaemia and sexual dysfunction may occur in men with metastatic prostate cancer including those undergoing treatment with Ablax® 250.
Skeletal muscle effects
Cases of myopathy and rhabdomyolysis have been reported in patients treated with Abiraterone acetate. Most cases developed within the first 6 months of treatment and recovered after Abiraterone acetate withdrawal. Caution is recommended in patients concomitantly treated with medicinal products known to be associated with myopathy/rhabdomyolysis.
Interactions with other medicinal products
Strong inducers of CYP3A4 during treatment are to be avoided unless there is no therapeutic alternative, due to risk of decreased exposure to abiraterone.
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 Ablax® 250 in combination with prednisone/prednisolone.
Effects on ability to drive and use machines
Abiraterone acetate has no or negligible influence on the ability to drive and use machines.

FERTILITY, PREGNANCY AND LACTATION
Women of childbearing potential
There are no human data on the use of Ablax® 250 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.

Pregnancy

Ablax® 250 is contraindicated in women who are or may potentially be pregnant.

Breast-feeding

Ablax® 250 is not for use in breast-feeding women.

Fertility

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

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-metabolizing 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 AUC24 for dextrorphan, the active metabolite of dextromethorphan, increased approximately 33%. Caution is advised when administering with medicinal products activated by or metabolized by CYP2D6, particularly with medicinal products that have a narrow therapeutic index. Dose reduction of medicinal products with a narrow therapeutic index that are metabolized by CYP2D6 should be considered. Examples of medicinal products metabolized by CYP2D6 include 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. Although these results indicate that no clinically meaningful increases in exposure are expected when Abiraterone acetate is combined with medicinal products that are predominantly eliminated by CYP2C8, patients should be monitored for signs of toxicity related to a CYP2C8 substrate with a narrow therapeutic index if used concomitantly. In vitro, the major metabolites abiraterone sulphate and N-oxide abiraterone sulphate were shown to inhibit the hepatic uptake transporter OATP1B1 and as a consequence it may increase the concentrations of 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 Ablax® 250 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 Ablax® 250 is not recommended.

ADVERSE EFFECTS

Abiraterone acetate may cause hypertension, hypokalaemia and fluid retention as a pharmacodynamic consequence of its mechanism of action.

Adverse effects are listed below by system organ class and frequency. Frequencies are defined as: 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); not known (cannot be estimated from the available data).

Infections and infestations: urinary tract infection (very common); sepsis (common).

Immune system disorders: anaphylactic reactions (not known).

Endocrine disorders: adrenal insufficiency (uncommon).

Metabolism and nutrition disorders: hypokalaemia (very common); hypertriglyceridaemia (common).

Cardiac disorders: cardiac failure, angina pectoris, atrial fibrillation, tachycardia (common); other arrythmias (uncommon); myocardial infarction, QT prolongation (not known).

Vascular disorders: hypertension (very common).

Respiratory, thoracic and mediastinal disorders: allergic alveolitis (rare).

Gastrointestinal disorders: diarrhea (very common); dyspepsia (common).

Hepatobiliary disorders: alanine aminotransferase increased and/or aspartate aminotransferase increased (very common); hepatitis fulminant, acute hepatic failure (rare).

Skin and subcutaneous tissue disorders: rash (common).

Musculoskeletal and connective tissue disorders: myopathy, rhabdomyolysis (uncommon).

Renal and urinary disorders: haematuria (common).

General disorders and administration site conditions: oedema peripheral (very common).

Injury, poisoning and procedural complications: fractures (common).

DOSAGE AND ADMINISTRATION

This medicinal product should be prescribed by an appropriate healthcare professional.

Posology

The recommended dose is 1,000 mg (four 250 mg tablets) as a single daily dose that must not be taken with food. Taking the tablets with food increases systemic exposure to abiraterone.

Dosage of prednisone or prednisolone

For mHSPC, Ablax® 250 is used with 5 mg prednisone or prednisolone daily.

For mCRPC, Ablax® 250 is used with 10 mg prednisone or prednisolone daily.

Medical castration with luteinising hormone releasing hormone (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 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 Ablax® 250, 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 Ablax® 250 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 Ablax® 250, 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 (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 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 Ablax® 250 should be cautiously assessed in patients with moderate hepatic impairment, in whom the benefit clearly should outweigh the possible risk. Ablax® 250 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.

Paediatric population

There is no relevant use of Ablax® 250 in the paediatric population.

Method of administration

Oral use.

The tablets must be taken as a single dose once daily on an empty stomach. Ablax® 250 must be taken at least two hours after eating and food must not be eaten for at least one hour after taking Ablax® 250. These must be swallowed whole with water.

OVERDOSAGE

Human experience of overdose with abiraterone acetate tablets 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.

STORAGE CONDITIONS

Store below 30°C.

Keep in original pack in intact conditions.

Date of revision: April 2024.

Marketing Authorization Holder

Benta S.A.L. - Lebanon

Manufacturer

Manufactured by MSN laboratories private limited, India

For Benta S.A.L. – Lebanon