

SCHEDULING STATUS: S4

PROPRIETARY NAME (AND DOSAGE FORM):

BICADEX (Tablets)

COMPOSITION:

Each film-coated **BICADEX** tablet contains bicalutamide 50 mg. Inactive ingredients include lactose monohydrate, colloidal anhydrous silica, crospovidone, magnesium stearate, maize starch, opadry white, povidone, and sodium lauryl sulphate.

PHARMACOLOGICAL CLASSIFICATION:

A 21.12 Hormone inhibitors.

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

Bicalutamide is a non-steroidal anti-androgen that completely lacks other endocrine activity. It inhibits the androgen stimulus by binding to androgen receptors without activating gene expression. This inhibition of the androgen stimulus results in the regression of prostatic tumours. Bicalutamide is a racemate with the (R)-enantiomer almost exclusively responsible for its anti-androgenic activity. In animals bicalutamide is an anti-androgen and a mixed function oxidase enzyme inducer. These activities are associated with target organ changes, including tumour induction, in animals. No findings obtained during preclinical testing are thought to be relevant to the treatment of patients with advanced prostate cancer.

Pharmacokinetic properties:

Bicalutamide is highly bound to plasma proteins. It is extensively metabolised via oxidation and glucuronidation with approximately equal portions of its metabolites eliminated via the kidneys and bile.

INDICATIONS:

BICADEX is indicated for the treatment of patients with advanced prostate cancer in combination with Luteinising Hormone-Releasing Hormone (LHRH) analogue therapy or surgical castration.

CONTRA-INDICATIONS:

BICADEX is contra-indicated in:

- Patients who have demonstrated a hypersensitivity reaction to its use.
- Females and children, pregnant women or nursing mothers (see "**PREGNANCY AND LACTATION**").

WARNINGS:

Hepatic function impairment:

Metabolism of **BICADEX** may be delayed in patients with moderate to severe hepatic function impairment, resulting in a prolonged elimination half-life and an increased risk of toxicity. Periodic assessment of hepatic function should be considered during long-term use of **BICADEX**.

Medicines metabolised by cytochrome p450:

Clinical studies utilising antipyrine as a marker of cytochrome p450 (cyp) activity did not show any evidence of a potential drug interaction between midazolam and **BICADEX**. However, midazolam exposure (auc) was increased by up to 80 % after concomitant administration with **BICADEX** for 28 days. This increase is comparable to that observed in other studies following administration of grapefruit juice. Caution is required when **BICADEX** is co-administered with compounds such as these.

INTERACTIONS:

Luteinising hormone-releasing hormone (LHRH):

Evidence of any pharmacodynamic or pharmacokinetic interactions between **BICADEX** and LHRH analogues is absent.

Ketoconazole and cimetidine:

Since formal interaction studies have not been conducted, caution should be exercised when **BICADEX** is prescribed with other medicines, e.g. ketoconazole and cimetidine, which may inhibit its oxidation. This could result in increased plasma levels of **BICADEX** which in turn could give rise to an increase in side-effects.

Medicines metabolised by cytochrome P450:

Clinical studies utilising antipyrine as a marker of cytochrome P450 (CYP) activity did not demonstrate any evidence of a drug interaction potential with **BICADEX**. However, midazolam exposure (AUC) was increased by up to 80 % after concomitant administration with **BICADEX** for 28 days. This increase is comparable to that observed in other studies following administration of grapefruit juice. Caution is required when **BICADEX** is co-administered with compounds such as these (see "**WARNINGS**").

Coumarin anticoagulants:

Since **BICADEX** can displace the coumarin anticoagulant, warfarin, from its protein binding sites, prothrombin time should be closely monitored when **BICADEX** is initiated in patients who are already taking coumarin anticoagulants.

PREGNANCY AND LACTATION:

Safety and efficacy of **BICADEX** during pregnancy and lactation have not been established. **BICADEX** is contra-indicated during pregnancy and lactation (see "**CONTRA-INDICATIONS**").

DOSAGE AND DIRECTIONS FOR USE:

Adult males, including the elderly:

The dosage of **BICADEX** is one tablet (50 mg) once daily. Treatment with **BICADEX** should be initiated at least three days before starting treatment with a LHRH analogue, or at the same time as surgical castration.

Renal impairment:

No dosage adjustment is required for patients with renal impairment.

Hepatic impairment:

Patients with mild hepatic impairment do not require dosage adjustments. Patients with moderate to severe impairment of hepatic function may experience increased accumulation (see "**WARNINGS**" and "**Special Precautions**").

SIDE-EFFECTS AND SPECIAL PRECAUTIONS:

Side-Effects:

Due to its pharmacological action, **BICADEX** may cause certain expected effects, such as hot flushes and pruritus. In addition, it may give rise to breast tenderness and gynaecomastia, which may be reduced by concomitant castration. **BICADEX** may also be associated with the development of diarrhoea, nausea, vomiting, asthenia and dry skin. Hepatic changes (elevated levels of transaminases, jaundice), infrequently severe, have been seen in patients who received **BICADEX**. These changes were frequently transient in nature and resolved or improved despite continued therapy or after cessation of treatment. Periodic evaluation of liver function should be considered (see "**Special Precautions**").

Effects on the cardiovascular system, such as angina, heart failure, and conduction defects (including PR- and QT-interval prolongation, dysrhythmias and non-specific ECG changes) have been noted less frequently. Thrombocytopenia also occurred less frequently.

In addition, the following adverse events were reported:

Infections and infestations:

Frequent: Infection, including pulmonary or upper respiratory tract infections.

Blood and lymphatic system disorders:

Less frequent: Anaemia, leucopenia, thrombocytopenia, neutropenia.
The following side-effects have been reported and frequencies are unknown: Methaemoglobinaemia.

Immune system disorders:

Less frequent: Hypersensitivity reactions, including rash.

Endocrine disorders:

Frequent: Hot flushes.
Less frequent: Gynaecomastia, decreased libido.

Metabolism and nutrition disorders:

Less frequent: Diabetes mellitus, hyperglycaemia, oedema, weight gain, and weight loss.

Nervous system disorders:

Less frequent: Headaches, reversible neurological reactions, such as nervousness, dizziness, confusion, drowsiness and mental depression, insomnia, somnolence, and neuromuscular symptoms or neuropathy.

Eye disorders:

The following side-effects have been reported and frequencies are unknown: Impaired adaptation of eyes to dark, visual disturbances, including chromatopsia and increased sensitivity to light.

Cardiovascular system disorders:

Less frequent: Hypertension.
The following side-effects have been reported and frequencies are unknown: Myocardial infarction and cardiac failure.

Respiratory, thoracic and mediastinal disorders:

Frequent: Cough or hoarseness, runny nose, shortness of breath, troubled breathing and tightness in chest or wheezing, sneezing, sore throat.
Less frequent: Chest pain, dyspnoea, flu-like syndrome.

Gastrointestinal disorders:

Frequent: Diarrhoea, constipation, nausea.
Less frequent: Bloating feeling, indigestion, dyspepsia, dryness of mouth, gastrointestinal or rectal bleeding, loss of appetite, flatulence and vomiting.

Hepatobiliary disorders:

Less frequent: Hepatitis or jaundice, including cholestatic jaundice.

Skin and subcutaneous tissue disorders:

Less frequent: Skin rash, itching of skin, alopecia, sweating, hirsutism.

Musculoskeletal, connective tissue and bone disorders:

Frequent: Muscle and joint weakness.
Less frequent: Muscle weakness in hands, arms, feet and legs.

Renal and urinary disorders:

Less frequent: Impotence and nocturia.
The following side-effects have been reported and frequencies are unknown: Urine discolouration.

General disorders:

Frequent: Abdominal pain, pain, pelvic pain, fever, and weakness.
Less frequent: Chills.
The following side-effects have been reported and frequencies are unknown: Alcohol intolerance.

Special Precautions:

The liver extensively metabolises **BICADEX**. Evidence suggests that elimination of **BICADEX** may be slower in patients with severe impairment of liver function and this could give rise to increased **BICADEX** accumulation. Caution is therefore required when **BICADEX** is administered to patients with moderate to severe hepatic impairment. Due to the possibility of hepatic changes, periodic evaluation of liver function needs to be considered. Severe liver changes occur infrequently with **BICADEX** (see "**Side-Effects**"). In the case of severe changes, **BICADEX** therapy should be discontinued.

Lactose intolerance:

BICADEX contains lactose. Patients who are lactose intolerant and who take **BICADEX** may experience unwanted side-effects, such as nausea, cramping, bloating, diarrhoea, and flatulence. **BICADEX** should not be administered to patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.

Ability to drive and use machinery:

BICADEX is not likely to negatively influence the ability of patients to drive or operate machinery.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

There is no human experience of overdosage. There is no specific antidote; treatment should be symptomatic. Dialysis may not be helpful, since **BICADEX** is highly protein bound and is not recovered unchanged in the urine. General supportive care, including frequent monitoring of vital signs, is indicated.

IDENTIFICATION:

White to off-white, circular, biconvex, film-coated tablets plain on both sides.

PRESENTATION:

Aluminium foil blister strips of 10 tablets packed in 30's.

STORAGE INSTRUCTIONS:

Store below 25°C. Keep the blister strips in the outer carton until required for use.
KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:

A40/21.12/0304

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

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