Bicalutamide

Bicapros®

50 mg Film-Coated Tablet

Anti-androgens

FORMULATION
Each film-coated tablet contains:
Bicalutamide, USP ……..…….. 50 mg

PRODUCT DESCRIPTION
Round, biconvex, smooth, white film-coated tablets, 6 mm +/- 0.2 mm diameter.

PHARMACOLOGY

PHARMACODYNAMICS / MECHANISM OF ACTION
Bicalutamide is a selective nonsteroidal antiandrogen with no other endocrine activity. It binds to the androgen receptors in target tissue and competitively inhibits the action of androgen, resulting in regression of prostatic tumors.

Bicalutamide is a racemate and the (R)-enantiomer is primarily responsible for its anti-androgenic activity.

When bicalutamide is combined with luteinizing hormone-releasing hormone (LHRH) analog therapy, the suppression of serum testosterone induced by the LHRH analog is not affected.

Some patients may experience antiandrogen withdrawal syndrome upon bicalutamide discontinuation.

PHARMACOKINETICS
Bicalutamide is well absorbed after oral administration; food has no effect on its bioavailability. The R-enantiomer accumulates about 10-fold in plasma with daily administration due to its long half-life. Daily administration of bicalutamide 50 mg results in steady-state plasma concentrations of approximately 9 mcg/mL of the R-enantiomer accounting for 99% of the total circulating enantiomers.

Bicalutamide is highly protein-bound (racemate 96%, R-bicalutamide 99.6%) and undergoes extensive stereospecific metabolism. The S-isomer (inactive) is metabolized primarily by glucuronidation. The R-isomer (active) also undergoes glucuronidation but is mainly oxidized to an inactive metabolite and then glucuronidated. Both the parent and metabolite glucuronides are eliminated in the urine and feces. The S-enantiomer is rapidly eliminated relative to R-enantiomer, the latter having a plasma elimination half-life of about 1 week.

In a clinical trial, a dose of 150 mg bicalutamide has been shown to have an R-bicalutamide mean concentration of 4.9 mcg/mL in semen of men and the amount of bicalutamide potentially delivered to a female partner during intercourse is low and is extrapolated to be about 0.3 mcg/kg. This is below that required to induce changes in the offspring of laboratory animals.

Age, renal impairment or mild to moderate hepatic impairment do not affect the pharmacokinetics of the R-enantiomer. However, a slower elimination rate from the plasma of the R-enantiomer has been observed in patients with severe hepatic impairment.

INDICATIONS
- Treatment of advanced prostate cancer in combination with LHRH analog therapy or surgical castration.
- Prevention of disease flare associated with the use of LHRH agonists.

DOSAGE AND ADMINISTRATION
One tablet (50 mg) once daily, in the morning or evening at the same time each day, with or without food.
Start bicalutamide treatment at the same time as treatment with an LHRH analog or surgical castration.

CONTRAINDICATIONS
- Hypersensitivity to bicalutamide or any component of the product.
- Females and children

WARNINGS AND PRECAUTIONS
Hepatitis
The use of bicalutamide has been associated with rare cases of death or hospitalization due to severe liver injury which generally occurred within the first three to four months of treatment.

Liver function tests (bilirubin, transaminases, alkaline phosphatase) should be measured before starting bicalutamide treatment and at regular intervals for the first four months of treatment, and periodically thereafter. Measure serum transaminases (particularly serum alanine aminotransferase, ALT) immediately if clinical signs or symptoms suggestive of liver dysfunction occur (e.g., nausea, vomiting, abdominal pain, fatigue, anorexia, "flu-like" symptoms, dark urine, jaundice, or right upper quadrant tenderness). Discontinue bicalutamide immediately and closely follow-up liver function in the event of clinical and/or biochemical evidence of severe hepatotoxicity (e.g., jaundice or an increase in serum ALT concentration greater than 2 times the upper limit of normal).

Gynecomastia and Breast Pain
Gynecomastia and breast pain have been reported in clinical trials using bicalutamide 150 mg as a single agent for prostate cancer.

Glucose Tolerance
Reduced glucose tolerance manifested as diabetes or loss of glycemic control in patients with pre-existing diabetes, has been observed in males receiving LHRH agonists. Monitor blood glucose levels in patients receiving combination therapy with bicalutamide and LHRH agonists.

Serum Prostate Specific Antigen (PSA) Monitoring
Periodic monitoring of PSA levels may be useful in assessing patient's response to therapy. A treatment-free period of antiandrogen while continuing the LHRH analog may be considered in patients who have increased PSA levels and objective disease progression.

INTERACTION WITH OTHER MEDICAMENTS
R-bicalutamide has been shown *in vitro* to be an inhibitor of CYP3A4 activity, with lesser inhibitory effects on CYP 2C9, 2C19 and 2D6. Exercise caution when giving bicalutamide concomitantly with midazolam (a CYP 3A4 substrate) since midazolam C_{max} and AUC have been shown to increase 1.5 and 1.9 fold, respectively, in clinical trials.

Bicalutamide displaces warfarin (coumarin anticoagulant) from its protein binding site *in vitro*. Close monitoring of prothrombin time is therefore recommended in patients who are already receiving coumarin anticoagulants.

Although no pharmacodynamic or pharmacokinetic interaction exists between bicalutamide and LHRH agonists, bicalutamide may prevent the harmful clinical consequences of flare associated with LHRH agonist therapy.

Co-administration of ciclosporin and calcium channel blockers with bicalutamide may theoretically increase bicalutamide's plasma concentrations. Evidence of enhanced or adverse drug effect may warrant dose reduction and close monitoring of patients after initiation or cessation of bicalutamide.

Drugs which inhibit drug oxidation such as cimetidine and ketoconazole may theoretically increase plasma concentrations of bicalutamide which may result in increased side effects.

Concomitant administration with alcohol should be avoided to prevent facial flushing during bicalutamide therapy.

HIGH RISK GROUPS
Use in Pregnancy and Breastfeeding
Pregnancy Category X
Bicalutamide is contraindicated in females and must not be given to pregnant or breastfeeding women.

Use in Adult Males with Liver Impairment
Although no dosage adjustment is required in patients with mild liver impairment, increased accumulation may occur in patients with moderate to severe liver impairment. **(See Warnings and Precautions)**

Use in Adult Males with Renal Impairment
No dosage adjustment is required in patients with renal impairment.

UNDESIRABLE EFFECTS
Body (general): Edema, neoplasm, cyst, hernia, infection, fever, chills, sepsis fatigue, and flu syndrome. Pain in the back, pelvic, chest, neck, and abdomen.

Cardiovascular: Angina pectoris, congestive heart failure, hypertension, myocardial infarction, coronary artery disorder, and hot flushes. Conduction defects including PR and QT interval prolongations, arrhythmias and non-specific ECG changes have been observed.

Gastrointestinal: Anorexia, heartburn, dyspepsia, dysphagia, periodontal abscess, rectal hemorrhage, gastrointestinal cancer, dry mouth, melena, flatulence, constipation, diarrhea, nausea, and vomiting.

Endocrine: Breast pain and/or tenderness, gynecomastia and diabetes mellitus.

Metabolic and Nutritional: Weight gain, dehydration, gout, peripheral edema/fluid retention, hyperglycemia, and weight loss.

Hematological: Anemia, leukopenia and thrombocytopenia.

Musculoskeletal: Myasthenia, asthenia, arthritis, myalgia, leg cramps, pathological fracture, bone pain.

CNS: Anxiety, headache, depression, hypertonia, somnolence, confusion, neuropathy, nervousness, dizziness, paresthesia, and insomnia.

Respiratory: Interstitial lung disease, increased cough, pharyngitis, bronchitis, pneumonia, asthma, epistaxis, sinusitis, rhinitis, pulmonary disorders, and dyspnea.

Immune System Disorders: Hypersensitivity reactions, including angioneurotic edema and urticaria.

Skin and Appendages: Pruritus, dry skin, Herpes Zoster, skin carcinoma, alopecia, rash, sweating, and hirsutism.

Hepatic Effects: Jaundice and hepatic failure.

Urogenital: Increased urinary frequency, urinary impairment, dysuria, urinary retention, urinary urgency, nocturia, hematuria, urinary tract infection, impotence, and hydronephrosis.

Special senses: Cataract.

Abnormal Laboratory Test Values: Elevated aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin, blood urea nitrogen (BUN), and creatinine; decreased hemoglobin and white blood cells (WBC). Elevated hepatic enzymes and decreased hemoglobin were less frequently reported.

OVERDOSE AND TREATMENT
There is no clinical experience of bicalutamide overdose. Dosages up to 200 mg have been well tolerated in long-term clinical trials. The single dose of bicalutamide that results in overdosage symptoms considered to be life-threatening has not been established.

Since there is no known antidote for bicalutamide intoxication, patients must be observed and be given symptomatic and supportive treatment including frequent monitoring of vital signs.

Bicalutamide is not removed by hemodialysis.

Store at temperatures not exceeding 30 °C.

AVAILABILITY
Alu/PVC Blister Pack of 14's. Box of 28's. - DR-XY40573

CAUTION
Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

ADVERSE DRUG REACTION REPORTING STATEMENT
For suspected adverse drug reaction, seek medical attention immediately and report to the FDA at www.fda.gov.ph AND Unilab at (+632) 858-1000 or productsafety@unilab.com.ph. By reporting undesirable effects, you can help provide more information on the safety of this medicine.

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