PRESCRIBING INFORMATION
(For the Use of a Registered Medical Practitioner or a Hospital or a Laboratory only)

BICAL 50
Bicalutamide Tablets 50 mg

Name and strength of active ingredient
Bicalutamide Ph. Eur. 50 mg.

Product Description
White to off white, round, biconvex, film coated tablets debossed 'B 50' on one side and plain on other side.

Pharmacological properties
Pharmacodynamic properties
Bicalutamide is non steroidal antiandrogen, devoid of other endocrine activity. It binds to androgen receptors without activating gene expression, and thus inhibits the androgen stimulus. Regression of prostatic tumors results from this inhibition. Clinically, discontinuation of Bicalutamide can result in antiandrogen withdrawal syndrome in a subset of patients.

Bicalutamide is a racemate with its antiandrogenic activity being almost exclusively in the (R)-enantiomer.

Pharmacokinetic properties
Bicalutamide is well absorbed following oral administration. There is no evidence of any clinically relevant effect of food on bioavailability.
The (S)-enantiomer is rapidly cleared relative to the (R)-enantiomer, the latter having a plasma elimination half life of about 1 week.

On daily administration of Bicalutamide Tablets 50mg, the (R)-enantiomer accumulates about 10 fold in plasma as a consequence of its long half life.

Steady state plasma concentrations of the (R)-enantiomer of approximately 9 microgram/ml are observed during daily administration of 50 mg doses of Bicalutamide Tablets. At steady state the predominantly active (R)-enantiomer accounts for 99% of the total circulating enantiomer.

The pharmacokinetics of the (R)-enantiomer are unaffected by age, renal impairment or mild to moderate hepatic impairment. There is evidence that for subjects with severe hepatic impairment, the (R)-enantiomer is more slowly eliminated from plasma.

Bicalutamide is highly protein bound (racemate 96%, R-Bicalutamide 99.6%) and extensively metabolized (via oxidation and glucuronidation): Its metabolites are eliminated via the kidneys and bile in approximately equal proportions.

In a clinical study the mean concentration of Bicalutamide in semen of men receiving Bicalutamide 150 mg was 4.9 microgram/ml. The amount of Bicalutamide potentially delivered to a female partner during intercourse is low and by extrapolation possibly equates to approximately 0.3 microgram/kg. This is below that required to induce changes in off spring of laboratory animals.

Preclinical safety data
Bicalutamide is a pure and potent androgen receptor antagonist in experimental animals and humans. The main secondary pharmacological action is induction of CYP450 dependent mixed function oxidases in the liver. Enzyme induction has not been observed in humans. Target organ changes in animals are clearly related to the primary and secondary pharmacological action of Bicalutamide. These comprise involution of androgen dependent tissues; Thyroid follicular adenomas, hepatic and Leydig cell hyperplasias and neoplasias or cancer; disturbance of male offspring sexual differentiation; reversible impairment of fertility in males. Genotoxicity studies did not reveal any mutagenis potential of Bicalutamide. All adverse effects observed in animal studies are considered to have no relevance to the treatment of patients with advanced prostate cancer.

Indication/Usage
Bicalutamide Tablets 50 mg is used in treatment of advanced prostate cancer in combination with LHRH analogue therapy or surgical castration.

Recommended Dose
Adult males including the elderly: one tablet (50 mg) once a day.

Treatment with Bicalutamide Tablets 50 mg should be started at least 3 days before commencing treatment with an LHRH analogue, or at the same time as surgical castration.

Children and adolescents: Bicalutamide is not indicated in children and adolescents.

Renal impairment: no dosage adjustment is necessary for patients with renal impairment. There is no experience with the use of Bicalutamide in patients with severe renal impairment (creatinine clearance < 30 ml/min).

Hepatic impairment: no dosage adjustment is necessary for patients with mild hepatic impairment. Increased accumulation may occur in patients with moderate to severe hepatic impairment.

Route of Administration
Oral use

Contraindication
Hypersensitivity to Bicalutamide or to any of the excipients. Use in females, children and adolescents is contraindicated.

Co administration of Terfenadine, Astemizole or Cisapride with Bicalutamide is contraindicated.

Special warnings and precautions for use
Initiation of treatment should be under the direct supervision of a specialist.

As there is no experience with the use of Bicalutamide in patients with severe renal impairment (creatinine clearance < 30/min), Bicalutamide should only be used with caution in these patients. Bicalutamide is extensively metabolized in the liver. Data suggests that its elimination may be lower in subjects with severe hepatic impairment and this could lead to increased accumulation of Bicalutamide. Therefore, Bicalutamide should be used with caution in patients with moderate to severe hepatic impairment.

Periodic liver function testing should be considered due to the possibility of hepatic changes. The majority of changes are expected to occur within the first 6 months of Bicalutamide therapy. Severe hepatic changes and hepatic failure have been observed rarely with Bicalutamide, and fatal outcomes have been reported. Bicalutamide therapy should be discontinued if changes are severe.

A reduction in glucose tolerance has been observed in males receiving LHRH agonists. This may manifest as diabetes or loss of glycaemic control in those with preexisting diabetes. Consideration should therefore be given to monitoring blood glucose in patients receiving Bicalutamide in combination with LHRH agonists.
Bicalutamide has been shown to inhibit Cytochrome P450 (CYP 3A4), as such caution should be exercised when co administered with drugs metabolized predominantly by CYP 3A4.

Lactose: This product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucosegalactose malabsorption should not take this medicinal product.

Interaction with other medicaments
There is no evidence of any Pharmacodynamic or pharmacokinetic interactions between Bicalutamide and LHRH analogues.

In vitro studies have shown that R-Bicalutamide is an inhibitor of CYP 3A4, with lesser inhibitory effects on CYP 2C9, 2C19 and 2D6 activity.

Although clinical studies using antipyrine as a marker of cytochrome P450 (CYP) activity showed no evidence of a drug interaction potential with 'Bicalutamide', mean midazolam exposure (AUC) was increased by up to 80%, after co administration of Bicalutamide for 28 days. For drugs with a narrow therapeutic index such an increase could be of relevance. As such, concomitant use of terfenadine, astemizole and cisapride is contraindicated and caution should be exercised with the co-administration of Bicalutamide with compounds such as cyclosporin and calcium channel blockers. Dosage reduction may be required for these drugs particularly if there is evidence of enhanced or adverse drug effect. For cyclosporin, it is recommended that plasma concentrations and clinical condition are closely monitored following initiation or cessation of Bicalutamide therapy.

Caution should be exercised when prescribing Bicalutamide with other drugs which may inhibit drug oxidation e.g. cimetidine and ketoconazole. In theory, this could result in increased plasma concentrations of Bicalutamide, which theoretically could lead to an increase in side effects.

In vitro studies have shown that Bicalutamide can displace the coumarin anticoagulant, warfarin, from its protein binding sites. It is therefore recommended that if Bicalutamide is started in patients who are already receiving coumarin anticoagulants, prothrombin time should be closely monitored.

Pregnancy and lactation
Bicalutamide Tablets 50 mg are contraindicated in females and must not be given to pregnant women or breastfeeding mothers.

Effects on ability to drive and use machines
No studies on the effects on the ability to drive and use machines have been performed. However, it should be noted that occasionally dizziness or somnolence may occur. Any affected patients should exercise caution.

Side effects/Adverse Reactions

The frequencies of adverse events are ranked according to the following: very common (≥1/10) ; Common (≥1/100, < 1/10); Uncommon (≥1/1,000, < 1/100) ; Rare (≥1/10,000, < 1/1,000) ; Very rare (< 1/10,000) ; Not known (cannot be estimated from the available data).

Table 1 Frequency of Adverse Reactions

Blood and lymphatic system disorders	
Very common:	Anaemia
Immune system disorders	
Uncommon:	Hypersensitivity, angioedema and urticaria
Metabolism and nutrition disorders	
Common:	Decreased appetite
Psychiatric disorders	
Common:	Decreased libido depression
Nervous system disorders	
Very common:	Dizziness
Common:	Somnolence
Cardiac disorders	
Common:	Myocardial infarction (fatal outcomes have been reported)[4], Cardiac failure[4]
Vascular disorders	
Very Common:	Hot flush
Respiratory, thoracic and mediastinal disorders	
Uncommon:	Interstitial lung disease[5] (fatal outcomes have been reported).
Gastrointestinal disorders	
Very common:	Abdominal pain, constipation, nausea
Common:	Dyspepsia, flatulence
Hepatobiliary disorders	
Common:	Hepatotoxicity, jaundice, hypertransaminasaemia[1]
Rare:	Hepatic failure[2] (fatal outcomes have been reported).
Skin and subcutaneous tissue disorders	
Common:	Alopecia, hirsutism/hair regrowth, dry skin, pruritus rash
Renal and urinary disorders	
Very common:	Haematuria
Reproductive system and breast disorders	
Very common:	Gynaecomastia and breast tenderness[3]
Common:	Erectile dysfunction
General disorders and administration site conditions	
Very common:	Asthenia oedema
Common:	Chest pain
Investigations	
Common:	Weight increased

1. Hepatic changes are rarely severe and were frequently transient, resolving or improving with continued therapy or following cessation of therapy
2. Listed as an adverse drug reaction following review of postmarketed data. Frequency has been determined from the incidence of reported adverse events of hepatic failure in patients receiving treatment in the open label bicalutamide arm of the 150 mg EPC studies.
3. May be reduced by concomitant castration.
4. Observed in a pharmacoepidemiology study of LHRH agonists and antiandrogens used in the treatment of prostate cancer. The risk appears to be increased when bicalutamide was used in combination with LHRH agonists but no increase in risk was evident when bicalutamide was used as a monotherapy to treat prostate cancer.
5. Listed as an adverse drug reaction following review of postmarketed data. Frequency has been determined from the incidence of reported adverse events of interstitial pneumonia in the randomised treatment period of the 150 mg EPC studies.

Overdose

No case of overdose has been reported. Since Bicalutamide belongs to the anilide compounds there is a theoretical risk of the development of methaemoglobinaemia. Methaemoglobinaemia has been observed in animals after an overdose.

Accordingly, a patient with an acute intoxication can be cyanotic. There is no specific antidote, treatment should be symptomatic. Dialysis is unlikely to be helpful, since Bicalutamide is highly protein bound and is not recovered unchanged in the urine. General supportive care, including frequent monitoring of vital signs, is indicated.

Ingredients

Active ingredient

Bicalutamide

Inactive ingredient

Core tablet:
Lactose Monohydrate
Sodium Starch Glycolate (Type A)
Povidone K30
Magnesium Stearate
Coating: Hypromellose E5
Titanium Dioxide
Macrogol 400

Storage Conditions

Do not store above 25°C.

Dosage forms and packaging available

BICAL 50 is available in PVC/PVDC –Alu Blister pack of 15 tablets, each carton contains 2 Blisters.

Manufactured by:

INTAS

INTAS PHARMACEUTICALS LTD.

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Village-Matoda, Bavla Road, And
Plot No: 191/218 P,
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