BICALOX

Bicalutamide 50 mg tablets

Presentation

BICALOX 50 mg is a white to off-white, round, film coated, biconvex tablets, engraved with 'BC 50' on one face and plain on the other.

Uses

Actions

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

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

Pharmacokinetics

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, 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 µg/mL are observed during daily administration of 50 mg doses of BICALUTAMIDE. At steady state the predominantly active (R)-enantiomer accounts for 99% of the total circulating enantiomers.

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 metabolised (oxidation and glucuronidation); its metabolites are eliminated via the kidneys and bile in approximately equal proportions.

In a clinical study the mean concentration of R-bicalutamide in semen of men receiving 150 mg of bicalutamide was 4.9 μg/mL. The amount of bicalutamide potentially delivered to a female partner during intercourse is low and equates to approximately 0.3 μg/kg. This is below that required to induce changes in offspring of laboratory animals.

### Indications

Treatment of advanced prostate cancer in combination with GnRH (LHRH) agonist therapy or surgical castration.

Prevention of disease flare associated with the use of LHRH agonists.

### Dosage and Administration

**As combination therapy in adult males including the elderly**

One tablet (50 mg) once a day.

Treatment with BICALOX should be started at the same time as treatment with a GnRH (LHRH) agonist or surgical castration.

**Children**

BICALOX is contraindicated in children.

**Use in adult males with renal impairment**

No dosage adjustment is necessary for patients with renal impairment.

**Use in adult males with 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 (see WARNINGS AND PRECAUTIONS).

### Contraindications

BICALOX is contraindicated in females and children.
BICALOX must not be given to any patient who has shown a hypersensitivity reaction to the active substance or to any of the excipients.

Co-administration of terfenadine, astemizole or cisapride with BICALOX is contraindicated (see WARNINGS AND PRECAUTIONS).

**Warnings and Precautions**

BICALOX is extensively metabolised in the liver. Data suggest that its elimination may be slower in subjects with severe hepatic impairment and this could lead to increased accumulation of bicalutamide. Therefore, BICALOX 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 BICALOX therapy.

Severe hepatic changes have been observed rarely with BICALOX, and fatal outcomes have been reported (see ADVERSE EFFECTS). BICALOX 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 pre-existing diabetes. Consideration should therefore be given to monitoring blood glucose in patients receiving BICALOX in combination with LHRH agonists.

BICALOX has shown to inhibit cytochrome P450 (CYP 3A4), as such caution should be exercised when co-administered with drugs metabolised predominantly by CYP 3A4 (see CONTRAINDICATIONS and INTERACTIONS).

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

**Pregnancy and Lactation**

BICALOX is contraindicated in females and must not be given to pregnant women or nursing mothers.

**Effects on ability to drive and use machines**

During treatment with BICALOX, somnolence has been reported and those patients who experience this symptom should observe caution when driving or using machines.
# Adverse Effects

Unless specified, the following frequency categories were assigned based on the incidence of the adverse event in the 50 mg BICALUTAMIDE plus LHRH analogue arm of the pivotal LHRH combination study.

<table>
<thead>
<tr>
<th>Frequency</th>
<th>System Organ Class</th>
<th>Event</th>
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</thead>
<tbody>
<tr>
<td><strong>Very common</strong></td>
<td>Blood and lymphatic</td>
<td>Anaemia</td>
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<tr>
<td>(≥ 10%)</td>
<td>Nervous system disorders</td>
<td>Dizziness</td>
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<tr>
<td></td>
<td>Vascular disorders</td>
<td>Hot flush</td>
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<tr>
<td></td>
<td>Gastrointestinal disorders</td>
<td>Abdominal pain, constipation, nausea</td>
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<tr>
<td></td>
<td>Renal and urinary disorders</td>
<td>Haematuria</td>
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<tr>
<td></td>
<td>Reproductive system and breast disorders</td>
<td>Gynaecomastia and breast tenderness&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td></td>
<td>General disorders and administration site</td>
<td>Asthenia, oedema</td>
</tr>
<tr>
<td></td>
<td>conditions</td>
<td></td>
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<tr>
<td><strong>Common</strong></td>
<td>Metabolism and nutrition Disorders</td>
<td>Decreased appetite</td>
</tr>
<tr>
<td>(≥ 1% and &lt; 10%)</td>
<td>Psychiatric disorders</td>
<td>Decreased libido, depression</td>
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<tr>
<td></td>
<td>Nervous system disorders</td>
<td>Somnolence</td>
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<tr>
<td></td>
<td>Cardiac disorders</td>
<td>Myocardial infarction (fatal outcomes have been reported)&lt;sup&gt;b&lt;/sup&gt;, Cardiac failure&lt;sup&gt;c&lt;/sup&gt;</td>
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<tr>
<td></td>
<td>Gastrointestinal disorders</td>
<td>Dyspepsia, flatulence</td>
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<tr>
<td></td>
<td>Hepatobiliary disorders</td>
<td>Hepatotoxicity, jaundice, hypertransaminasaemia&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
<td></td>
<td>Skin and subcutaneous tissue disorders</td>
<td>Alopecia, hirsutism/ hair regrowth, rash, dry skin, pruritus</td>
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<tr>
<td></td>
<td>Reproductive system and breast disorders</td>
<td>Erectile dysfunction</td>
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<tr>
<td></td>
<td>General disorders and administration site</td>
<td>Chest pain</td>
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<tr>
<td></td>
<td>conditions</td>
<td>Weight increased</td>
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<td></td>
<td>Investigations</td>
<td></td>
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<tr>
<td>Uncommon (≥ 0.1% and &lt; 1%)</td>
<td>Immune system disorders</td>
<td>Hypersensitivity, angioedema, and urticaria</td>
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<tr>
<td></td>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Interstitial lung disease. Fatal outcomes have been reported.</td>
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<tr>
<td>Rare (≥ 0.01% and &lt; 0.1%)</td>
<td>Hepatobiliary disorders</td>
<td>Hepatic failure. Fatal outcomes have been reported.</td>
</tr>
</tbody>
</table>

a May be reduced by concomitant castration.
b Hepatic changes are rarely severe and were frequently transient, resolving or improving with continued therapy or following cessation of therapy.
c Listed as an adverse drug reaction following review of post-marketed 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.
d Listed as an adverse drug reaction following review of post-marketed 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.
e Observed in a pharmaco-epidemiology study of LHRH agonists and anti-androgens used in the treatment of prostate cancer. The risk appeared to be increased when BICALUTAMIDE 50 mg was used in combination with LHRH agonists.

**Interactions**

There is no evidence of any pharmacodynamic or pharmacokinetic interactions between BICALUTAMIDE and GnRH analogues.

*In vitro* studies have shown that R-bicalutamide is an inhibitor of CYP3A4, 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 (see CONTRAINDICATIONS) and caution should be exercised with the co-administration of BICALUTAMIDE with compounds such as ciclosporin and calcium channel blockers. Dosage reduction may be required for these drugs particularly if there is evidence of enhanced or adverse drug effect. For ciclosporin, 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.

Although there is no evidence of any pharmacodynamic or pharmacokinetic interactions between BICALUTAMIDE and LHRH agonists at steady state, BICALUATMIDE 50 mg may prevent the harmful clinical consequences of flare associated with the start of LHRH agonist therapy.

**Overdosage**

There is no human experience of overdosage. There is no specific antidote; treatment should be symptomatic. Dialysis may not 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.

**Pharmaceutical Precautions**

**Instructions for Use/Handling**

No special precautions required.

**Incompatibilities**

None known.

**Shelf Life**

36 Months

**Special Precautions for Storage**

Store below 25°C, Protect from light and moisture.
Medicine Classification

Prescription Medicine.

Package Quantities

Cartons of blisters containing 28, 30, 56 and 98 tablets. Bottles containing 100 and 500 tablets.

Further Information

Preclinical information

BICALUTAMIDE is a potent antiandrogen and a mixed function oxidase enzyme inducer in animals. Target organ changes, including tumour induction and minor clinical pathology changes, are related to these activities. Enzyme induction and minor cardiac changes seen in dogs have not been observed in man. There are no preclinical findings that preclude the administration of BICALUTAMIDE to prostate cancer patients.

List of Excipients

- Lactose
- Sodium Starch Glycollate
- Povidone
- Magnesium Stearate
- Opadry White Y-1-7000

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Date of Preparation

25 March 2013