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This information is intended for use by health professionals

1. Name of the medicinal product

Bicalutamide 50 mg Film-coated Tablets

2. Qualitative and quantitative composition

Each film-coated tablet contains 50 mg Bicalutamide.

Excipients with known effect:

Each tablet contains 56mg of Lactose monohydrate.

For the full list of excipients, see section 6.1

3. Pharmaceutical form

Film-coated tablet (tablets).

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

4. Clinical particulars

4.1 Therapeutic indications

Treatment of advanced prostate cancer in combination with luteinizing-hormone releasing hormone (LHRH) analogue therapy or surgical castration.

4.2 Posology and method of administration

Posology

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

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

Paediatric population: Bicalutamide is contraindicated for use in children (see section 4.3).

Renal impairment: no dosage adjustment is necessary for patients with renal impairment.

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 Section 4.4).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Use in females, children and adolescents is contraindicated (see section 4.6).

Co-administration of terfenadine, astemizole or cisapride with Bicalutamide is contra-indicated (see section 4.5).

4.4 Special warnings and precautions for use

Initiation of treatment should be under the direct supervision of a specialist.

Bicalutamide is extensively metabolized in the liver. Data suggests that its elimination may be slower 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 (see Section 4.8).

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 pre-existing 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 metabolised predominantly by CYP 3A4, see Sections 4.3 and 4.5.

Androgen deprivation therapy may prolong the QT interval.

In patients with a history of or risk factors for QT prolongation and in patients receiving concomitant medicinal products that might prolong the QT interval (see section 4.5) physicians should assess the benefit risk ratio including the potential for Torsade de pointes prior to initiating Bicalutamide tablets.

Antiandrogen therapy may cause morphological changes in spermatozoa. Although the effect of bicalutamide on sperm morphology has not been evaluated and no such changes have been reported for patients who received Bicalutamide tablets, patients and/or their partners should follow adequate contraception during and for 130 days after Bicalutamide therapy.

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

An increased Prothrombin Time (PT) and International Normalised Ratio (INR)have been reported in patients receiving bicalutamide and coumarin anticoagulants concomitantly.. Some cases have been associated with risk of bleeding. Close monitoring of PT/INR is advised and anticoagulant dose adjustment should be considered (see sections 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

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 contra-indicated (see Section 4.3) 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. There have been reports of increased Prothrombin Time (PT) and International Normalised Ratio (INR) when co-administered with bicalutamide. It is therefore recommended that if bicalutamide is administered in patients who are already receiving coumarin anticoagulants, PT/INR should be closely monitored.and adjustments of anticoagulant dose considered (see sections 4.4).

Since androgen deprivation treatment may prolong the QT interval, the concomitant use of Bicalutamide tablets with medicinal products known to prolong the QT interval or medicinal products able to induce Torsade 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. should be carefully evaluated (see section 4.4).

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy

Bicalutamide is contra-indicated in females and must not be given to pregnant women.

Breast-feeding

Bicalutamide is contraindicated during breast-feeding.

Fertility

Reversible impairment of male fertility has been observed in animal studies (see section 5.3). A period of subfertility or infertility should be assumed in man.

4.7 Effects on ability to drive and use machines

Bicalutamide is unlikely to impair the ability of patients to drive or operate machinary. However, it should be noted that occasionally somnolence may occur. Any affected patients should exercise caution.

4.8 Undesirable effects

In this section, undesirable effects are defined as follows: 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

System Organ Class	Frequency	Event
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]
	Not known	QT prolongation (see sections 4.4 and 4.5)
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
Hepato-biliary disorders	Common	Hepatotoxicity, jaundice, hypertransaminasaemia[1]
	Rare	Hepatic failure[2] (fatal outcomes have been reported).
Skin and subcutaneous tissue disorders	Common	Alopecia hirsutism/hair re-growth dry skin pruritus rash
	Rare	Photosensitivity reaction
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 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.

3. May be reduced by concomitant castration.

4. Observed in a pharmaco-epidemiology study of LHRH agonists and anti-androgens 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 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Yellow Card Scheme. Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store

4.9 Overdose

There is no human experience of overdosage. There is no specific antidote; treatment should be symptomatic. Dialysis is 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.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Hormone antagonists and related agent,Antiandrogens, ATC code: L02BB03

Mechanism of action

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.

5.2 Pharmacokinetic properties

Absorption

Bicalutamide is well absorbed following oral administration. There is no evidence of any clinically relevant effect of food on bioavailability.

Distribution

Bicalutamide is highly protein bound (racemate 96% (R)-enantiomer >99%) and extensively metabolised (via oxidation and glucuronidation): Its metabolites are eliminated via the kidneys and bile in approximately equal proportions.

Biotranformation

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 enantiomers.

Elimination

In a clinical study the mean concentration of R-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 offspring of laboratory animals.

Special Populations

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.

5.3 Preclinical safety data

Bicalutamide is a potent antiandrogen and a mixed function oxidase enzyme inducer in animals. Target organ changes, including tumour induction, in animals, are related to these activities. Atrophy of seminiferous tubules of the testes is a predicted class effect with antiandrogens and has been observed for all species examined. Reversal of testicular atrophy occurred 4 months after the completion of dosing in a 6-month rat study. No recovery was observed at 24 weeks after the completion of

dosing in a 12-month rat study. Following 12-months of repeated dosing in dogs (at doses of approximately 7 times human therapeutic concentrations at the recommended human dose of 50 mg), the incidence of testicular atrophy was the same in dosed and control dogs after a 6 month recovery period. In a fertility study, male rats had an increased time to successful mating immediately after 11 weeks of dosing; reversal was observed after 7 weeks off-dose.

6. Pharmaceutical particulars

6.1 List of excipients

Core tablet: Lactose monohydrate ; Sodium starch glycolate ; Povidone ; Magnesium stearate

Coating: Hypromellose; Macrogol; Titanium dioxide

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions

6.5 Nature and contents of container

Tablets are packed in PVC-PVdC/ aluminium blisters

Bicalutamide 50 mg film-coated Tablets are packed in blisters in pack of 14, 20,or 100 tablets

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Marketing authorisation holder

Ningbo Voice Biochemic Co., Ltd.

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