

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Bicalutamide 50 mg film-coated tablets

Almus Bicalutamide 50 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 50 mg bicalutamide.

Excipient with known effect:

Each tablet contains 33.25 mg lactose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film coated tablet.

White to off-white biconvex film-coated tablets, debossed with “93” on one side and “220” on the other

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology

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

Treatment with Bicalutamide should be started the same as treatment with an LHRH analogue or as surgical castration.

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 sections 4.4).

Paediatric population

Bicalutamide is contraindicated for use in children (see section 4.3)

4.3 Contraindications

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

Bicalutamide is contraindicated in females and children (see section 4.6).

Co-administration of terfenadine, astemizole or cisapride with Bicalutamide is contraindicated (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 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, 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.

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, patients and/or their partners should follow adequate contraception during and for 130 days after bicalutamide therapy.

Potential of coumarin anticoagulant effects have been reported in patients receiving concomitant bicalutamide therapy, which may result in increased Prothrombin Time (PT) and International Normalised Ratio (INR). 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 and 4.8).

Excipients

Lactose

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

Sodium

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

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 contraindicated (see section 4.3) 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 products, particularly if there is evidence of enhanced or adverse 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. There have been reports of increased effect of warfarin and other coumarin anticoagulants when co-administered with bicalutamide it is therefore recommended that if Bicalutamide is administered in patients who are concomitantly receiving coumarin anticoagulants, PT/INR should be closely monitored and adjustments of anticoagulant dose considered (see sections 4.4 and 4.8).

Since androgen deprivation treatment may prolong the QT interval, the concomitant use of Bicalutamide 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).

4.6 Fertility, pregnancy and lactation

Pregnancy

Bicalutamide is contraindicated 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. Bicalutamide may cause morphological

changes in spermatozoa. Patients and/or their partners should follow adequate contraception during and for 130 days after Bicalutamide therapy (see section 4.4).

4.7 Effects on ability to drive and use machines

Bicalutamide is unlikely to impair the ability of patients to drive or operate machinery. 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 ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $\leq 1/100$); rare ($\geq 1/10,000$ to $\leq 1/1,000$); very rare ($\leq 1/10,000$); 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 |
| 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 re-growth dry skin pruritus rash |
| | Rare | Photosensitivity reaction |
| Renal and urinary disorders | Very common | Haematuria |
| Reproductive system and breast | Very common | Gynaecomastia and breast |

| | | |
|--|-------------|-------------------------|
| disorders | | 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 appeared to be increased when bicalutamide 50 mg was used in combination with LHRH agonists, but no increase in risk was evident when bicalutamide 150 mg 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

Increased PT/INR: Accounts of coumarin anticoagulants interacting with bicalutamide have been reported in post-marketing surveillance (see sections 4.4. and 4.5).

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 the Yellow Card Scheme at: 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 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: Anti-androgens, ATC code: L02BB03

Mechanism of action

Bicalutamide is a 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 tumours 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.

Biotransformation

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 microgram/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.

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. Expected pharmacological effects of antiandrogens seen in animal studies include the following: atrophy of the prostate and seminal vesicles, benign Leydig cell tumours (rats) and adrenal cortical hypertrophy.

Bicalutamide is a mixed function oxidase inducer in animals and thyroid hypertrophy and adenoma (rat) and hepatocellular carcinoma (male mice) are a consequence of this. Enzymeinduction has not been observed in man. 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 (at doses of approximately 1.5 or 0.6 times human therapeutic concentrations at the recommended dose of 50 mg or 150 mg, respectively). No recovery was observed at 24 weeks after the completion of dosing in a 12-month rat study (at doses of approximately 2 or 0.9 times human concentrations at the recommended human dose of 50 mg or 150 mg, respectively). Following 12-months of repeated dosing in dogs (at doses of approximately 7 or 3 times human therapeutic concentrations at the recommended human dose of 50 mg or 150 mg, respectively), the incidence of testicular atrophy was the same in dosed and control dogs after a 6 month recovery period. In a fertility study (at doses of approximately 1.5 or 0.6 times

human therapeutic concentrations at the recommended human dose of 50 mg or 150 mg, respectively), 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

Tablet core:

Microcrystalline cellulose
Povidone
Croscarmellose sodium
Sodium laurilsulfate
Lactose monohydrate
Anhydrous colloidal silica
Magnesium stearate

Coating:

Hypromellose
Polydextrose
Titanium dioxide
Macrogol 4000

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store in the original package

6.5 Nature and contents of container

Transparent PVC/PVdC/Al blister, cardboard carton.
20, 28, 30, 40, 50, 56, 60, 84, 90, and 100 film coated tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Teva UK Limited
Ridings Point,
Whistler Drive,
Castleford, WF10 5HX,

United Kingdom

8. MARKETING AUTHORISATION NUMBERS

PL 00289/0980

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE
AUTHORISATION**

04/04/2008 / 27/10/2008

10. DATE OF REVISION OF THE TEXT

26/05/2022