

IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA1330/004/002

Case No: 2078605

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Gedeon Richter Ltd

Gyomroi ut 19-21, 1103 Budapest, Hungary

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Bicalutamide 150 mg Film-coated tablets

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **22/02/2010** until **21/08/2013**.

Signed on behalf of the Irish Medicines Board this

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Bicalutamide 150 mg Film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One tablet contains 150 mg of bicalutamide.

Excipients: Contains 193.2 mg lactose monohydrate

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

White or almost white, round, biconvex film-coated tablet, with engraved sign "X" on one side, and "RG" on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Bicalutamide 150 mg film-coated tablet is indicated either alone or as adjuvant to radical prostatectomy or radiotherapy in patients with locally advanced prostate cancer at high risk for disease progression (see section 5.1)

4.2 Posology and method of administration

Adult males including the elderly

One 150 mg tablet once a day.

Route: oral

The tablets should be swallowed whole with liquid.

Bicalutamide 150 mg should be taken continuously for at least 2 years or until disease progression.

Children and adolescents

Bicalutamide is not indicated in children and adolescents.

Renal impairment

No dose 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) (see section 4.4).

Hepatic impairment

No dose adjustment is necessary for patients with mild hepatic impairment.

The medicinal product may accumulate in patients with moderate to severe hepatic impairment (see section 4.4).

4.3 Contraindications

Hypersensitivity to bicalutamide or any of the excipients.

Bicalutamide is contra-indicated in women and children.

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 and subsequently patients should be kept under regular surveillance.

Bicalutamide is metabolised in the liver. Research results suggest that bicalutamide's elimination may be slower in patients with severe hepatic impairment and that this could lead to increased accumulation of bicalutamide. Therefore, bicalutamide should be used with caution in patients with moderate to severe hepatic impairment.

Severe hepatic damages have been rarely observed with bicalutamide (see section 4.8). Bicalutamide therapy should be discontinued if changes are severe.

Periodic liver function testing is warranted in order to find out about possible hepatic changes. The majority of changes are expected to occur within the first 6 months of bicalutamide therapy.

As there is no experience with the use of bicalutamide in patients with severe renal impairment (creatinine clearance < 30 ml/min), bicalutamide should only be used with caution in these patients.

Periodical monitoring of cardiac function is advisable in patients with heart disease.

For patients who have an objective progression of disease together with elevated PSA, cessation of bicalutamide therapy should be considered.

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

4.5 Interaction with other medicinal products and other forms of interaction

In vitro studies have shown that the R-enantiomer of bicalutamide is an inhibitor of CYP 3A4, with lesser inhibitory effects on CYP 2C9, 2C19 and 2D6 activity. Although *in vitro* studies have indicated the possibility of bicalutamide inhibiting cytochrome 3A4, a number of clinical studies show that the scale of this inhibition for most drugs metabolised by cytochrome P450 is probably not clinically significant.

Nonetheless, for drugs with a narrow therapeutic index metabolised in the liver, the CYP 3A4 inhibition caused by bicalutamide could be of relevance. As such, concomitant use of terfenadine, astemizole and cisapride is contra-indicated.

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 administering bicalutamide to patients taking medicinal products that inhibit the oxidation processes in the liver, e.g. cimetidine and ketoconazole. 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 site. It is therefore recommended that prothrombin time is closely monitored if bicalutamide is started in patients who are already receiving coumarin anticoagulants.

4.6 Pregnancy and lactation

Not applicable, since this medicinal product is not used in women.

4.7 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 (see section 4.8). Any affected patients should exercise caution.

4.8 Undesirable effects

Very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$), not known (cannot be estimated from the available data).

Immune system disorders

Uncommon: Hypersensitivity reactions, including angio-oedema and urticaria

Psychiatric disorders

Uncommon: Depression

Respiratory, thoracic and mediastinal disorders

Uncommon: Interstitial lung disease

Gastrointestinal disorders

Common: Diarrhoea, nausea

Rare: Vomiting

Hepatobiliary disorders

Common: Hepatic changes (elevated levels of transaminases, cholestasis and jaundice)¹

Very rare: Hepatic failure²

Skin and subcutaneous tissue disorders

Common: Pruritus

Rare: Dry skin

Renal and urinary disorders

Uncommon: Haematuria

Reproductive system and breast disorders

Very common: Breast tenderness³, gynaecomastia³

General disorders and administration site conditions

Very common: Hot flushes³

Common: Asthenia

¹ Hepatic changes are rarely severe and were frequently transient, resolving or improving with continued therapy or following cessation of therapy (see section 4.4).

² Hepatic failure has occurred very rarely in patients treated with bicalutamide, but a casual relationship has not been established with certainty. Periodic liver function testing should be considered (see also section 4.4).

³ May be reduced by concomitant castration.

In addition, the following adverse experiences were reported in clinical trials during treatment with bicalutamide with/without a LHRH analogue:

Blood and lymphatic system disorders

Common: Anaemia

Very rare: Thrombocytopenia

Metabolism and nutrition disorders

Common: Diabetes mellitus, weight gain

Uncommon: Anorexia, hyperglycaemia, weight loss

Nervous system disorders

Common: Dizziness, insomnia

Uncommon: Somnolence

Cardiac disorders

Very rare: Heart failure, angina, conduction defects including PR and QT interval prolongations, arrhythmias and non-specific ECG changes

Respiratory, thoracic and mediastinal disorders

Uncommon: Dyspnoea

Gastrointestinal disorders

Common: Constipation

Uncommon: Dry mouth, dyspepsia, flatulence

Skin and subcutaneous tissue disorders

Common: Rash, sweating, hirsutism

Uncommon: Alopecia

Renal and urinary disorders

Uncommon: Nocturia

Reproductive system and breast disorders

Very common: Decreased libido, erectile dysfunction, impotence

General disorders and administration site conditions

Common: Oedema, general pain, pelvic pain, chills

Uncommon: Abdominal pain, chest pain, headache, pain in the back, neck pain

4.9 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Hormone antagonists and related agents, anti-androgens

ATC code: L02BB03.

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 150 mg film-coated tablet (Bicalutamide) was studied as a treatment for patients with localised (T1-T2, N0 or NX, M0) or locally advanced (T3-T4, any N, M0; T1-T2, N+, M0) non-metastatic prostate cancer in a combined analysis of 3 placebo controlled double-blind studies in 8113 patients, where bicalutamide was given as immediate hormonal therapy or as adjuvant to radical prostatectomy or radiotherapy, (primarily external beam radiation). At 7.4 years median follow up, 27.4% and 30.7% of all bicalutamide and placebo-treated patients, respectively, had experienced objective disease progression.

A reduction in risk of objective disease progression was seen across most patient groups but was most evident in those at highest risk of disease progression. Therefore, clinicians may decide that the optimum medical strategy for a patient at low risk of disease progression, particularly in the adjuvant setting following radical prostatectomy, may be to defer hormonal therapy until signs that the disease is progressing. No overall survival difference was seen at 7.4 years median follow up with 22.9% mortality (HR=0.99; 95% CI 0.91 to1.09). However, some trends were apparent in exploratory subgroup analyses.

Progression-free survival and overall survival data for patients with locally advanced disease are summarised in the following tables:

Table 1 Progression-free survival in locally advanced disease by therapy sub-group

Analysis population	Events (%) in bicalutamide patients	Events (%) in placebo patients	Hazard ratio (95% CI)
Watchful waiting	193/335 (57.6)	222/322 (68.9)	0.60 (0.49 to 0.73)
Radiotherapy	66/161 (41.0)	86/144 (59.7)	0.56 (0.40 to 0.78)
Radical prostatectomy	179/870 (20.6)	213/849 (25.1)	0.75 (0.61 to 0.91)

Table 2 Overall survival in locally advanced disease by therapy sub-group

Analysis population	Deaths (%) in bicalutamide patients	Deaths (%) in placebo patients	Hazard ratio (95% CI)
Watchful waiting	164/335 (49.0)	183/322 (56.8)	0.81 (0.66 to 1.01)
Radiotherapy	49/161 (30.4)	61/144 (42.4)	0.65 (0.44 to 0.95)
Radical prostatectomy	137/870 (15.7)	122/849 (14.4)	1.09 (0.85 to 1.39)

For patients with localised disease receiving bicalutamide alone, there was no significant difference in progression free survival. In these patients there was also a trend toward decreased survival compared with placebo patients (HR=1.16; 95% CI 0.99 to 1.37). In view of this, the benefit-risk profile for the use of bicalutamide is not considered favourable in this group of patients.

5.2 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.

Following a long-term administration of bicalutamide, the peak concentration of the (R)-enantiomer in the plasma is about 10-fold, as compared to the levels measured after a single dose of 50 mg of bicalutamide.

A dosing scheme of 150 mg bicalutamide daily will result in a steady-state concentration of the R-enantiomer of 22 µg/ml and as a consequence of its long half-life, steady state is reached after approximately 1 month of therapy.

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

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

In clinical study the mean concentration of (R)-enantiomer in semen of men receiving bicalutamide 150 mg 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.

5.3 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 mutagenic 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Lactose monohydrate,
Sodium starch glycolate (type A),
Povidone K-30,
Silica, colloidal anhydrous,
Magnesium stearate

Film-coating:

Opadry II. White 33G28523 (Hypromellose, Titanium dioxide (E171), Lactose monohydrate, Macrogol 3350, Triacetin)

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

5 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

10, 14, 20, 28, 30, 40, 50, 56, 80, 84, 90, 100, 140, 200, 280 *film-coated tablets* in blister packs (PVC/PVDC/aluminium foil)

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Gedeon Richter Plc
Gyomroi ut 19-21
1103 Budapest
Hungary

8 MARKETING AUTHORISATION NUMBER

PA1330/4/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 22nd August 2008

10 DATE OF REVISION OF THE TEXT

February 2010