

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Bicalutamide 150 mg film-coated tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 150 mg bicalutamide.

Excipient(s): One tablet contains 188.0 mg lactose monohydrate

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

White, round, biconvex, film coated tablets, with diameter of 10.5mm, and a score line on one side. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Bicalutamide 150 mg 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 film-coated tablet (150mg) daily with or without food.

Route: Oral

The tablets should be swallowed whole with liquid.

Treatment with Bicalutamide 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 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) (see section 4.4).

Hepatic impairment: no dosage 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

Bicalutamide 150 mg is contra-indicated in females and children (see section 4.6)

Bicalutamide 150 tablets mg must not be given to any patient who has shown a hypersensitivity reaction to the active substance or to any of the excipients listed in section 6.1.

Co-administration of terfenadine, astemizole or cisapride with Bicalutamide 150 mg 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 specialist. Bicalutamide is extensively metabolised in the liver. Research results 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.

Severe hepatic changes and hepatic failure have been observed rarely with Bicalutamide 150 mg and fatal outcomes have been reported (see section 4.8). Bicalutamide therapy should be discontinued if changes are severe.

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.

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

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 (see sections 4.3 and 4.5).

In rare cases, photosensitivity reactions have been reported for patients taking Bicalutamide 150 mg. Patients should be advised to avoid direct exposure to

excessive sunlight or UV-light while on Bicalutamide 150 mg and the use of sunscreens may be considered. In cases where the photosensitivity reaction is more persistent and/or severe, an appropriate symptomatic treatment should be initiated.

Bicalutamide 150 mg contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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).

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 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). 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 ciclosporine, 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 site. 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 150 mg 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).

Paediatric population

Interaction studies have only been performed in adults.

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.

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 available data).

Table 1 Frequency of Adverse Reactions

| System Organ Class | Frequency | Event |
|------------------------------------------------------|-------------|-------------------------------------------------------------------------------|
| Blood and the lymphatic system disorders | 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 | Common | Dizziness, Somnolence |
| Cardiac disorders | Not known | QT prolongation (see section 4.4 and 4.5) |
| Vascular disorders | Common | Hot flush |
| Respiratory, thoracic and mediastinal disorders | Uncommon | Interstitial lung disease ^(c) (fatal outcomes have been reported). |
| Gastrointestinal disorders | Common | Abdominal pain, Constipation, Dyspepsia, Flatulence, Nausea |
| Hepato-biliary disorders | Common | Hepatotoxicity, jaundice, hypertransaminasaemia ^(a) |
| | Rare | Hepatic failure ^(d) (fatal outcomes have been reported). |
| Skin and subcutaneous tissue disorders | Very common | Rash |
| | Common | Alopecia, Hirsutism/hair re-growth, Dry skin ^(c) , Pruritis |
| | Rare | Photosensitivity reaction |
| Renal and urinary disorders | Common | Haematuria |
| Reproductive system and breast disorders | Very common | Gynaecomastia and breast tenderness ^(b) |
| | Common | Erectile dysfunction |
| General disorders and administration site conditions | Very common | Asthenia |
| | Common | Chest pain, Oedema |
| Investigations | Common | Weight increased |

- a. Hepatic changes are rarely severe and were frequently transient, resolving or improving with continued therapy or following cessation of therapy.
- b. The majority of patients receiving Bicalutamide 150 mg as monotherapy experience gynaecomastia and/or breast pain. In studies these symptoms were considered to be severe in up to 5% of the patients. Gynaecomastia may not resolve spontaneously following cessation of therapy, particularly after prolonged treatment.
- c. Due to the coding conventions used in the EPC studies, adverse events of 'dry skin' were coded under the COSTART term of 'rash'. No separate frequency descriptor can therefore be determined for the 150 mg Bicalutamide dose however the same frequency as the 50mg dose is assumed.

- 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. 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 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 over dosage. 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: Antiandrogens. ATC code: L02BB03.

Mechanism of action

Bicalutamide is a non-steroidal antiandrogen devoid of other endocrine activity. It binds to wild type or normal 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.

Clinical efficacy and safety

Bicalutamide 150mg was studied as a treatment for patients with localized (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 9.7 years median follow up, 36.6% and 38.17% 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 9.7 years median follow up with 31.4% mortality (HR=1.01; 95% CI 0.94 to 1.09). However, some trends were apparent in exploratory subgroup analyses.

Data on progression-free survival and overall survival over time based on Kaplan-Meier estimates for patients with locally advanced disease are summarised in the following tables:

Table 2 Proportion of locally advanced disease patients with disease progression over time by therapy sub-group

| Analysis population | Treatment arm | Events (%) at 3 years | Events (%) at 5 years | Events (%) at 7 years | Events (%) at 10 years |
|-------------------------------------|---------------------|-----------------------|-----------------------|-----------------------|------------------------|
| Watchful waiting (n = 657) | Bicalutamide 150 mg | 19.7 % | 36.3 % | 52.1 % | 73.2 % |
| | placebo | 39.8 % | 59.7 % | 70.7 % | 79.1 % |
| Radiotherapy (n = 305) | Bicalutamide 150 mg | 13.9 % | 33.0 % | 42.1 % | 62.7 % |
| | placebo | 30.7 % | 49.4 % | 58.6 % | 72.2 % |
| Radical prostatectomy (n = 1719) | Bicalutamide 150 mg | 7.5 % | 14.4 % | 19.8 % | 29.9 % |
| | placebo | 11.7 % | 19.4 % | 23.2 % | 30.9 % |

Table 3 Overall survival in locally advanced disease by therapy sub-group

| Analysis population | Treatment arm | Events (%) at 3 years | Events (%) at 5 years | Events (%) at 7 years | Events (%) at 10 years |
|-------------------------------|---------------------|-----------------------|-----------------------|-----------------------|------------------------|
| Watchful waiting (n = 657) | Bicalutamide 150 mg | 14.2 % | 29.4 % | 42.2 % | 65.0 % |
| | placebo | 17.0 % | 36.4 % | 53.7 % | 67.5 % |
| Radiotherapy (n = 305) | Bicalutamide 150 mg | 8.2 % | 20.9 % | 30.0 % | 48.5 % |
| | placebo | 12.6 % | 23.1 % | 38.1 % | 53.3 % |

| | | | | | |
|----------------------------------|---------------------|-------|--------|--------|--------|
| Radical prostatectomy (n = 1719) | Bicalutamide 150 mg | 4.6 % | 10.0 % | 14.6 % | 22.4 % |
| | placebo | 4.2 % | 8.7 % | 12.6 % | 20.2 % |

For patients with localised disease receiving bicalutamide alone, there was no significant difference in progression free survival. There was no significant difference in overall survival in patients with localised disease who received bicalutamide as adjuvant therapy, following radiotherapy (HR = 0.98; 95% CI 0.80 to 1.20) or radical prostatectomy (HR = 1.03; 95% CI 0.85 to 1.25). In patients with localised disease, who would otherwise have been managed by watchful waiting, there was also a trend toward decreased survival compared with placebo patients (HR = 1.15; 95% CI 1.00 to 1.32). In view of this, the benefit-risk profile for the use of bicalutamide is not considered favourable in patients with localised disease.

In a separate programme, the efficacy of bicalutamide 150mg for the treatment of patients with locally advanced non-metastatic prostate cancer for whom immediate castration was indicated, was demonstrated in a combined analysis of two studies with 480 previously untreated patients with non-metastatic (M0) prostate cancer. At 56% mortality and a median follow-up of 6.3 years, there was no significant difference between bicalutamide and castration in survival (HR = 1.05; CI = 0.81 to 1.36); however, equivalence of the two treatments could not be concluded statistically.

In a combined analysis of 2 clinical studies with 805 previously untreated patients with metastatic (M1) disease at 43% mortality, bicalutamide 150mg was demonstrated to be less effective than castration in survival time (HR = 1.30; CI 1.04 to 1.65), with a numerical difference in estimated time to death of 42 days (6 weeks) over a median survival time of 2 years.

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

Paediatric population

No studies have been conducted in paediatric patients (see sections 4.3 and 4.6).

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 22µg/ml are observed during daily administration of Bicalutamide 150mg. At steady state, the predominantly active (R)-enantiomer accounts for 99 % of the total circulating enantiomers.

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.

Elimination

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

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 (Leydig cells, thyroid, liver) in animals, are related to these activities. Enzyme induction has not been observed in man. Atrophy of seminiferous tubules 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 0.6 times human therapeutic concentrations at the recommended dose of 150 mg). No recovery was observed at 24 weeks after the completion of dosing in a 12-month rat study (at doses of approximately 0.9 times human concentrations at the recommended human dose of 150 mg). Following 12 months of repeated dosing in dogs (at doses of approximately 3 times human therapeutic concentrations at the recommended human dose of 150 mg), 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 0.6 times human therapeutic concentrations at the recommended human dose of 150 mg), 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:

Lactose monohydrate
Povidone K- 25
Sodium starch glycolate Type A
Magnesium Stearate

Film-Coating:

Opadry OY-S-9622 consisting of:
Hypromellose
Titanium dioxide (E171)
Propylene Glycol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/PVDC/Aluminium blisters

28 tablets contained in a carton.

6.6 Special precautions for disposal

No special requirements.

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

7 MARKETING AUTHORISATION HOLDER

Relonchem Limited
27 Old Gloucester Street
London
WC1 3XX

8. MARKETING AUTHORISATION NUMBER(S)

PL 20395/0077

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

15/10/2008

10 DATE OF REVISION OF THE TEXT

04/03/2019