

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Bicalutamide 150 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 150 mg of bicalutamide.

Excipients: each tablet contains 181 mg lactose monohydrate.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

White, round, biconvex, film-coated tablet, debossed with BCM 150 on one side.

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 elderly patients: 150 mg (1 tablet) once per day, always at the same time (usually in the morning or evening).

Children and adolescents

Bicalutamide is not indicated in children or adolescents.

The tablets should be swallowed whole with liquid.

Minimum treatment duration is two years.

Renal impairment

No dose adjustment is necessary in 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

Bicalutamide is contraindicated in females and children.

Bicalutamide must not be given to any patient who has shown a hypersensitivity reaction to its use.

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. *[this may not apply to all EU member states]*

Bicalutamide is extensively metabolised 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 (see section 4.8). Bicalutamide therapy should be discontinued if changes are severe.

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 metabolised predominantly by CYP 3A4, (see sections 4.3 and 4.5).

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 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 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 site. It is therefore recommended that if bicalutamide is started in patients who are already receiving coumarin anticoagulants, prothrombin time should be closely monitored.

4.6 Pregnancy and lactation

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

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

Table 1: frequency of adverse reactions

System Organ Class	Frequency	Bicalutamide 150 mg (monotherapy)
Blood and lymphatic system disorders	Common	Anaemia
Immune system disorders	Uncommon	Hypersensitivity reactions (including angioneurotic oedema and urticaria)
Metabolism and nutrition disorders	Common	Anorexia
Psychiatric disorders	Common	Decreased libido, Depression
Nervous system disorders	Common	Dizziness, Somnolence
Vascular disorders	Common	Hot flush
Respiratory, thoracic and mediastinal disorders	Uncommon	Interstitial lung disease
Gastrointestinal disorders	Common	Abdominal pain, Constipation, Dyspepsia, Flatulence, Nausea
Hepatobiliary disorders	Common	Hepatic changes (including elevated levels of transaminases, jaundice)/hepatobiliary disorders ^a
	Rare	Hepatic failure ^b
Skin and subcutaneous tissue disorders	Very common	Rash
	Common	Alopecia, Hirsutism/ hair re-growth, Dry skin, Pruritis
Renal and urinary disorders	Common	Haematuria
Reproductive system and breast disorders	Very common	Gynaecomastia and breast tenderness ^c
	Common	Impotence
General disorders and administration site conditions	Very common	Asthenia
	Common	Chest pain, Oedema
Investigations	Common	Weight gain

- ^a Hepatic changes are rarely severe and were frequently transient, resolving or improving with continued therapy or following cessation of therapy.
- ^b Hepatic failure has occurred rarely in patients treated with bicalutamide, but a causal relationship has not been established with certainty. Periodic liver function testing should be considered (see also section 4.4).
- ^c 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.

In addition, cardiac failure was reported in clinical trials (as a possible adverse drug reaction in the opinion of investigating clinicians, with a frequency of > 1 %) during treatment with bicalutamide plus an LHRH analogue. There is no evidence of a causal relationship with drug treatment.

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: anti-androgens, ATC code: L02BB03

Bicalutamide is a non-steroidal anti-androgen without any other endocrine activity. It binds to androgen receptors without activating gene expression and thus inhibits androgen stimulation. Inhibition results in the regression of prostatic tumours. Treatment discontinuation may result in anti-androgen withdrawal syndrome in some patients.

Bicalutamide is a racemate, the R-enantiomer of which has most of the anti-androgen activity.

Bicalutamide 150 mg 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 8,113 patients, where the product was given as immediate hormone therapy or as adjuvant to radical prostatectomy or radiotherapy (primarily external beam radiation). At 7.4 years median follow-up, 27.4 % of all bicalutamide-treated patients and 30.7 % of all placebo-treated patients 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 % confidence interval 0.91 to 1.09). However some trends were apparent for patients in exploratory subgroup analyses.

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

Table 2: 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 3: 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.

The effectiveness of bicalutamide 150 mg in the treatment of patients with locally advanced prostatic carcinoma without metastases, for whom primary treatment with hormones was indicated, was evaluated separately using the meta-analysis of two studies comprising 480 patients with prostatic carcinoma without metastases (M0) who had not been treated before. There was no significant difference in survival (HR=1.05 (CI=0.81-1.36), p=0.669) or in the interval until progression (HR=1.20 (CI 0.96-1.51), p=0.107) between the group treated with bicalutamide 150 mg and the group treated with castration. A general trend with respect to quality of life in favour of bicalutamide 150 mg in comparison with castration was observed; the subgroups that provided these data showed significantly higher sexual appetite (p=0.029) and fitness (p=0.046).

Combined analysis of 2 clinical studies comprising 805 patients with metastatic prostatic carcinoma, who had not been treated before with expected mortality 43 %, showed that the treatment with bicalutamide 150 mg is less effective than castration as for the survival time (HR=1.30 [confidence interval 1.04–1.65]). The estimated difference is 42 days while the mean survival time is 2 years.

5.2 Pharmacokinetic properties

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

The S-enantiomer is rapidly cleared in comparison to the R-enantiomer, which plasma elimination half-life is approximately 1 week.

With regular daily administration of bicalutamide, the concentration of the R-enantiomer in plasma compared to the S-enantiomer is approximately tenfold, which is caused by its lengthy elimination half-life.

With daily doses of 150 mg bicalutamide, equilibrium plasmatic concentrations of the R-enantiomer reach approximately 22 micrograms/ml. From the total number of enantiomers present in plasma at equilibrium condition, 99 % consists of the R-enantiomer, which has a dominant share in the therapeutic effect.

The pharmacokinetics of the R-enantiomer are not influenced by age, renal impairment or mild to moderate hepatic impairment. It has been proven that the R-enantiomer is eliminated more slowly from plasma in patients with severe hepatic impairment.

Bicalutamide is highly protein bound (racemate 96 %, R-bicalutamide 99.6 %) and is largely metabolised (by oxidation and glucuronidation): its metabolites are eliminated via the kidneys and bile in approximately equal proportions. The hydrolysis of glucuronides sets in after excretion into the bile. Metabolised bicalutamide is rarely present in urine.

In the sperm of males using bicalutamide 150 mg, an average concentration of 4.9 µg/ml of R-bicalutamide was found. The bicalutamide dose that can transfer to a woman by sexual intercourse is small and fluctuates around 0.3 µg/kg. This amount is lower than the dose necessary to cause changes in the 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 CYP 450 dependent mixed function oxidases in liver. Enzyme induction has not been observed in humans. Target organ changes, including tumour induction (Leydig cells, thyroid, liver) in animals, are clearly related to the primary and secondary pharmacological action of bicalutamide. Enzyme induction has not been observed in man and none of these findings is considered to have relevance to the treatment of patients with prostate cancer. Atrophy of seminiferous tubules is a predicted class effect with anti-androgens and has been observed for all species examined. Full reversal of testicular atrophy was 24 weeks after a 12 month repeated dose toxicity study in rats, although functional reversal was evident in reproduction studies 7 weeks after the end of an 11 week dosing period. A period of subfertility or infertility should be assumed in man.

Genotoxicity studies did not reveal any mutagenic potential of bicalutamide.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

lactose monohydrate
Povidone K-29/32
Crospovidone
Sodium laurilsulfate
Magnesium stearate

Coating:

Lactose monohydrate
Hypromellose
Titanium oxide (E171)
Macrogol 4000

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

PVC/PE/PVDC/Al blister pack, box.

The packaging contains 5, 7, 10, 14, 20, 28, 30, 40, 50, 56, 80, 84, 90, 98, 100, 140, 200 or 280 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Synthon BV
Microweg 22
6545 CM Nijmegen
Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

PL 14048/0023

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

16/10/2007

10. DATE OF REVISION OF THE TEXT

12/2009