Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Bicalutamide Synthon 50mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 50 mg of bicalutamide
Excipients with known effect: each tablet contains 60.44 mg lactose monohydrate

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.
White, round, biconvex, film-coated tablet, debossed with BCM 50 on one side.

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

Adult males, including elderly patients: the dosage is one 50 mg tablet to be taken orally once a day.

Children and adolescents
Bicalutamide is not indicated in children and adolescents.

The tablets should be swallowed whole with liquid.

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

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 (see section 4.6).

Bicalutamide must not be given to any patient who has shown a hypersensitivity reaction to the active substance or to any of the excipients of this product listed in section 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 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).

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

There is no evidence of any pharmacodynamic or pharmacokinetic interactions between bicalutamide and LHRH analogues.

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) 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 Fertility, 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 (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to ≤1/100); rare (≥1/10,000 to ≤1/1,000); very rare (≤1/10,000), not known (cannot be estimated form the available data).

Table 1: frequency of adverse reactions

System Organ Class	Frequency	Bicalutamide 50mg (+ LHRH analogue)
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
Cardiac disorders	Common	Myocardial infarction (fatal outcomes have been reported)[a],Cardiac failure[a]
Nervous System Disorders	Very common Common	Dizziness Somnolence
Vascular disorders	Very common	Hot flush
Respiratory, thoracic and mediastinal disorders	Uncommon	Interstitial lung disease[b] (fatal outcomes have been reported)
Gastrointestinal disorders	Very common Common	Abdominal pain, Constipation, Nausea Dyspepsia, Flatulence
Hepato-biliary disorders	Common Rare	Hepatotoxicitiy, jaundice, hypertransaminasaemia[c] Hepatic failure[d] (fatal outcomes have been

		reported
Skin and subcutaneous tissue disorders	Common	Alopecia, Hirsuitism/ hair re-growth, Dry skin, Pruritis, Rash
Renal and urinary disorders	Very common	Haematuria
Reproductive system and breast disorders	Very common	Gynaecomastia and breast tenderness[e]
	Common	Erectile dysfunction
General disorders and administration site conditions	Very common	Asthenia, Oedema
	Common	Chest pain
Investigations	Common	Weight gain

[a] 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.

[b] 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.

[c] Hepatic changes are rarely severe and were frequently transient, resolving or improving with continued therapy or following cessation of therapy.

[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] May be reduced by concomitant castration.

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: L02 B B03

Bicalutamide is a non-steroid anti-androgen; it has no additional endocrine activity. It is bound to androgen receptors without activating gene expression and thereby inhibits androgen stimulation. The result of this inhibition is regression of prostate tumours. From the clinical point of view interruption of therapy in some patients could result in manifestation of the anti-androgen withdrawal syndrome.

Bicalutamide is a racemate with an anti-androgen effect, which is present almost exclusively in its R-enantiomer.

5.2 Pharmacokinetic properties

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

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

With regular daily administration of bicalutamide the concentration of the R-enantiomer in plasma in comparison with S-enantiomer is approximately ten-fold, which is caused by its lengthy elimination half-life.

The plasma concentrations of R-enantiomer reach approximately 9 microgram/ml in the case of a daily dose of 50 mg of bicalutamide. From the total number of enantiomers present in plasma in the steady state there is 99% of R-enantiomer, which has a dominant share in the therapeutic effect.

Pharmacokinetics of R-enantiomer are not affected by age, renal impairment or mild to moderate hepatic impairment. It has been shown that in patients with severe liver impairment the R-enantiomer is eliminated slower from plasma.

Bicalutamide is highly protein bound (racemate 96%, R-Bicalutamide 99.6%) and is extensively metabolised (by oxidation and glucuronidation): its metabolites are eliminated via the kidneys and bile in approximately equal proportions. After excreting to bile, hydrolysis of glucuronides occurs.

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 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 comprised of involution of androgen-dependent tissues; thyroid gland, 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 be species-specific, having no relevance for humans in the indicated clinical setting.

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 dioxide (E171)
Macrogol 4,000

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

PVC/PE/PVDC/Al blister, 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

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Synthon BV
Microweg 22
6545 CM Nijmegen
The Netherlands

8 MARKETING AUTHORISATION NUMBER

PA 840/6/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 10th August 2007

Date of last renewal: 21st April 2011

10 DATE OF REVISION OF THE TEXT

June 2012