Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Bicalutamide Hikma 50mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains 50 mg bicalutamide.

Excipient(s): Each tablet contains 62.7 mg of 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 6.5 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

4.2 Posology and method of administration

Adult males including the elderly: one film coated tablet tablet (50mg) daily with or without food.
Route: Oral
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.

Children and adolescents: Bicalutamide Hikma 50 mg 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/mi.)

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 Hikma 50 mg is contra-indicated in women, children and adolescents (see Section 4.6). Bicalutamide Hikma 50 mg is contraindicated in patients hypersensitivity to the active substance or any of the excipients of this product. Co-administration of terfenadine, astemizole or cisapride with Bicalutamide Hikma 50 mg is contra-indicated.

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 extensively metabolised in the liver. Research results 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.
Severe hepatic changes 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.
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.
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.

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 Hikma 50 mg 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

No pharmacological or pharmacokinetic interactions have been demonstrated 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 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 metabolized by cytochrome P450 is probably not clinically significant.

Nonetheless, for drugs with a narrow therapeutic index metabolized 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 cyclosporine, 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 Fertility, 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

The following undesirable effects may occur during treatment with Bicalutamide Hikma 50 mg.

System Organ Class	Frequency	Bicalutamide 50 mg (+ LHRH analogue)
Blood and Lymphatic system disorder	Very common	Anaemia
	Common	
Nervous System Disorders	Very common	Dizziness
	Common	Somnolence
Vascular disorders	Very common	Hot flush
	Common	
Gastrointestinal disorders	Very common	Abdominal pain, constipation, nausea
	Common	Dyspepsia, flatulence
Skin and subcutaneous tissue disorders	Very common	
	Common	Alopecia, hirsutism/ hair re-growth, rash, dry skin, pruritus
Renal and urinary disorders	Very common	Haematuria
	Common	
Reproductive system and breast disorders	Very common	Gynaecomastia and breast tenderness[a]
	Common	Erectile dysfunction
General disorders and administration site conditions	Very common	Asthenia, oedema
	Common	Chest pain
Metabolism and nutrition disorders	Common	Decreased appetite
Psychiatric disorders	Common	Decreased libido, depression
Cardiac disorders	Common	Myocardial infarction (fatal outcomes have been reported)[e], Cardiac failure[e]
Hepatobiliary disorders	Common	Hepatotoxicitiy, jaundice, hypertransaminasaemia[b]
	Rare	Hepatic failure[d] (fatal outcomes have been reported)
Investigations	Common	Weight increased
Immune system disorders	Uncommon	Hypersensitivity, angioedema, and urticaria
Respiratory, thoracic and mediastinal disorders	Uncommon	Interstitial lung disease[c] (fatal outcomes have been reported)

[a] May be reduced by concomitant castration.

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

[c] 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.

[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] 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.

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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

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 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: Hormone antagonists and related agents, antiandrogens, 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 is a racemate with its antiandrogenic activity being almost exclusively in the (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.
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 50mg of Bicalutamide.
A dosing scheme of 50mg Bicalutamide daily will result in a steady-state concentration of the R-enantioner of 9 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 for subjects with severe hepatic impairment, the (R)-enantiomer is more slowly eliminated from plasma.
Bicalutamide is highly protein bound (racemate to 96%, R-enantiomer > 99%) and extensively metabolised (via oxidation and glucuronidation): Its metabolites are eliminated via the kidneys and bile in approximately equal proportions.

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. Target organs 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. This enzyme induction observed in animals has not been found in humans. 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
Povidone K- 25
Sodium starch glycolate Type A
Magnesium Stearate

Film-Coating:
Opadry OY-S-9622 consisting of:
Hypromellose 5 cp (E464)
Titanium dioxide (E171)
Propylene Glycol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

48 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

10, 28, 30 and 90 tablets contained in a carton.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Hikma Farmaceutica (Portugal) SA
Estrada do Rio da Mó,
8, 8A e 8B - Fervença,
2705-906 Terrugem-SNT,
Portugal

8 MARKETING AUTHORISATION NUMBER

PA1217/003/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 12th February 2010

Date of last renewal: 9th October 2013

10 DATE OF REVISION OF THE TEXT

September 2016