Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Bicalutamide Farmaprojects 50 mg, film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 50 mg of bicalutamide.

Excipients with known effect:
Each tablet contains 56 mg of lactose monohydrate

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.
White, round, biconvex, film-coated tablet.

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 the elderly: one tablet once daily at the same time each day (usually in the morning or in the evening), with or without food.
Treatment with bicalutamide should be started at least 3 days prior to the administration of an LHRH analogue or at the same time as surgical castration.

Children and adolescents: There is no relevant indication for the use of bicalutamide 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.
Increased accumulation may occur in patients with moderate to severe hepatic impairment (see Section 4.4).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1

Bicalutamide is contraindicated in females and children (see Section 4.6).

Concomitant 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 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.

Periodic liver function testing should be considered due to the possibility of hepatic changes. The majority of cases are expected to occur within the first 6 months of bicalutamide therapy.

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.
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 bicalutamid in combination with LHRH agonists.

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.

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).

The product contains lactose monohydrate. 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 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 sites. 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

Pregnancy
Bicalutamide is contraindicated in women: therefore it must not be given to pregnant women or nursing mothers.

Breast-feeding
Bicalutamide is contraindicated in women: therefore it must not be given to pregnant women or nursing mothers.

Fertility
Reversible impairment of male fertility has been observed in animal studies (see section 5.3). A period of sub-fertility 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 dizziness or somnolence may occur (see section 4.8). Any affected patient should exercise caution.

4.8 Undesirable effects

In this section, undesirable effects defined as follows: very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <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 50 mg (+ LHRH analogue)**
Blood and Lymphatic system disorders	Very common	Anaemia
Nervous System Disorders	Very common	Dizziness
	Common	Somnolence
Vascular disorders	Very common	Hot flush
Gastrointestinal disorders	Very common	Abdominal pain, constipation, nausea
	Common	Dyspepsia, flatulence
Skin and subcutaneous tissue disorders	Common	Alopecia, hirsutism/ hair re-growth, rash, dry skin, pruritus
Renal and urinary disorders	Very common	Haematuria
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)[b], cardiac failure[b]
Hepatobiliary disorders	Common	Hepatotoxicity, jaundice, hypertransaminasaemia[c],
	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[e] (fatal outcomes have been reported)

[a] May be reduced by concomitant castration.

[b] 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.

[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] 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.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization 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 IMB Pharmacovigilance
Earlsfort Terrace
IRL - Dublin 2
Tel: +353 1 6764971
Fax: +353 1 6762517
Website: http://www.imb.ie/
e-mail: imbpharmacovigilance@imb.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, anti-androgens
ATC code L02 B B03.

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 (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 compared to the (S)-enantiomer in plasma as a consequence of its long elimination half-life.

Steady state plasma concentrations of the (R)-enantiomer, of approximately 9 micrograms/ml are observed during daily administration of Bicalutamide 50 mg. At steady state, the predominantly active (R)-enantiomer accounts for 99% of the total circulating enantiomers.

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 96%, (R)-enantiomer >99%) and extensively metabolised (oxidation and glucuronidation); its metabolites are eliminated via the kidneys and bile in approximately equal proportions.

In a clinical study the mean concentration of R-bicalutamide in semen of men receiving bicalutamide 150 mg 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 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 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 and comprise involution of androgen-dependent tissues, thyroid, hepatic and Leydig cell hyperplasias and neoplasias or cancer; disturbance of male offspring sexual differentiation; reversible impairment of fertility in males. Atrophy of seminiferous tubules is a predicted class effect with antiandrogens 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
Sodium starch glycolate type A
Povidone
Crospovidone type B
Magnesium stearate

Film-coating

Hypromellose
Macrogol 300
Titanium dioxide (E171)

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 / aluminium blisters.
Pack sizes: 28, 30 and 90 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

Farmaprojects SA
Ava. Santa Eulalia 240-242
08902 L'Hospitalet de Llobregat
Barcelona
Spain

8 MARKETING AUTHORISATION NUMBER

PA 1391/001/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 4th July 2008

Date of last renewal: 3rd November 2011

10 DATE OF REVISION OF THE TEXT

October 2014