Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Biluta 50 mg Film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 50 mg bicalutamide.

Excipient with known effect: Lactose 57 mg.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

White and round film-coated tablet with a diameter of approximately 7 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Combination therapy with Biluta 50 mg:
Treatment of advanced prostate cancer in combination with luteinizing hormone-releasing hormone (LHRH) analogue therapy or surgical castration.

Monotherapy with 3 tablets of Biluta 50 mg (150 mg bicalutamide):
Biluta at a dose of 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

Combination therapy with Biluta 50 mg:
Adult males including elderly patients: one tablet (50mg) once daily with or without food. Treatment with bicalutamide may be started either 3 days before or at the same time as commencing treatment with an LHRH analogue, or at the same time as surgical castration.

Renal impairment: no dosage adjustment is necessary for patients with renal impairment.

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).

Monotherapy with 3 tablets of Biluta 50 mg (150 mg bicalutamide):
Adult males including elderly patients: three tablets (150 mg) once daily with or without food. Bicalutamide 150 mg should be taken continuously for at least 2 years or until disease progression.

Renal impairment: no dosage adjustment is necessary for patients with renal impairment.

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

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 6.1.

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.

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).

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 therapy.

Combination therapy with Biluta 50 mg:
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.

Monotherapy with 3 tablets of Biluta 50 mg (150 mg bicalutamide):
For patients who have an objective progression of disease together with elevated PSA, cessation of bicalutamide therapy should be considered.

This medicinal product 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

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 cyclosporin and calcium channel blockers. Dosage reduction may be required for these drugs particularly if there is evidence of enhanced or adverse drug effetc. 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.

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).

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 dizziness or 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).

System Organ Class	**Frequency**	**Bicalutamide 150 mg (monotherapy)**	**Bicalutamide 50 mg (+ LHRH analogue)**
Blood and lymphatic system disorders	Very common		Anaemia
	Common	Anaemia	
Immune system disorders	Uncommon	Hypersensitivity, angioedema and urticaria	Hypersensitivity, angioedema and urticaria
Metabolism and nutrition disorders	Common	Decreased appetite	Decreased appetite
Psychiatric disorders	Common	Decreased libido, Depression	Decreased libido, Depression
Nervous System Disorders	Very common		Dizziness
	Common	Dizziness, Somnolence	Somnolence
Cardiac disorders	Common		Myocardial infarction (fatal outcomes have been reported)[1] ,Cardiac failure[1]
	Not known	QT prolongation (see section 4.4 and 4.5)	QT prolongation (see section 4.4 and 4.5)
Vascular	Very common		Hot flush

disorders	Common	Hot flush	
Respiratory, thoracic and mediastinal disorders	Uncommon	Interstitial lung disease[2] (fatal outcomes have been reported)	Interstitial lung disease[2] (fatal outcomes have been reported)
Gastrointestinal disorders	Very common		Abdominal pain, Constipation, Nausea
	Common	Abdominal pain, Constipation, Dyspepsia, Flatulence, Nausea	Dyspepsia, Flatulence
Hepato-biliary disorders	Common	Hepatotoxicitiy, jaundice, hypertransaminasaemia[3]	Hepatotoxicitiy, jaundice, hypertransaminasaemia[3]
	Rare	Hepatic failure [4](fatal outcomes have been reported)	Hepatic failure [4](fatal outcomes have been reported)
Skin and subcutaneous tissue disorders	Very common	Rash	
	Common	Alopecia, Hirsuitism/ hair re-growth, Dry skin[5], Pruritis	Alopecia, Hirsuitism/ hair re-growth, Dry skin, Pruritis, Rash
	Rare	Photosensitivity	Photosensitivity
Renal and urinary disorders	Very common		Haematuria
	Common	Haematuria	
Reproductive system and breast disorders	Very common	Gynaecomastia and breast tenderness[6]	Gynaecomastia and breast tenderness[7]
	Common	Erectile dysfunction	Erectile dysfunction
General disorders and administration site conditions	Very common	Asthenia	Asthenia, Oedema
	Common	Chest pain, Oedema	Chest pain
Investigations	Common	Weight increased	Weight increased

[1] 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.

[2] 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.

[3] Hepatic changes are rarely severe and were frequently transient, resolving or improving with continued therapy or following cessation of therapy (see section 4.4).

[4] 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.

[5] 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 50 mg dose is assumed.

[6] 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.

[7] May be reduced by concomitant castration.

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

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: Hormone antagonists and related agents, anti-androgens, ATC code: L02B B03

Mechanism of action
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.

Clinical efficacy and safety
Bicalutamide 150 mg was studied as a treatment for patients with localised (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 three placebo controlled, double-blind studies in 8113 patients, where bicalutamide 150 mg was given as immediate hormonal therapy or as adjuvant to radical prostatectomy or radiotherapy, (primarily external beam radiation). At 7.4 years median follow up, 27.4% and 30.7% 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 7.4 years median follow up with 22.9% mortality (HR=0.99; 95% CI 0.91 to 1.09). However, some trends were apparent in exploratory subgroup analyses.

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

Table 1: 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 2: 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.

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
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 9 µg/ml are observed during daily administration of 50 mg doses of bicalutamide. 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.

Biotransformation and Elimination
Bicalutamide is highly protein bound (racemate 96%, R-bicalutamide 99.6%) and extensively metabolised (via oxidation and glucuronidation): Its metabolites are eliminated via the kidneys and bile in approximately equal proportions. After excretion in the bile, hydrolysis of the glucuronides takes place. In the urine scarcely altered bicalutamide is found.

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 potent antiandrogen and a mixed function oxidase enzyme inducer in animals. Target organ changes, including tumour induction, in animals, are related to these activities. None of the findings in the preclinical testing is considered to have relevance to the treatment of advanced prostate cancer patients.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Lactose monohydrate
Sodium starch glycolate type A
Povidone K 30 (E1201)
Maize starch
Magnesium stearate (E572)

Tablet coating:
Methylcellulose
Titanium dioxide (E171)
Triacetin (E1518)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 25° C.

6.5 Nature and contents of container

PVC/Aclar//Al blister: 10, 28, 30, 56, 84, 90 or 100 film-coated tablets.
PVC/Aclar//Al unit dose blister: 100 film-coated tablets.

The blisters are packed in carton boxes.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Rowex Ltd
Bantry
Co. Cork

8 MARKETING AUTHORISATION NUMBER

PA0711/100/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27th April 2007

Date of last renewal: 1st October 2011

10 DATE OF REVISION OF THE TEXT

January 2017