Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Bicalutamide Actavis 50mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One tablet contains 50 mg bicalutamide.

Excipient with known effect: One tablet contains 56.56 mg lactose monohydrate.

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film-coated tablet.

Bicalutamide Actavis 50 mg film-coated tablets are round, biconvex, white, 7 mm in diameter, with “B 50” printed on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of advanced prostate cancer in combination with LHRH analogue therapy or surgical castration.

4.2 Posology and method of administration

Adult males including the elderly: one film-coated tablet (50 mg) daily with or without food.
Treatment with Bicalutamide Actavis should be started at least 3 days before commencing treatment with an LHRH analogue, or at the same time as surgical castration.

Paediatric population
Bicalutamide is not indicated in children and adolescents

Renal impairment
No dose adjustment is necessary for patients with renal impairment.

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 Actavis is contraindicated in females and children (see section 4.6).

Bicalutamide Actavis must not be given to any patient who has shown a hypersensitivity reaction to the active substance or to any of the excipients listed in section 6.1.

Co-administration of terfenadine, astemizole or cisapride with Bicalutamide Actavis 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 and alternative treatments should be considered.

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), caution should therefore be exercised when co-administered with drugs metabolised predominantly by CYP 3A4 (see sections 4.3 and 4.5).

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.

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.

Bicalutamide Actavis 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.

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 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 from the available data).

Table 1 – Frequency of Adverse Reactions

System Organ Class	Frequency	Undesirable effect
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
Nervous System Disorders	Very common	Dizziness
	Common	Somnolence
Cardiac disorders	Common Not known	Myocardial infarction (fatal outcomes have been reported)[a] , Cardiac failure[a] QT prolongation (see sections 4.4 and 4.5)
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	Abdominal pain, constipation, nausea
	Common	Dyspepsia, flatulence
Hepato-biliary disorders	Common	Hepatotoxicitiy, jaundice, hypertransaminasaemia[c]
	Rare	Hepatic failure[d] (fatal outcomes have been reported)
Skin and subcutaneous tissue disorders	Common	Alopecia, hirsutism/ hair re-growth, rash, dry skin, pruritus
Renal and urinary disorders	Very common	Haematuria
	Rare	Photosensitivity reaction
Reproductive system and breast disorders	Very common	Gynaecomastia and breast tenderness[e]
	Common	Erectile dysfunction
General disorders and administration	Very common	Asthenia, oedema

site conditions	Common	Chest pain
Investigations	Common	Weight increased

[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.

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: Anti-androgens, ATC code: L02BB03

Bicalutamide is a non-steroidal antiandrogen, devoid of other endocrine activity. It binds to the wild type or normal androgen receptor without activating gene expression, and thus inhibits the androgen stimulus. Regression of prostatic tumors results from this inhibition. Clinically, discontinuation result in the antiandrogen withdrawal syndrome in a subset of patients.

Bicalutamide is a racemate with its antiandrogen 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.

On daily administration of bicalutamide 150 mg, 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 22 microgram/ml are observed during daily administration of bicalutamide 150 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 to 96%, (R)-enantiomer > 99%) and extensively metabolised (by oxidation and glucuronidation); its metabolites are eliminated via the kidneys and bile in approximately equal proportions.

In clinical study the mean concentration of R-bicalutamide in semen of men receiving bicalutamide 150 mg was 4.9 µg/ml. The amount of bicalutamide potentially delivered to a female partner during intercourse is low and equates to approximately 0.3 µg/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 oxidaze enzyme inducer in animals. Target organ changes, including tumor induction (Leydig cells, thyroid, liver) in animals are related to these activities. Enyzme 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 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 7 week after the end of an 11 week dosing period. A period of subfertility or infertility should be assumed in man.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Lactose monohydrate
Povidone
Sodium starch glycolate, type A
Magnesium stearate

Tablet coating:
Macrogol 3350
Polyvinyl alcohol
Talc
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

HDPE bottles after opening: 6 months

6.4 Special precautions for storage

No special precautions for storage.

6.5 Nature and contents of container

Blister pack PVC/aluminium: 10, 14, 28, 30, 40, 50, 56, 84, 90, 98 and 100 tablets.
HDPE Bottle with LDPE cap: 10, 14, 28, 30, 40, 50, 56, 84, 90, 98 and 100 tablets.

Not all pack sizes may be marketed

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Actavis Group PTC ehf.
Reykjavikurvegi 76-78
220 Hafnarfjörður
Iceland

8 MARKETING AUTHORISATION NUMBER

PA1380/153/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 7th November 2014

10 DATE OF REVISION OF THE TEXT

December 2015