Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Bicalutamide Fair-Med 150mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 150 mg Bicalutamide
Excipient(s) with known effect: Each tablet contains 188.0 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.
White, round, biconvex, scored, film coated tablet.
The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Bicalutamide Fair-Med 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

Adult males including the elderly: The dosage is one 150 mg tablet to be taken orally once a day.
The tablets should be swallowed whole with liquid.
Bicalutamide Fair-Med 150 mg should be taken continuously for at least 2 years or until disease progression.
Children and adolescents: Bicalutamide Fair-Med is contraindicated 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 Fair-Med is contraindicated in females, children and adolescents (see section 4.6).
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 and subsequently patients should be kept under regular surveillance.
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 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.

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.
For patients who have an objective progression of disease together with elevated PSA, cessation of bicalutamide therapy should be considered.
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).
This product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.
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 Fair-Med.

4.5 Interaction with other medicinal products and other forms of interaction

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 Fair-Med 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.

Fertility
Reversible impairment of male fertility has been observed in animal studies (see section 5.3). A period of subfertility 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. 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	Event
Blood and lymphatic system disorders	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	Common	Dizziness Somnolence
Vascular disorders	Common	Hot flush
Respiratory, thoracic and mediastinal disorders	Uncommon	Interstitial lung disease. Fatal outcomes have been reported.
Gastrointestinal disorders	Common	Abdominal pain Constipation Nausea Dyspepsia flatulence
Hepato-biliary disorders	Common	Hepatotoxicity, jaundice, hypertransaminasaemia[a]
	Rare	Hepatic failure. Fatal outcomes have been reported.
Skin and subcutaneous tissue disorders	Very common	Rash
	Common	Alopecia Hirsutism / hair re growth dry skin pruritus
Renal and urinary disorders	Common	Haematuria
Reproductive system and breast disorders	Very common	Gynaecomastia and breast tenderness[b]
	Common	Erectile dysfunction
General disorders and administration site conditions	Very common	Asthenia
	Common	Chest pain oedema
Investigations	Common	Weight increased

a. Hepatic changes are rarely severe and were frequently transient, resolving or improving with continued therapy or following cessation of therapy.
b. 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 (≤ 1/10,000), not known

(cannot be estimated from the available data).

4.9 Overdose

There is no human experience of over dosage. 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: L02B B03
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 tumours results from this inhibition. Clinically, discontinuation of Bicalutamide can result in the 'antiandrogen withdrawal syndrome' in a subset of patients.
Bicalutamide 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 was given as immediate hormonal therapy or as adjuvant to radical prostatectomy or radiotherapy, (primarily external beam radiation). At 9.7 years median follow up, 36.6% and 38.17% 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 9.7 years median follow up with 31.4% mortality (HR= 1.01; 95% CI 0.94 to1.09). However, some trends were apparent in exploratory subgroup analyses.
Data on progression-free survival and overall survival over time based on Kaplan-Meier estimates for patients with locally advanced disease are summarised in the following tables:

Table 1 Proportion of locally advanced disease patients with disease progression over time by therapy sub-group

Analysis population	Treatment Arm	Events (%) at 3 years	Events (%) at 5 years	Events (%) at 7 years	Events (%) at 10 years
Watchful waiting (n=657)	Bicalutamide 150 mg	19.7 %	36.3 %	52.1 %	73.2 %
	Placebo	39.8 %	59.7 %	70.7 %	79.1 %
Radiotherapy (n=305)	Bicalutamide 150mg	13.9 %	33.0 %	42.1 %	62.7 %
	Placebo	30.7 %	49.4 %	58.6 %	72.2 %
Radical prostatectomy (n=1719)	Bicalutamide 150mg	7.5 %	14.4 %	19.8 %	29.9 %
	Placebo	11.7 %	19.4 %	23.2 %	30.9 %

Table 2 Overall survival in locally advanced disease by therapy sub-group

Analysis population	Treatment Arm	Events (%) at 3 years	Events (%) at 5 years	Events (%) at 7 years	Events (%) at 10 years
Watchful	Bicalutamide	14.2 %	29.4 %	42.2 %	65.0 %

waiting (n=657)	150 mg				
	Placebo	17.0 %	36.4 %	53.7 %	67.5 %
Radiotherapy (n=305)	Bicalutamide 150mg	8.2 %	20.9 %	30.0 %	48.5 %
	Placebo	12.6 %	23.1 %	38.1 %	53.3 %
Radical prostatectomy (n=1719)	Bicalutamide 150mg	4.6 %	10.0 %	14.6 %	22.4 %
	Placebo	4.2 %	8.7 %	12.6 %	20.2 %

For patients with localised disease receiving Bicalutamide alone, there was no significant difference in progression free survival. There was no significant difference in overall survival in patients with localized disease who received Bicalutamide as adjuvant therapy, following radiotherapy (HR=0.98; 95% CI 0.80 to 1.20) or radical prostatectomy (HR=1.03; 95% CI 0.85 to 1.25). In patients with localised disease, who would otherwise have been managed by watchful waiting, there was also a trend toward decreased survival compared with placebo patients (HR=1.15; 95% CI 1.00 to 1.32). In view of this, the benefit-risk profile for the use of Bicalutamide is not considered favourable in patients with localised disease.
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, 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 microgram/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.
Bicalutamide is highly protein bound (racemate 96% (R)-enantiomer>99%) and extensively metabolised (via 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 by extrapolation possibly 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 (Leydig cells, thyroid, liver) in animals, are related to these activities. Enzyme 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 studies 7 weeks 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 K- 25
Sodium starch glycolate (type A)
Magnesium Stearate

Coating:
Hypromellose (5cP)
Titanium dioxide (E171)
Propylene Glycol

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/ PVDC/Aluminium blisters.
10, 14, 20, 28, 30, 40, 50, 56, 60, 80, 84, 86, 90, 98, 100, 140, 200, 280 film coated tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

Fair-Med Healthcare GmbH
Planckstrasse 13
22765 Hamburg
Germany

8 MARKETING AUTHORISATION NUMBER

PA1789/001/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14th September 2012

10 DATE OF REVISION OF THE TEXT

January 2017