1.3.1.1 Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

Bicalutamide Sandoz 150 mg film-coated tablet
Bicalutamide Sandoz 50 mg film – coated tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 50mg bicalutamide

Each film-coated tablet contains 150 mg bicalutamide.

Excipient with known effect:
Each 150 mg film-coated tablet contains 200.66 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

White round film-coated tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Bicalutamide 150 mg tablets are 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 older patients: one tablet (150 mg) once daily with or without food. Bicalutamide 150 mg tablets should be taken continuously for at least 2 years or until disease progression.

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

Patients with 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 bicalutamide or to any of the excipients listed in section 6.1.

Concomitant administration of terfenadine, astemizole or cisapride (see section 4.5).

Females, and children and adolescents (see section 4.6).

4.4. Special warnings and precautions for use

Initiation of treatment should be under the direct supervision of a specialist. [this may not apply to all EU member states]

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.

For patients who have an objective progression of disease together with elevated PSA, cessation of bicalutamide therapy should be considered.

For patients who have a heart disease regular monitoring of cardiac functions is recommended.

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.

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 medicinal product contains 200.66 mg 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

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 contra-indicated (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.

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. 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).

Table 1: Frequency of Adverse Reactions

System Organ Class	**Frequency**	**Adverse reaction**
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[1] (fatal outcomes have been reported)
Gastrointestinal disorders	Common	Abdominal pain, Constipation, Dyspepsia, Flatulence, Nausea
Hepatobiliary disorders	Common	Hepatotoxicitiy, jaundice, hypertransaminasaemia[2]
	Rare	Hepatic failure[3] (fatal outcomes have been reported)

Skin and subcutaneous tissue disorders	Very common	Rash
	Common	Alopecia, Hirsuitism/ hair re-growth, Dry skin[4], Pruritis
	Rare	Photosensitivity reaction
Renal and urinary disorders	Common	Haematuria
Reproductive system and breast disorders	Very common	Gynaecomastia and breast tenderness[5]
	Common	Erectile dysfunction
General disorders and administration site conditions	Very common	Asthenia
	Common	Chest pain, Oedema
Investigations	Common	Weight increased
	Unknown	QT prolongation (see section 4.4 and 4.5)

[1] 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.

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

[3] 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.

[4] 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.

[5] 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 form the available data).

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: drug.safetyssa@novartis.com.

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, the (R)-enantiomer of which has most of the anti-androgen activity.

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 22 µg/ml are observed during daily administration of 150 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 (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 11week dosing period. A period of subfertility or infertility should be assumed in man.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:150mg
Lactose monohydrate
Sodium starch glycolate type A
Povidone K30
Maize starch
Magnesium stearate

Tablet coating:
Hypromellose

Titanium dioxide (E171)
Macrogol
Polysorbate 80

Tablet core:50mg
Lactose monohydrate
Sodium starch glycolate type A
Povidone K30
Maize starch
Magnesium stearate

Tablet coating:
Methylcellulose
Titanium dioxide (E171)
Triacetin

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 year

6.4 Special precautions for storage

Do not store above 30ºC.

6.5 Nature and contents of container

PVC/ Aclar//Aluminium blisters
Pack sizes: 20, 28, 30, 40, 50, 56, 60, 200 and 280 film-coated tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

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