**SUMMARY OF PRODUCT CHARACTERISTICS**

## 1. NAME OF THE MEDICINAL PRODUCT

Bicalutamide 150 mg film-coated tablet

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 150 mg bicalutamide.

Excipient with known effect:
Each film-coated tablet contains 190.63 mg lactose (as 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 elderly: 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).

Paediatric population
Bicalutamide is contraindicated for use in children (see section 4.3).

## 4.3 Contraindications

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

Co- administration of terfenadine, astemizole or cisapride with bicalutamide is contraindicated (see section 4.5).

Biccalutamide is contraindicated in females and children (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.

Bicalutamide has been shown to inhibit cytochrome P450 (CYP 3A4), as such caution should be exercised when co-administered with medicinal products metabolised predominantly by CYP 3A4 (see sections 4.3 and 4.5).

In rare cases, photosensitivity reactions have been reported for patients taking bicalutamide. Patients should be advised to avoid direct exposure to excessive sunlight or UV-light while on bicalutamide and the use of sunscreens may be considered. In cases where the photosensitivity reaction is more persistent and/or severe, an appropriate symptomatic treatment should be initiated.

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.

Antiandrogen therapy may cause morphological changes in spermatozoa. Although the effect of bicalutamide on sperm morphology has not been evaluated and no such changes have been reported for patients who received bicalutamide, patients and/or their partners should follow adequate contraception during and for 130 days after bicalutamide therapy.
Potentiation of the effects of coumarin anticoagulants in patients concomitantly receiving bicalutamide may result in an increase in prothrombin time (PT) and International Normalised Ratio (INR). Some of these cases have been associated with a bleeding risk. Close monitoring of PT/INR is therefore recommended and adjustment of the anticoagulant dose should be considered (see section 4.5).

This medicine contains less than 1 mmol sodium (23 mg) per dosage unit, that is to say essentially ‘sodium-free’.

This medicinal product contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the total 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.

There have been reports of an increased effect of warfarin and other coumarin anticoagulants when administered concomitantly with bicalutamide. It is therefore recommended that in patients who are receiving coumarin anticoagulants, prothrombin time should be closely monitored. A dose adjustment of the anticoagulant medicinal product should be considered (see section 4.4).

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

Pregnancy

Bicalutamide is contraindicated in females and must not be given to pregnant women.

Breast-feeding

Bicalutamide is contraindicated during breast-feeding.

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, urticaria |
| Metabolism and nutrition disorders | Common | Decreased appetite |
| Psychiatric disorders | Common | Decreased libido, Depression |
| Nervous System Disorders | Common | Dizziness, Somnolence |
| Cardiac disorders | Not known: | QT prolongation (see sections 4.4 and 4.5) |
| 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], Pruritus |
| | 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 |
| | | |

[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.

[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.

**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 the national reporting system listed in Appendix V*.

### 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: 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.

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 2 Proportion of locally advanced disease patients with disease progression over time by therapy subgroup**

| **Analysis population** | **Treatment Arm** | **Events (%) at 3 years** | **Events (%) at 5 years** | **Events (%) at 7 years** | **Events (%) at 10 years** |
|---|---|---|---|---|---|
| Watchful waiting (n=657) | Bicalutamide150 mg | 19.7% | 36.3% | 52.1% | 73.2% |
| | placebo | 39.8% | 59.7% | 70.7% | 79.1% |
| Radiotherapy (n=305) | Bicalutamide150 mg | 13.9% | 33.0% | 42.1% | 62.7% |
| | placebo | 30.7% | 49.4% | 58.6% | 72.2% |
| Radical prostatectomy (n=1719) | Bicalutamide150 mg | 7.5% | 14.4% | 19.8% | 29.9% |
| | placebo | 11.7% | 19.4% | 23.2% | 30.9% |

**Table 3: 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 waiting (n=657) | Bicalutamide150 mg | 14.2% | 29.4% | 42.2% | 65.0% |
| | placebo | 17.0% | 36.4% | 53.7% | 67.5% |
| Radiotherapy | Bicalutamide150 mg | 8.2% | 20.9% | 30.0% | 48.5% |

| | | | | | |
|---|---|---|---|---|---|
| (n=305) | placebo | 12.6% | 23.1% | 38.1% | 53.3% |
| Radical prostatectomy (n=1719) | Bicalutamide150 mg | 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 localised 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.

In a separate programme, the efficacy of bicalutamide 150 mg for the treatment of patients with locally advanced non-metastatic prostate cancer for whom immediate castration was indicated, was demonstrated in a combined analysis of 2 studies with 480 previously untreated patients with non-metastatic (M0) prostate cancer. At 56% mortality and a median follow-up of 6.3 years, there was no significant difference between bicalutamide and castration in survival (hazard ratio = 1.05 [CI 0.81 to 1.36]); however, equivalence of the two treatments could not be concluded statistically.

In a combined analysis of 2 studies with 805 previously untreated patients with metastatic (M1) disease at 43% mortality, bicalutamide 150 mg was demonstrated to be less effective than castration in survival time (hazard ratio = 1.30 [CI 1.04 to 1.65]), with a numerical difference in estimated time to death of 42 days (6 weeks) over a median survival time of 2 years.

Bicalutamide is a racemate with its antiandrogen activity being almost exclusively in the R-enantiomer.

## 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
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.

Biotransformation and Elimination

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 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.

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.

Special Populations
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.

### 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. Atrophy of seminiferous tubules is a predicted class effect with antiandrogens and has been observed for all species examined. Reversal of testicular atrophy occurred 4 months after the completion of dosing in a 6-month rat study (at doses of approximately 0.6 times human therapeutic concentrations at the recommended dose of 150 mg). No recovery was observed at 24 weeks after the completion of dosing in a 12-month rat study (at doses of approximately 0.9 times human concentrations at the recommended human dose of 150 mg). Following 12 months of repeated dosing in dogs (at doses of approximately 3 times human therapeutic concentrations at the recommended human dose of 150 mg), the incidence of testicular atrophy was the same in dosed and control dogs after a 6-month recovery period. In a fertility study (at doses of approximately 0.6 times human therapeutic concentrations at the recommended human dose of 150 mg), male rats had an increased time to successful mating immediately after 11 weeks of dosing; reversal was observed after 7 weeks off-dose.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

*Tablet core:*

Lactose monohydrate
Sodium starch glycolate type A
Povidone K30
Maize starch
Magnesium stearate

*Tablet coating:*
Hypromellose
Titanium dioxide (E171)
Macrogol
Polysorbate 80

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

24 months

### 6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

### 6.5 Nature and contents of container

*AT/H/0199*
PVC/ Aclar//Aluminium blisters
Pack sizes: 5, 7, 10, 14, 20, 28, 30, 40, 50, 56, 60, 80, 84, 90, 98, 100, 140, 200 and 280 film-coated tablets

*AT/H/0200*
PVC/ Aclar //Aluminium blisters
Pack sizes:
5, 10, 14, 20, 28, 30, 90 and 100 film-coated tablets

*AT/H/0201*

PVC/Aclar//Aluminium blisters
Pack sizes:
5, 10, 14, 20, 28, 30, 60, 90 and 100 film-coated tablets

Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal

No special requirements.

## 7. MARKETING AUTHORISATION HOLDER

Sandoz GmbH, Kundl Biochemiestrasse 10, A-6250 Austria 10, A-6250 AUSTRIA