SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Casodex® 150 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 150 mg bicalutamide (INN).

Excipients with known effect

Each film-coated tablet contains 183 mg of lactose monohydrate (see section 4.4).
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).
White.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Casodex 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).

Casodex 150 mg is also indicated for the management of patients with locally advanced, non-metastatic prostate cancer for whom surgical castration or other medical intervention is not considered appropriate or acceptable.

4.2 Posology and method of administration

Posology
Adult males including the elderly: The dosage is one 150 mg tablet to be taken orally once a day.

Casodex 150 mg should be taken continuously for at least 2 years or until disease progression.

Special populations
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).

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

4.3 Contraindications

Casodex 150 mg is contraindicated in females and children (see section 4.6).

Casodex 150 mg 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 Casodex 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 suggest that its elimination may be slower in subjects with severe hepatic impairment and this could lead to increased accumulation of bicalutamide. Therefore, Casodex 150 mg 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 Casodex therapy.

Severe hepatic changes and hepatic failure have been observed rarely with Casodex 150 mg, and fatal outcomes have been reported (see section 4.8). Casodex 150 mg therapy should be discontinued if changes are severe.

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

Bicalutamide has been shown to inhibit cytochrome P450 (CYP3A4), as such, caution should be exercised when co-administered with drugs metabolised predominantly by CYP 3A4 (see sections 4.3 and 4.5).

In rare cases, photosensitivity reactions have been reported for patients taking Casodex 150 mg. Patients should be advised to avoid direct exposure to excessive sunlight or UV-light while on Casodex 150 mg 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 Casodex.

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 Casodex, patients and/or their partners should follow adequate contraception during and for 130 days after Casodex therapy.

Potentiation of coumarin anticoagulant effects have been reported in patients receiving concomitant Casodex therapy, which may result in increased Prothrombin Time (PT) and International Normalised Ratio (INR). Some cases have been associated with risk of bleeding. Close monitoring of PT/INR is advised and anticoagulant dose adjustment should be considered (see sections 4.5 and 4.8).

This product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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

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 Casodex, mean midazolam exposure (AUC) was increased by up to 80% after co-administration of Casodex 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 Casodex 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 Casodex therapy.

Caution should be exercised when prescribing Casodex 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. There have been reports of increased effect of warfarin and other coumarin anticoagulants when co-administered with Casodex. It is therefore recommended that if Casodex 150 mg is administered in patients who are concomitantly receiving coumarin anticoagulants, PT/INR should be closely monitored and adjustments of anticoagulant dose considered (see sections 4.4 and 4.8).

Since androgen deprivation treatment may prolong the QT interval, the concomitant use of Casodex 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).

Paediatric population
Interaction studies have only been performed in adults.

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 subfertility or infertility should be assumed in man.

4.7. Effects on ability to drive and use machines

Casodex 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***	**Event**
Blood and the 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
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[e] (fatal outcomes have been reported).
Gastrointestinal disorders	Common	Abdominal pain Constipation Dyspepsia Flatulence Nausea
Hepato-biliary disorders	Common	Hepatotoxicity, jaundice, hypertransaminasaemia[a]
	Rare	Hepatic failure[d] (fatal outcomes have been reported).
Skin and subcutaneous tissue disorders	Very common	Rash
	Common	Alopecia Hirsutism/hair re-growth Dry skin[c] Pruritus
	Rare	Photosensitivity reaction

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 Casodex 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.

c. 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 Casodex dose however the same frequency as the 50 mg dose is assumed.

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 Casodex arm of the 150 mg EPC studies.

e. 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.

Increased PT/INR: Accounts of coumarin anticoagulants interacting with Casodex have been reported in post-marketing surveillance (see sections 4.4 and 4.5).

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 Yellow Card Scheme website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App store.

4.9 Overdose

There is no human experience of overdosage. 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: Antiandrogen, ATC code L02 B B03

Mechanism of action
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 Casodex can result in the 'antiandrogen withdrawal syndrome' in a subset of patients.

Clinical efficacy and safety
Casodex 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 Casodex 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 Casodex 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 to 1.09). 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 2 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)	Casodex 150 mg	19.7%	36.3%	52.1%	73.2%
	placebo	39.8%	59.7%	70.7%	79.1%
Radiotherapy (n=305)	Casodex 150 mg	13.9%	33.0%	42.1%	62.7%
	placebo	30.7%	49.4%	58.6%	72.2%
Radical prostatectomy (n=1719)	Casodex 150 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)	Casodex 150 mg	14.2%	29.4%	42.2%	65.0%
	placebo	17.0%	36.4%	53.7%	67.5%
Radiotherapy (n=305)	Casodex 150 mg	8.2%	20.9%	30.0%	48.5%
	placebo	12.6%	23.1%	38.1%	53.3%
Radical prostatectomy (n=1719)	Casodex 150 mg	4.6%	10.0%	14.6%	22.4%
	placebo	4.2%	8.7%	12.6%	20.2%

For patients with localised disease receiving Casodex 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 Casodex 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 Casodex is not considered favourable in patients with localised disease.

In a separate programme, the efficacy of Casodex 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 Casodex 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, Casodex 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.

Paediatric population
No studies have been conducted in paediatric patients (see sections 4.3 and 4.6).

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
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 Casodex 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 Casodex 150 mg. At steady state, the predominantly active (R)-enantiomer accounts for 99% of the total circulating enantiomers.

Elimination
In a clinical study, the mean concentration of R-bicalutamide in semen of men receiving Casodex 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
Magnesium Stearate
Povidone
Carboxymethyl amidon sodium.

Film-coating material
Hypromellose
Macrogol 300
Titanium Dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

Do not store above 30^{o}C.

6.5 Nature and contents of container

PVC/Aluminium foil blister pack comprising strips of 5, 10 and 14 tablets to give pack sizes of 10, 20, 30, 40, 50, 80, 90, 100, 200 or 14, 28, 56, 84, 140 and 280 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

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

7 MARKETING AUTHORISATION HOLDER

AstraZeneca UK Limited,

1 Francis Crick Avenue,

Cambridge,

CB2 0AA,

UK.

8. MARKETING AUTHORISATION NUMBER(S)

PL 17901/0006

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18th June 2000
Date of latest renewal: 16th June 2004

10 DATE OF REVISION OF THE TEXT

17/01/2024