PACKAGE INSERT

SCHEDULING STATUS: S4

PROPRIETARY NAME (and dosage form):

Casodex® 50 (Tablet)

COMPOSITION:

Each tablet contains 50 mg bicalutamide.

Contains sugar (lactose monohydrate).

List of excipients: lactose monohydrate; sodium starch glycollate; polyvidone; magnesium stearate; methylhydroxypropylcellulose; polyethylene glycol and titanium dioxide

PHARMACOLOGICAL CLASSIFICATION:

A 21.12 Hormone inhibitors

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

Bicalutamide is a non-steroidal anti-androgen, 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.

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

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 (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 micrograms per 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- bicalutamide 99,6 %) 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 CASODEX 150 was 4,9 µg/ml. The amount of bicalutamide potentially delivered to a female partner during intercourse equates to approximately 0,3 µg/kg.

Bicalutamide is a potent anti-androgen and a mixed function oxidase enzyme inducer in animals. Target organ changes, including tumour induction in animals, are related to these activities. None of the findings in the preclinical testing is considered to have relevance to the treatment of advanced prostate cancer patients.

INDICATIONS:

Treatment of advanced prostate cancer in combination with Luteinising Hormone Releasing Hormone (LHRH) analogue therapy or surgical castration.

CONTRAINDICATIONS:

CASODEX is contraindicated in females and children.

CASODEX must not be given to any patient who has shown a hypersensitivity reaction to the bicalutamide or to any of the excipients of CASODEX.

WARNINGS AND SPECIAL PRECAUTIONS:

CASODEX 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 CASODEX. Therefore, CASODEX 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.

Severe hepatic changes and hepatic failure have been observed rarely with CASODEX and fatal outcomes have been reported (see "*Side Effects*"). CASODEX therapy should be discontinued if changes are severe.

A reduction in glucose tolerance has been observed in males receiving LHRH agonists and CASODEX. 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 CASODEX in combination with LHRH agonists.

Clinically discontinuation of Casodex can result in anti-androgen withdrawal syndrome in a subset of patients. This is characterised by a decline in PSA (prostate specific antigen) or clinical response following withdrawal of the anti-androgen component of Maximal Androgen Blockade (MAB). This syndrome has been well described in scientific literature although the pathophysiology is unknown and may reflect multiple mechanisms, but is believed to represent the development of agonistic activity by the medicine at the receptor level due to receptor mutations with advancing disease.

Lactose warning:

The tablets contain lactose anhydrous. Patients with rare hereditary problems of galactose intolerance e.g. galactosaemia, the Lapp lactase deficiency, or glucose-galactose malabsorption should not take CASODEX.

Effects on ability to drive and use machines:

During treatment with CASODEX, somnolence has been reported and those patients who experience this symptom should not drive or use machines.

INTERACTIONS:

There is no evidence of any pharmacodynamic or pharmacokinetic interactions between CASODEX and LHRH analogues.

In vitro studies have shown that (R)-CASODEX is an inhibitor of CYP 3A4, with lesser inhibitory effects on CYP 2C9, 2C19 and 2D6 activity.

As formal interaction studies have not been undertaken, caution should be exercised when prescribing CASODEX with other medicines which may inhibit oxidation of the agent e.g. ketoconazole and cimetidine. In theory this could result in increased plasma concentrations of CASODEX, which could lead to an increase in side effects.

Although clinical studies using antipyrine as a marker of cytochrome P450 (CYP) activity showed no evidence of a CASODEX interaction potential with CASODEX, the mean midazolam exposure (AUC) was increased by up to 80 %, after co-administration of CASODEX for 28 days. This rise is comparable to that seen in other studies after administration of grapefruit juice. An increase of this magnitude may be of clinical significance for medicines with a narrow therapeutic index (e.g. astemizole, cisapride and ciclosporin) such an increase could be of relevance. As such, caution should be exercised with the co-administration of CASODEX with compounds such as these.

In vitro studies have shown that CASODEX can displace the coumarin anticoagulant, warfarin, from its protein binding sites. It is therefore recommended that if CASODEX is started in patients who are already receiving coumarin anticoagulants, prothrombin time should be closely monitored.

PREGNANCY AND LACTATION:

CASODEX is contraindicated in females and must not be given to pregnant women or nursing mothers.

DOSAGE AND DIRECTIONS FOR USE:

Adult males including the elderly: 1 tablet (50 mg) once a day.

Treatment with CASODEX should be started at least 3 days before commencing treatment with an LHRH analogue, or at the same time as surgical castration.

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 "Special precautions").

SIDE EFFECTS:

Unless specified, the following frequency categories were assigned based on the incidence of the adverse event in the CASODEX 50 plus LHRH analogue arm of the pivotal LHRH combination study

Frequency	System Organ Class	Adverse Event
Very common (≥ 10 %)	Reproductive system and breast disorders	Breast tenderness[1] Gynaecomastia[1]
	General disorders and administration site conditions	Asthenia Oedema
	Nervous system disorders	Dizziness
	Vascular disorders	Hot flush
	Blood and lymphatic	Anaemia
	Gastrointestinal disorders	Abdominal pain Nausea Constipation

Frequency	System Organ Class	Adverse Event
	Renal and urinary disorders	Haematuria
Common (≥ 1 % and < 10 %)	Gastrointestinal disorders	Dyspepsia Flatulence
	Metabolism and nutrition disorders	Decreased appetite
	Psychiatric disorders	Decreased libido Depression
Common (≥ 1 % and < 10 %)	Reproductive system and breast disorders	Erectile dysfunction
	Nervous system Disorders	Somnolence
	Skin and subcutaneous tissue disorders	Alopecia Dry skin Hirsutism/hair re-growth Rash Pruritus
	Hepatobiliary disorders	Hepatotoxicity, jaundice, hypertransaminasaemia[2]
	General disorders and administration site condition	Chest pain
	Investigations	Weight increased
	Cardiac disorders	Myocardial infarction (fatal outcomes have been reported) Cardiac failure
Uncommon (≥ 0,1 % and < 1 %)	Immune system disorders	Hypersensitivity, angioedema and urticaria

[1] May be reduced by concomitant castration.

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

Cardiovascular effects such as angina, conduction defects including PR and QT interval prolongation, dysrhythmias and non-specific ECG changes have been observed, less frequently. Thrombocytopenia has been observed less frequently.

No casual relationship to CASODEX therapy has been established.

Post-marketing studies:

Frequency	System Organ Class	Adverse Event
Common (≥ 1 % and < 10 %)	Cardiac disorders	Myocardial infarction (fatal outcomes have been reported)[5] Cardiac failure[5]
Uncommon (≥ 0,1 % and < 1 %)	Respiratory, thoracic and mediastinal disorders	Interstitial lung disease[3] Fatal outcomes have been reported
Rare (≥ 0,01 % and < 0,1 %)	Hepatobiliray disorders	Hepatic failure[4] Fatal outcomes have been reported

[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 interstitial pneumonia in the randomised treatment period of the 150 mg EPC studies.

[4] 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.

[5] Observed in pharmaco-epidemiology study of LHRH agonists and anti-androgens used in the treatment of prostate cancer. The risk appeared to be increased when CASODEX 50 mg was used in combination with LHRH agonists, but no increase in risk was evident when CASODEX 150 mg was used as a monotherapy to treat prostate cancer.

Post-marketing adverse events:

The following adverse reactions have been identified during post-approval use of CASODEX: Hypersensitivity reactions, including angioedema and urticaria have been seen. Cases of interstitial lung disease (some fatal), have been reported with CASODEX. A few cases of fatal hepatic failure have been reported.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

There is no human experience of overdosage. There is no specific antidote; treatment should be symptomatic. Dialysis may not be helpful, since CASODEX is highly protein bound and is not recovered unchanged in the urine. General supportive care, including frequent monitoring of vital signs, is indicated.

IDENTIFICATION:

Round, biconvex, white film-coated tablet. The tablet is intagliated CDX50 on one side and a logo on the other side.

PRESENTATION:

Blister packs of 30 tablets.

STORAGE INSTRUCTIONS:

Store at or below 30°C. Keep out of reach of children.

REGISTRATION NUMBER:

30/21.12/0012

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

AstraZeneca Pharmaceuticals (Pty) Limited
Building 2, Northdowns Office Park
17 Georgian Crescent West,
Bryanston
2191

DATE OF PUBLICATION OF THIS PACKAGE INSERT:

Date on registration certificate:
18/01/1995

Date of the most recently revised approved package insert:

17/02/2017

NAMIBIA: NS2

Reg. No.: 04/21.12/1806

BOTSWANA: S2

Reg. No.: BOT 1101928