PACKAGE INSERT

SCHEDULING STATUS: **S 4**

PROPRIETARY NAME (and dosage form):

Casodex® 150 (Tablet)

COMPOSITION:

Each tablet contains 150 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 the (R)-enantiomer, the latter having a plasma elimination half-life of about 1 week.

On daily administration of CASODEX 150, 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 CASODEX 150. 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 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 pre-clinical testing is considered to have relevance to the treatment of advanced prostate cancer patients.

INDICATIONS:

In patients with locally advanced prostate cancer (T3-4, any N, M0/T1-2, N+, M0) CASODEX 150 is indicated as immediate therapy either alone or as adjuvant to treatment by radical prostatectomy or radiotherapy.

CASODEX 150 is indicated as monotherapy for the management of patients with locally advanced, non-metastatic prostate cancer for whom surgical or medical castration is not appropriate.

CONTRAINDICATIONS:

CASODEX 150 is contraindicated in females and children.

CASODEX 150 must not be given to any patient who has shown a hypersensitivity reaction to the bicalutamide or to any of the excipients of CASODEX 150.

WARNINGS AND SPECIAL PRECAUTIONS:

CASODEX 150 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 150. Therefore, CASODEX 150 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 150, and fatal outcomes have been reported (see "*Side Effects*"). CASODEX 150 therapy should be discontinued if changes are severe.

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. Although this effect has only been reported with the 50 mg dose (approved for use in combination therapy), given the likely mode of action the phenomenon could theoretically occur with the 150 mg dose used as single agent therapy.

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 150.

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:
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.

Although clinical studies using antipyrine as a marker of cytochrome P450 (CYP) activity showed no evidence of a CASODEX 150 interaction potential with CASODEX 150, the mean midazolam exposure (AUC) was increased by up to 80 %, after co-administration of CASODEX 150 for 28 days. This rise is comparable to that seen in other studies after administration of grapefruit juice. An increase of this magnitude is may to 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 150 with compounds such as these.

In vitro studies have shown that CASODEX 150 can displace the coumarin anticoagulant, warfarin, from its protein binding sites. It is therefore recommended that if CASODEX 150 is started in patients who are already receiving coumarin anticoagulants, prothrombin time should be closely monitored.

PREGNANCY AND LACTATION:
CASODEX 150 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: 150 mg once a day for 2 years or until progression.
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 under "*Special precautions*").

SIDE EFFECTS:

Unless specified, the following frequency categories were assigned based on the incidence of the adverse event in the CASODEX 150 arm of the combined Early Prostate Cancer studies (for CASODEX monotherapy).

Frequency	**System Organ Class**	**Adverse Event**
Very common (≥ 10 %)	Skin and subcutaneous tissue disorders	Rash
	Reproductive system and breast disorders	Gynaecomastia[1] Breast tenderness[1]

Frequency	**System Organ Class**	**Adverse Event**
Very common (≥ 10 %)	General disorders and administration site conditions	Asthenia
Common (≥ 1 % and < 10 %)	Blood and lymphatic	Anaemia
	General disorders and administration site conditions	Chest pain Oedema
	Psychiatric disorders	Decreased libido Depression
	Skin and subcutaneous tissue disorders	Alopecia Hirsutism/ Hair re-growth Dry skin[3] Pruritus
	Nervous system disorders	Dizziness Somnolence
	Vascular disorders	Hot flush
	Reproductive system and breast disorders	Erectile dysfunction
	Metabolism and nutrition disorders	Decreased appetite

Frequency	**System Organ Class**	**Adverse Event**
Common (≥ 1 % and < 10 %)	Gastro-intestinal disorders	Nausea Abdominal pain Dyspepsia Constipation Flatulence
	Investigations	Weight increased
	Hepatobiliary disorders	Hepatotoxicity, jaundice, hypertransaminasaemia[2]
	Renal and urinary disorders	Haematuria
Uncommon (> 0,1 % and < 1 %)	Respiratory, thoracic and mediastinal disorders	Fatal outcomes have been reported
	Immune system disorders	Hypersensitivity, angioedema and urticaria
Rare (> 0,01 % and < 0,1 %)	Hepatobiliary disorders	Fatal outcomes have been reported

[1] The majority of patients receiving CASODEX 150 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.

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

[3] 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 from the CASODEX 150 dose however the same frequency as the CASODEX 50 dose is assumed.

Post-marketing studies:

Frequency	System Organ Class	Adverse Event
Uncommon (> 0,1 % and < 1 %)	Respiratory, thoracic and mediastinal disorders	Interstitial lung disease[4]
Rare (> 0,01 % and < 0,1 %)	Hepatobiliary disorders	Hepatic failure[5]

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

[5] 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 the open-label CASODEX arm of the CASODEX 150 EPC.

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. Interstitial lung disease has been reported most often at doses greater than 50 mg. 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 150 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 tablets. A logo is impressed on one side and a tablet strength marking (CASODEX 150) is impressed 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:

33/21.12/0081

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

AstraZeneca Pharmaceuticals (Pty) Limited
17 Georgian Crescent West,
Bryanston
2191

DATE OF PUBLICATION OF THIS PACKAGE INSERT:

Date on registration certificate:

13/02/2000

Date of the most recently revised approved package insert:

17/02/2017

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NAMIBIA: NS2 Reg. No.: 10/21.12/0267

BOTSWANA: S2 Reg. No.: BOT 1101929