CASODEX®
(bicalutamide)

1. NAME OF THE MEDICINAL PRODUCT

CASODEX 50 mg
Film coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 50 mg bicalutamide (INN).

3. PHARMACEUTICAL FORM

White film-coated tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of advanced prostate cancer in combination with luteinizing hormone-releasing hormone (LHRH) analogue therapy or surgical castration.

4.2 Posology and method of administration

Adult males including the elderly: one tablet (50 mg) once a day. Treatment with CASODEX should be started at the same time as treatment with an LHRH analogue or surgical castration.

Children: CASODEX is contraindicated in children

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).

4.3 Contraindications

CASODEX is contraindicated in females and children (see section 4.6).

CASODEX must not be given to any patient who has shown a hypersensitivity reaction to the active substance or to any of the excipients of this product.

Co-administration of terfenadine, astemizole or cisapride with CASODEX is contraindicated.

4.4 Special warnings and special precautions for use

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. 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 (see section 4.8). CASODEX therapy should be discontinued if changes are severe.

CASODEX 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).

Androgen deprivation therapy may prolong the QT interval, although a causal association has not been established with CASODEX. In patients with a history of or who have risk factors for QT prolongation and in patients receiving concomitant medicinal products that may 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.

Each tablet of CASODEX contains 61 mg of lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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).

4.5 Interaction with other medicinal products and other forms of interaction

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

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 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 CASODEX 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 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 should be carefully evaluated (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

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

Breastfeeding

CASODEX is contraindicated during breastfeeding.

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

CASODEX in general, has been well tolerated with few withdrawals due to adverse events.

Table 1 Frequency of Adverse Reactions

Frequency	System Organ Class	Event
Very common (≥ 10%)	Blood and lymphatic	Anaemia
	Nervous system disorders	Dizziness
	Vascular disorders	Hot flush

Frequency	System Organ Class	Event
	Gastrointestinal disorders	Abdominal pain Constipation Nausea
	Renal and urinary disorders	Haematuria
	Reproductive system and breast disorders	Breast tenderness[1] Gynaecomastia[1]
	General disorders and administration site conditions	Asthenia Oedema
Common (≥ 1% and < 10%)	Gastrointestinal disorders	Diarrhoea
	Metabolism and nutrition disorders	Decreased appetite
	Psychiatric disorders	Decreased libido Depression
	Nervous system disorders	Somnolence
	Cardiac disorders	Myocardial infarction (fatal outcomes have been reported)[3] Cardiac failure[3]
	Gastrointestinal disorders	Dyspepsia Flatulence
	Hepato-biliary disorders	Hepatotoxicity Jaundice Hypertransaminasaemia[1]
	Skin and subcutaneous tissue disorders	Alopecia Hirsutism/ hair re-growth Rash Dry skin Pruritus
	Reproductive system and breast disorders	Erectile dysfunction
	General disorders and administration site conditions	Chest pain
	Investigations	Weight increased
Uncommon (≥ 0.1% and <	Immune system disorders	Hypersensitivity reactions, including angioneurotic

Frequency	System Organ Class	Event
1%)		oedema Angioedema Urticaria
	Respiratory, thoracic and mediastinal disorders	Interstitial lung disease[4]. Fatal outcomes have been reported.
Rare (≥ 0.01% and < 0.1%)	Gastrointestinal disorders	Vomiting
	Hepato-biliary disorders	Hepatic failure. Fatal outcomes have been reported.
	Skin and subcutaneous tissue disorders	Photosensitivity reaction

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 (see section 4.4).
3. Observed in a 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.
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 the 150 mg EPC studies.

Rare cardiovascular effects such as angina, heart failure, conduction defects including PR and QT interval prolongations, arrhythmias and non-specific ECG changes have been observed.

Thrombocytopenia has been reported uncommonly.

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

In addition, the following adverse experiences were reported in clinical trials (as possible adverse drug reactions in the opinion of investigating clinicians, with a frequency of ≥ 1%) during treatment with CASODEX plus an LHRH analogue. No causal relationship of these experiences to drug treatment has been made and some of the experiences reported are those that commonly occur in elderly patients:

Cardiovascular system: heart failure.

Gastrointestinal system: anorexia, dry mouth, dyspepsia, constipation, flatulence.

Central nervous system: dizziness, insomnia, somnolence, decreased libido.

Respiratory system: dyspnoea.

Urogenital: impotence, nocturia.

Haematological: anaemia.

Skin and appendages: alopecia, rash, sweating, hirsutism.

Metabolic and nutritional: diabetes mellitus, hyperglycaemia, oedema, weight gain, weight loss.

Whole body: abdominal pain, chest pain, headache, pain, pelvic pain, chills.

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 CASODEX 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

CASODEX 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. Clinically, discontinuation of CASODEX can result in antiandrogen withdrawal syndrome in a subset of patients.

CASODEX is a racemate with its antiandrogenic activity being almost exclusively in the (R)-enantiomer.

5.2 Pharmacokinetic properties

CASODEX 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, 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 mcg/mL are observed during daily administration of 50 mg doses of CASODEX. 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.

CASODEX 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 mg was 4.9 mcg/mL. The amount of bicalutamide potentially delivered to a female partner during intercourse is low and by extrapolation possibly equates to approximately 0.3 mcg/kg. This is below that required to induce changes in offspring of laboratory animals.

5.3 Preclinical safety data

CASODEX is a potent antiandrogen and a mixed function oxidase enzyme inducer in animals. Target organ changes, including tumour induction, in animals, are related to these activities. Enzyme induction has not been observed in man. Atrophy of seminiferous tubules of the testes 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 1.5 or 0.6 times human therapeutic concentrations at the recommended dose of 50 mg or 150 mg, respectively). No recovery was observed at 24 weeks after the completion of dosing in a 12-month rat study (at doses of approximately 2 or 0.9 times human concentrations at the recommended human dose of 50 mg or 150 mg, respectively). Following 12-months of repeated dosing in dogs (at doses of approximately 7 or 3 times human therapeutic concentrations at the recommended human dose of 50 mg or 150 mg, respectively), 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 1.5 or 0.6 times human therapeutic concentrations at the recommended human dose of 50 mg or 150 mg, respectively), 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

CASODEX includes the following excipients:
Lactose Monohydrate
Magnesium Stearate
Hypromellose
Macrogol 300
Povidone
Sodium Starch Glycolate
Titanium Dioxide (E171).

6.2 Incompatibilities

None known.

6.3 Shelf life

Please refer to expiry date on the blister strip or outer carton.

6.4 Special precautions for storage

Do not store above 30^{O}C.

6.5 Instructions for use, handling and disposal

No special precautions required.

6.6 Pack size

Please refer to the outer carton for pack size.

Product owner

AstraZeneca UK Limited
1 Francis Crick Avenue
Cambridge Biomedical Campus
Cambridge, CB2 0AA
United Kingdom

Date of revision of text

August 2022

08/BB/SG/Doc ID-001951831 V8.0