Casodex 50 mg

Bicalutamide

Film coated tablets

Qualitative and quantitative composition

Each tablet contains 50 mg bicalutamide (INN)

Pharmaceutical form

White film-coated tablet.

Therapeutic indications

Treatment of advanced prostate cancer in combination with LHRH analogue therapy or surgical castration.

Posology and method of administration

Adult males including the elderly: one 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.

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 Special warnings and precautions for use).

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, Contraindications) 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.

Contraindications

Casodex is contraindicated in females and children (see section, Pregnancy and lactation).

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 (see section, Interaction with other medicinal products and other forms of interaction).

increase in side effects.

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.

Special warnings and precautions for use

Initiation of treatment should be under the direct supervision of a specialist.

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, and fatal outcomes have been reported (see section Undesirable effects). Casodex therapy should be discontinued if changes are severe.

A reduction in glucose tolerance has been observed in males receiving LHRH agonists. 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.

Casodex has been shown to inhibit cytochrome P450 (CYP 3A4), as such caution should be exercised when co-administered with drugs metabolised predominantly

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.

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 lymphatic system disorders	Very 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	Very common	Dizziness
	Common	Somnolence
Cardiac disorders		
	Common	Myocardial infarction (fatal outcomes have been reported)[4], Cardiac failure[4]
Vascular disorders	Very common	Hot flush
Respiratory, thoracic and mediastinal disorders	Uncommon	Interstitial lung disease. Fatal outcomes have been reported.
Gastrointestinal disorders	Very common	Abdominal pain constipation Nausea
	Common	Dyspepsia flatulence
Hepato-biliary disorders	Common	Hepatotoxicity, jaundice, raised transaminases[1]
	Rare	Hepatic failure[2]. Fatal outcomes have been reported.
Skin and subcutaneous	Common	Alopecia

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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.

Reproductive system and breast disorders	Very common	Gynaecomastia and breast tenderness[3]
	Common	Erectile dysfunction
General disorders and administration site conditions	Very common	Asthenia Oedema
	Common	Chest pain
Investigations	Common	Weight increased

1. Hepatic changes are rarely severe and were frequently transient, resolving or improving with continued therapy or following cessation of therapy.
2. Hepatic failure has occurred rarely in patients treated with Casodex, but a causal relationship has not been established with certainty. Periodic liver function testing should be considered (see also section Special warnings and precautions for use).
3. May be reduced by concomitant castration.
4. 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.

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.

Pharmacological properties

Pharmacodynamic properties

Antiandrogen, ATC code L02 B B03

Casodex 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 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.

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 microgram/ml are observed during daily administration of 50 mg doses of Casodex. At steady state the predominantly active (R)-enantiomer accounts for 99% of

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

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. None of the findings in the preclinical testing is considered to have relevance to the treatment of advanced prostate cancer patients.

List of excipients

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

Incompatibilities
None known.

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

Special precautions for storage
Do not store above 30°C.

Instructions for use, handling and disposal
No special precautions required.

Pack size
Please refer to the outer carton for pack size.

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AstraZeneca

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