CASODEX 50mg

bicalutamide

Tablets

P016259

PRESENTATION

White film-coated tablet. Each tablet contains 50mg bicalutamide (INN)

INDICATION

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

DOSAGE AND ADMINISTRATION

Adults

Adult males including the elderly: one tablet (50mg) 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 contra-indicated 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 under warnings/ precautions).

CONTRA-INDICATIONS

'Casodex' is contra-indicated in females and children.

'Casodex' must not be given to any patient who has shown a hypersensitivity reaction to its use.

Co-administration of terfenadine, astemizole or cisapride with 'Casodex' is contra-indicated.

WARNINGS AND 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. The majority of changes are expected to occur within the first 6 months of 'Casodex' therapy.

Severe hepatic changes have been observed rarely with 'Casodex' (see ***'Possible Adverse Reactions'*** section). '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 ***'Contra-indication'*** Section and also ***'Interactions with other Medicaments and other forms of Interaction'*** Section).

Rare (≥ 0.01% and < 0.1%)	Gastrointestinal disorders	Vomiting
	Skin and subcutaneous tissue disorders	Dry skin
	Hepato-biliary disorders	Hepatic failure[3]

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 ***'Warnings and Precautions'***).
3. Hepatic failure has occurred very 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 ***'Warnings and Precautions'***).

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.

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

'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.

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, which

INTERACTION WITH OTHER MEDICAMENTS 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 contra-indicated and caution should be exercised with the co-administration of 'Casodex' with compounds such as cyclosporin and calcium channel blockers. Dosage reduction may be required for these drugs particularly if there is evidence of enhanced or adverse drug effect. For cyclosporin, 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 '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 contra-indicated in females and must not be given to pregnant women or nursing mothers.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

'Casodex' is unlikely to impair the ability of patients to drive or operate machinery.

POSSIBLE ADVERSE DRUG REACTIONS

'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%)	Reproductive system and breast disorders	Breast tenderness[1] Gynaecomastia[1]
	General disorders	Hot flushes[1]
Common (≥ 1% and < 10%)	Gastrointestinal disorders	Diarrhoea Nausea
	Hepato-biliary disorders	Hepatic changes (elevated levels of transaminases, jaundice)[2]
	General disorders	Asthenia Pruritus
Uncommon (≥ 0.1% and < 1%)	Immune system disorders	Hypersensitivity reactions, including angioneurotic oedema and urticaria
	Respiratory, thoracic and mediastinal disorders	Interstitial lung disease

also makes it suitable for once daily dosing.

Steady state plasma concentrations of the (R)-enantiomer of approximately 9μg per 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.

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

PHARMACEUTICAL PARTICULARS

Storage

Do not store above 30°C.

Shelf life

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

Pack size

Please refer to the outer carton for pack size.

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AstraZeneca UK Ltd., Macclesfield, Cheshire, United Kingdom

THIS IS A MEDICAMENT

- Medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are experts in medicine, its benefits and risks.
- Do not, by yourself, interrupt the period of treatment prescribed for you.
- Do not repeat the same prescription without consulting your doctor.

Keep medicament out of reach of children

Council of Arab Health Ministers
Union of Arab Pharmacists

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