CASODEX™ 150 mg Film-coated Tablets

Trade Mark

P018686

PRESENTATION

White film-coated tablet. Each tablet contains 150 mg bicalutamide (INN)

INDICATIONS

In patients with locally advanced prostate cancer (T3–T4, any N, MO; T1–T2, N+, MO), 'Casodex' 150 mg is indicated as immediate therapy either alone or as adjuvant to treatment by radical prostatectomy or radiotherapy. (See Pharmacodynamics section).

'Casodex' 150 mg is also indicated for the management of patients with locally advanced, non-metastatic prostate cancer for whom surgical castration or other medical intervention is not considered appropriate or acceptable.

DOSAGE AND ADMINISTRATION

Adult males including the elderly: The dosage is one 150 mg tablet to be taken orally once a day.

'Casodex' 150 mg should be taken continuously for at least 2 years or until disease 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 'WARNINGS AND PRECAUTIONS' section.)

CONTRA-INDICATIONS

'Casodex' 150 mg is contra-indicated in females and children.

'Casodex' 150 mg must not be given to any patient who has shown a hypersensitivity to the active substance or any of the excipients.

Co-administration of terfenadine, astemizole or cisapride with 'Casodex' is contra-indicated. (See 'INTERACTIONS WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION' section.)

WARNINGS AND PRECAUTIONS

Bicalutamide is extensively metabolised in the liver. Data suggest that its elimination may be slower in subjects with severe hepatic impairment and this could lead to increased accumulation of bicalutamide. Therefore, 'Casodex' 150 mg 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 cases are expected to occur within the first 6 months of 'Casodex' therapy.

Severe hepatic changes have been observed rarely with 'Casodex' 150 mg. (See 'POSSIBLE ADVERSE REACTIONS' section.) 'Casodex' 150 mg therapy should be discontinued if changes are severe.

For patients who have an objective progression of disease together with elevated PSA, cessation of 'Casodex' therapy should be considered.

Bicalutamide 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-INDICATIONS' Section and also 'INTERACTIONS WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION' section.)

Lactose sensitive patients should be aware that each 'Casodex' 150 mg tablet contains 183 mg of lactose monohydrate.

INTERACTIONS WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

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 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 bicalutamide 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. It is therefore recommended that if 'Casodex' 150 mg is started in patients who are already receiving coumarin anticoagulants, prothrombin time should be closely monitored.

PREGNANCY AND LACTATION

Bicalutamide is contra-indicated in females and must not be given to pregnant women or nursing mothers.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No effects on ability to drive and use machines have been observed during treatment with 'Casodex' 150 mg.

POSSIBLE ADVERSE REACTIONS

The pharmacological action of bicalutamide may give rise to certain undesirable effects. These include the following:

Very common (> 10%):
Gynaecomastia, breast tenderness. The majority of patients receiving 'Casodex' 150 mg 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.

Common or frequent (≥ 1%):
Hot flushes, pruritus, asthenia, alopecia, hair regrowth, dry skin, decreased libido, nausea, impotence and weight gain.

Uncommon or infrequent (≥ 0.1% to < 1%):
Abdominal pain, depression, dyspepsia, haematuria and interstitial lung disease.
Hypersensitivity reactions, including angioneurotic oedema and urticaria

Hepatic changes (elevated levels of transaminases, cholestasis and jaundice), which are rarely severe. The changes were frequently transient, resolving or improving with continued therapy or following cessation of therapy. Hepatic failure has occurred very rarely in patients treated with bicalutamide but a causal relationship has not been established with certainty. Periodic liver function testing should be considered. (See 'WARNINGS AND PRECAUTIONS' section.)

OVERDOSE

There is no human experience of overdosage. There is no specific antidote; treatment should be symptomatic. Dialysis may not be helpful, since bicalutamide 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

Bicalutamide is a non-steroidal antiandrogen, devoid of other endocrine activity. It binds to the wild type or normal androgen receptor 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 the 'antiandrogen withdrawal syndrome' in a subset of patients.

'Casodex' 150 mg was studied as a treatment for patients with localised (T1–T2, N0 or NX, M0) or locally advanced (T3–T4, any N, M0; T1–T2, N+, M0) non metastatic prostate cancer in a combined analysis of three placebo controlled, double-blind studies in 8113 patients, where 'Casodex' was given as immediate hormonal therapy or as adjuvant to radical prostatectomy or radiotherapy (primarily external beam radiation). At 7.4 years median follow up, 27.4% and 30.7% of all 'Casodex'

and placebo treated patients, respectively, had experienced objective disease progression

In the subgroup of patients with locally advanced prostate cancer who did not receive treatment with radical prostatectomy or radiotherapy, immediate therapy with 'Casodex' 150 mg significantly reduced the risk of objective disease progression (Hazard Ratio (HR)=0.60; 95% CI 0.49 to 0.73). A statistically significant reduction in the risk of objective disease progression was also seen in the subgroup of patients with locally advanced disease who received 'Casodex' as adjuvant to radical prostatectomy or radiotherapy (HR=0.69; 95% CI 0.58 to 0.82). There was no significant difference in progression in patients with localised disease.

A reduction in risk of objective disease progression was seen across most patients groups but was most evident in those at highest risk of disease progression. Therefore, clinicians may decide that the optimum medical strategy for a patient at low risk of disease progression, particularly in the adjuvant setting following radical prostatectomy, may be to defer hormonal therapy until signs that the disease is progressing.

No overall survival difference was seen at 7.4 years median follow up with 22.9% mortality (HR=0.99; 95% CI 0.91 to 1.09). However, some trends were apparent in exploratory subgroup analyses:

For patients with localised disease receiving 'Casodex' alone showed a trend toward decreased survival compared with placebo patients (HR= 1.16; 95% CI 0.99 to 1.37). In view of this, the benefit-risk profile for the use of 'Casodex' is not considered favourable in this group of patients.

For patients with locally advanced disease receiving 'Casodex' alone, there was a trend toward improved survival with 'Casodex' compared to placebo (HR=0.81; 95% CI 0.66 to 1.01).

The progression-free survival and overall survival data for patients with locally advanced disease are summarised in the following tables:

Progression-free survival in locally advanced disease by therapy sub-group

Analysis population	Events (%) in CASODEX patients	Events (%) in placebo patients	Hazard ratio (95% CI)
Watchful waiting	193/335 (57.6)	222/322 (68.9)	0.60 (0.49 to 0.73)
Radiotherapy	66/161 (41.0)	86/144 (59.7)	0.56 (0.40 to 0.78)
Radical prostatectomy	179/870 (20.6)	213/849 (25.1)	0.75 (0.61 to 0.91)

Overall survival in locally advanced disease by therapy sub-group

Analysis population	Deaths (%) in CASODEX patients	Deaths (%) in placebo patients	Hazard ratio (95% CI)
Watchful waiting	164/335 (49.0)	183/322 (56.8)	0.81 (0.66 to 1.01)
Radiotherapy	49/161 (30.4)	61/144 (42.4)	0.65 (0.44 to 0.95)
Radical prostatectomy	137/870 (15.7)	122/849 (14.4)	1.09 (0.85 to 1.39)

In a separate programme, the efficacy of 'Casodex' 150 mg for the treatment of patients with locally advanced non-metastatic prostate cancer for whom immediate castration was indicated, was demonstrated in a combined analysis of 2 studies with 480 previously untreated patients with non metastatic (M0) prostate cancer. At 56% mortality and a median follow-up of 6.3 years, there was no significant difference between 'Casodex' and castration in survival (hazard ratio = 1.05 [CI 0.81 to 1.36]); however, equivalence of the two treatments could not be concluded statistically.

In a combined analysis of 2 studies with 805 previously untreated patients with metastatic (M1) disease at 43% mortality, 'Casodex' 150 mg was demonstrated to be less effective than castration in survival time (hazard ratio = 1.30 [CI 1.04 to 1.65]), with a numerical difference in estimated time to death of 42 days (6 weeks) over a median survival time of 2 years.

Bicalutamide is a racemate with its antiandrogen 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 'Casodex' 150 mg, 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 microgram/ml are observed during daily administration of 'Casodex' 150 mg. 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 (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 equates to approximately 0.3 microgram/kg. This is below that required to induce changes in offspring of laboratory animals.

Pre-Clinical Safety Data Relevant to the Prescriber
Bicalutamide is a potent antiandrogen and a mixed function oxidase enzyme inducer in animals. Target organ changes, including tumour induction (Leydig cells, thyroid, liver) in animals, are related to these activities. Enzyme induction has not been observed in man and none of these findings is considered to have relevance to the treatment of patients with prostate cancer. Atrophy of seminiferous tubules is a predicted class effect with antiandrogens and has been observed for all species examined. Full reversal of testicular atrophy was 24 weeks after a 12-month repeated dose toxicity study in rats, although functional reversal was evident in reproduction studies 7 weeks after the end of an 11 week dosing period. A period of subfertility or infertility should be assumed in man.

PHARMACEUTICAL PARTICULARS

Special Precautions for 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.

Date of revision of the text
February 2006

ONC.000-170-292.4.0

AstraZeneca UK Limited, Macclesfield, Cheshire, United Kingdom

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