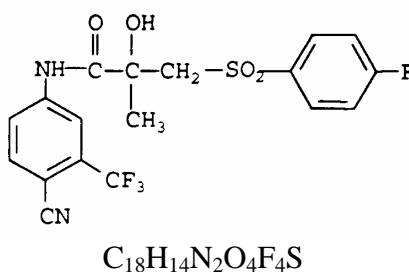


CASODEX®
(bicalutamide)
TABLETS

DESCRIPTION

CASODEX® (bicalutamide) Tablets for oral administration contain 50 mg of bicalutamide, a non-steroidal antiandrogen with no other known endocrine activity. The chemical name is propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl-,(+). The structural and empirical formulas are:



Bicalutamide has a molecular weight of 430.37. The pKa' is approximately 12. Bicalutamide is a fine white to off-white powder which is practically insoluble in water at 37°C (5 mg per 1000 mL), slightly soluble in chloroform and absolute ethanol, sparingly soluble in methanol, and soluble in acetone and tetrahydrofuran.

CASODEX is a racemate with its antiandrogenic activity being almost exclusively exhibited by the R-enantiomer of bicalutamide; the S-enantiomer is essentially inactive.

The inactive ingredients of CASODEX Tablets are lactose, magnesium stearate, methylhydroxypropylcellulose, polyethylene glycol, polyvidone, sodium starch glycollate, and titanium dioxide.

CLINICAL PHARMACOLOGY

Mechanism of Action

CASODEX is a non-steroidal antiandrogen. It competitively inhibits the action of androgens by binding to cytosol androgen receptors in the target tissue. Prostatic carcinoma is known to be androgen sensitive and responds to treatment that counteracts the effect of androgen and/or removes the source of androgen.

When CASODEX is combined with luteinizing hormone-releasing hormone (LHRH) analogue therapy, the suppression of serum testosterone induced by the LHRH analogue is not affected. However, in clinical trials with CASODEX as a single agent for prostate cancer, rises in serum testosterone and estradiol have been noted.

Pharmacokinetics

Absorption:

Bicalutamide is well-absorbed following oral administration, although the absolute bioavailability is unknown. Co-administration of bicalutamide with food has no clinically significant effect on rate or extent of absorption.

Distribution:

Bicalutamide is highly protein-bound (96%). See Drug-Drug Interactions below.

Metabolism/Elimination:

Bicalutamide undergoes stereospecific metabolism. The S (inactive) isomer is metabolized primarily by glucuronidation. The R (active) isomer also undergoes glucuronidation but is predominantly oxidized to an inactive metabolite followed by glucuronidation. Both the parent and metabolite glucuronides are eliminated in the urine and feces. The S-enantiomer is rapidly cleared relative to the R-enantiomer, with the R-enantiomer accounting for about 99% of total steady-state plasma levels.

Special Populations:

Geriatric:

In two studies in patients given 50 or 150 mg daily, no significant relationship between age and steady-state levels of total bicalutamide or the active R-enantiomer has been shown.

Hepatic Insufficiency:

No clinically significant difference in the pharmacokinetics of either enantiomer of bicalutamide was noted in patients with mild-to-moderate hepatic disease as compared to healthy controls. However, the half-life of the R-enantiomer was increased approximately 76% (5.9 and 10.4 days for normal and impaired patients, respectively) in patients with severe liver disease (n=4).

Renal Insufficiency:

Renal impairment (as measured by creatinine clearance) had no significant effect on the elimination of total bicalutamide or the active R-enantiomer.

Women, Pediatrics

Bicalutamide has not been studied in women or pediatric subjects.

Drug-Drug Interactions:

Clinical studies have not shown any drug interactions between bicalutamide and LHRH analogues (goserelin or leuprolide). There is no evidence that bicalutamide induces hepatic enzymes. *In vitro* protein-binding studies have shown that bicalutamide can displace coumarin anticoagulants from binding sites. Prothrombin times should be closely monitored in patients already receiving coumarin anticoagulants who are started on CASODEX.

Pharmacokinetics of the active enantiomer of CASODEX in normal males and patients with prostate cancer are presented in Table 1.

Table 1

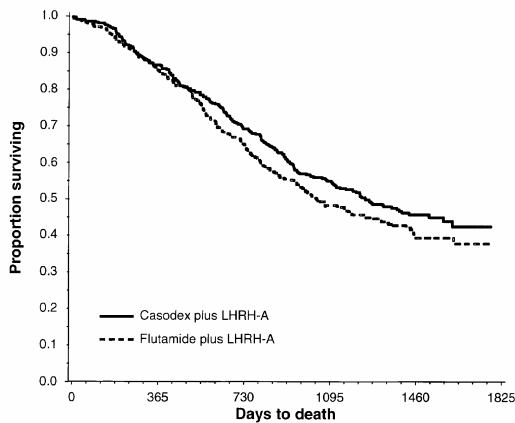
Parameter	Mean	Standard Deviation
<u>Normal Males (n=30)</u>		
Apparent Oral Clearance (L/hr)	0.320	0.103
Single Dose Peak Concentration (µg/mL)	0.768	0.178
Single Dose Time to Peak Concentration (hours)	31.3	14.6
Half-life (days)	5.8	2.29
<u>Patients with Prostate Cancer (n=40)</u>		
C _{ss} (µg/mL)	8.939	3.504
C _{ss} =Mean Steady-State Concentration		

Clinical Studies**CASODEX 50 mg Daily in Combination with an LHRH-A**

In a multicenter, double-blind, controlled clinical trial, 813 patients with previously untreated advanced prostate cancer were randomized to receive CASODEX 50 mg once daily (404 patients) or flutamide 250 mg (409 patients) three times a day, each in combination with LHRH analogues (either goserelin acetate implant or leuprolide acetate depot).

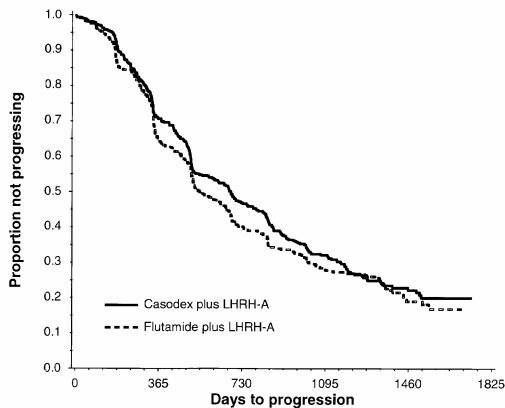
In an analysis conducted after a median follow-up of 160 weeks was reached, 213 (52.7%) patients treated with CASODEX-LHRH analogue therapy and 235 (57.5%) patients treated with flutamide-LHRH analogue therapy had died. There was no significant difference in survival between treatment groups (see Figure 1). The hazard ratio for time to death (survival) was 0.87 (95% confidence interval 0.72 to 1.05).

Figure 1 - The Kaplan-Meier probability of death for both antiandrogen treatment groups.



There was no significant difference in time to objective tumor progression between treatment groups (see Figure 2). Objective tumor progression was defined as the appearance of any bone metastases or the worsening of any existing bone metastases on bone scan attributable to metastatic disease, or an increase by 25% or more of any existing measurable extraskelatal metastases. The hazard ratio for time to progression of CASODEX plus LHRH analogue to that of flutamide plus LHRH analogue was 0.93 (95% confidence interval, 0.79 to 1.10).

Figure 2 - Kaplan-Meier curve for time to progression for both antiandrogen treatment groups



Quality of life was assessed with self-administered patient questionnaires on pain, social functioning, emotional well-being, vitality, activity limitation, bed disability, overall health, physical capacity, general symptoms, and treatment related symptoms. Assessment of the Quality of Life questionnaires did not indicate consistent significant differences between the two treatment groups.

Safety Data from Clinical Studies using CASODEX 150 mg
CASODEX 150 mg is not approved for use either alone or with other treatments.

Two identical multicenter, randomized, open label trials comparing CASODEX 150 mg daily monotherapy to castration were conducted in patients that had locally advanced (T3-4, NX, MO) or metastatic (M1) prostate cancer.

Monotherapy

M1 Group

CASODEX 150 mg daily is not approved for use in patients with M1 cancer of the prostate. Based on an interim analysis of the two trials for survival, the Data Safety Monitoring Board recommended that CASODEX treatment be discontinued in the M1 patients because the risk of death was 25% (HR 1.25, 95% CI 0.87 to 1.81) and 31% (HR 1.31, 95% CI 0.97 to 1.77) higher in the CASODEX-treated group compared to that in the castrated group, respectively.

Locally Advanced (T3-4, NX, MO) Group

CASODEX 150 mg daily is not approved for use in patients with locally advanced (T3-4, NX, MO) cancer of the prostate. Following discontinuation of all M1 patients, the trials continued with the T3-4, NX, MO patients until study completion. In the larger trial (N=352), the risk of death was 25% (HR 1.25, 95% CI 0.92 to 1.71) higher in the CASODEX group and in the smaller trial (N=140), the risk of death was 36% (HR 0.64, 95% CI, 0.39 to 1.03) lower in the CASODEX group.

In addition to the above two studies, there are three other on-going clinical studies that provide additional safety information for CASODEX 150 mg, a dose that is not approved for use. These are three multicenter, randomized, double-blind, parallel group trials comparing CASODEX 150 mg daily monotherapy (adjuvant to previous therapy or under watchful waiting) with placebo, for death or time to disease progression, in a population of 8113 patients with localized or locally advanced prostate cancer.

CASODEX 150 mg daily is not approved for use as therapy for patients with localized prostate cancer who are candidates for watchful waiting. Data from a planned subgroup analysis of two of these trials in 1,627 patients with localized prostate cancer who were under watchful waiting, revealed a trend toward decreased survival in the CASODEX arm after a median follow-up of 7.4 years. There were 294 (37.7%) deaths in the CASODEX treated patients versus 279 (32.9%) deaths in the placebo treated patients (localized watchful waiting group) for a hazard ratio of 1.16 (95% CI 0.99 to 1.37).

INDICATIONS AND USAGE

CASODEX 50 mg daily is indicated for use in combination therapy with a luteinizing hormone-releasing hormone (LHRH) analogue for the treatment of Stage D₂ metastatic carcinoma of the prostate.

CASODEX 150 mg daily is not approved for use alone or with other treatments. See **CLINICAL PHARMACOLOGY-Clinical Studies- Safety Data from Clinical Studies using CASODEX 150 mg** section for additional important safety information regarding CASODEX 150 mg.

CONTRAINDICATIONS

CASODEX is contraindicated in any patient who has shown a hypersensitivity reaction to the drug or any of the tablet's components.

CASODEX has no indication for women, and should not be used in this population, particularly for non-serious or non-life threatening conditions. Further, CASODEX should not be used by women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. CASODEX may cause fetal harm when administered to pregnant women. The male offspring of rats receiving doses of 10 mg/kg/day (plasma drug concentrations in rats equal to approximately 2/3 human therapeutic concentrations*) and above were observed to have reduced anogenital distance and hypospadias in reproductive toxicology studies. These pharmacological effects have been observed with other antiandrogens. No other teratogenic effects were observed in rabbits receiving doses up to 200 mg/kg/day (approximately 1/3 human therapeutic concentrations*) or rats receiving doses up to 250 mg/kg/day (approximately 2 times human therapeutic concentrations*).

*Based on a maximum dose of 50 mg/day of bicalutamide for an average 70 kg patient.

WARNINGS

Hepatitis:

Rare cases of death or hospitalization due to severe liver injury have been reported post-marketing in association with the use of CASODEX. Hepatotoxicity in these reports generally occurred within the first three to four months of treatment. Hepatitis or marked increases in liver enzymes leading to drug discontinuation occurred in approximately 1% of CASODEX patients in controlled clinical trials.

Serum transaminase levels should be measured prior to starting treatment with CASODEX, at regular intervals for the first four months of treatment, and periodically thereafter. If clinical symptoms or signs suggestive of liver dysfunction occur (e.g., nausea, vomiting, abdominal pain, fatigue, anorexia, "flu-like" symptoms, dark urine, jaundice, or right upper quadrant tenderness), the serum transaminases, in particular the serum ALT, should be measured immediately. If at any time a patient has jaundice, or their ALT rises above two times the upper limit of normal, CASODEX should be immediately discontinued with close follow-up of liver function.

PRECAUTIONS

General:

1. CASODEX should be used with caution in patients with moderate-to-severe hepatic impairment. CASODEX is extensively metabolized by the liver. Limited data in subjects with severe hepatic impairment suggest that excretion of CASODEX may be delayed and could lead to further accumulation. Periodic liver function tests should be considered for hepatic-impaired patients on long-term therapy (See WARNINGS).
2. In clinical trials with CASODEX as a single agent for prostate cancer, gynecomastia and breast pain have been reported in up to 38% and 39% of patients, respectively.

3. Regular assessments of serum Prostate Specific Antigen (PSA) may be helpful in monitoring the patient's response. If PSA levels rise during CASODEX therapy, the patient should be evaluated for clinical progression. For patients who have objective progression of disease together with an elevated PSA, a treatment-free period of antiandrogen, while continuing the LHRH analogue, may be considered.

Information for Patients:

Patients should be informed that therapy with CASODEX and the LHRH analogue should be initiated concomitantly, and that they should not interrupt or stop taking these medications without consulting their physician. Treatment with CASODEX should be started at the same time as treatment with an LHRH analogue.

Drug Interactions:

In vitro studies have shown CASODEX can displace coumarin anticoagulants, such as warfarin, from their protein-binding sites. It is recommended that if CASODEX is started in patients already receiving coumarin anticoagulants, prothrombin times should be closely monitored and adjustment of the anticoagulant dose may be necessary (see CLINICAL PHARMACOLOGY, Drug-Drug Interactions).

Carcinogenesis, Mutagenesis, Impairment of Fertility:

Two-year oral carcinogenicity studies were conducted in both male and female rats and mice at doses of 5, 15 or 75 mg/kg/day of bicalutamide. A variety of tumor target organ effects were identified and were attributed to the antiandrogenicity of bicalutamide, namely, testicular benign interstitial (Leydig) cell tumors in male rats at all dose levels (the steady-state plasma concentration with the 5 mg/kg/day dose is approximately 2/3 human therapeutic concentrations*) and uterine adenocarcinoma in female rats at 75 mg/kg/day (approximately 1 1/2 times the human therapeutic concentrations*). There is no evidence of Leydig cell hyperplasia in patients; uterine tumors are not relevant to the indicated patient population.

A small increase in the incidence of hepatocellular carcinoma in male mice given 75 mg/kg/day of bicalutamide (approximately 4 times human therapeutic concentrations*) and an increased incidence of benign thyroid follicular cell adenomas in rats given 5 mg/kg/day (approximately 2/3 human therapeutic concentrations*) and above were recorded. These neoplastic changes were progressions of non-neoplastic changes related to hepatic enzyme induction observed in animal toxicity studies. Enzyme induction has not been observed following bicalutamide administration in man. There were no tumorigenic effects suggestive of genotoxic carcinogenesis.

A comprehensive battery of both *in vitro* and *in vivo* genotoxicity tests (yeast gene conversion, Ames, *E. coli*, CHO/HGPRT, human lymphocyte cytogenetic, mouse micronucleus, and rat bone marrow cytogenetic tests) has demonstrated that CASODEX does not have genotoxic activity.

Administration of CASODEX may lead to inhibition of spermatogenesis. The long-term effects of CASODEX on male fertility have not been studied.

In male rats dosed at 250 mg/kg/day (approximately 2 times human therapeutic concentrations*), the precoital interval and time to successful mating were increased in the first pairing but no effects on fertility following successful mating were seen. These effects were reversed by 7 weeks after the end of an 11-week period of dosing.

No effects on female rats dosed at 10, 50 and 250 mg/kg/day (approximately 2/3, 1 and 2 times human therapeutic concentrations, respectively*) or their female offspring were observed. Administration of bicalutamide to pregnant females resulted in feminization of the male offspring leading to hypospadias at all dose levels. Affected male offspring were also impotent.

*Based on a maximum dose of 50 mg/day of bicalutamide for an average 70 kg patient.

Pregnancy:

Pregnancy Category X:
(See CONTRAINDICATIONS.)

Nursing Mothers:

CASODEX is not indicated for use in women. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when CASODEX is administered to a nursing woman.

Pediatric Use:

Safety and effectiveness of CASODEX in pediatric patients have not been established.

ADVERSE REACTIONS

In patients with advanced prostate cancer treated with CASODEX in combination with an LHRH analogue, the most frequent adverse experience was hot flashes (53%).

In the multicenter, double-blind, controlled clinical trial comparing CASODEX 50 mg once daily with flutamide 250 mg three times a day, each in combination with an LHRH analogue, the following adverse experiences with an incidence of 5% or greater, regardless of causality, have been reported.

Table 2 Incidence of Adverse Events (≥ 5% in Either Treatment Group) Regardless of Causality

Body System Adverse Event	Treatment Group Number of Patients (%)	
	CASODEX Plus LHRH Analogue (n=401)	Flutamide Plus LHRH Analogue (n=407)
Body as a Whole		
Pain (General)	142 (35)	127 (31)
Back Pain	102 (25)	105 (26)
Asthenia	89 (22)	87 (21)
Pelvic Pain	85 (21)	70 (17)
Infection	71 (18)	57 (14)

Abdominal Pain	46	(11)	46	(11)
Chest Pain	34	(8)	34	(8)
Headache	29	(7)	27	(7)
Flu Syndrome	28	(7)	30	(7)
Cardiovascular				
Hot Flashes	211	(53)	217	(53)
Hypertension	34	(8)	29	(7)
Digestive				
Constipation	87	(22)	69	(17)
Nausea	62	(15)	58	(14)
Diarrhea	49	(12)	107	(26)
Increased Liver Enzyme Test [†]	30	(7)	46	(11)
Dyspepsia	30	(7)	23	(6)
Flatulence	26	(6)	22	(5)
Anorexia	25	(6)	29	(7)
Vomiting	24	(6)	32	(8)
Hemic and Lymphatic				
Anemia ^{††}	45	(11)	53	(13)
Metabolic and Nutritional				
Peripheral Edema	53	(13)	42	(10)
Weight Loss	30	(7)	39	(10)
Hyperglycemia	26	(6)	27	(7)
Alkaline Phosphatase				
Increased	22	(5)	24	(6)
Weight Gain	22	(5)	18	(4)
Musculoskeletal				
Bone Pain	37	(9)	43	(11)
Myasthenia	27	(7)	19	(5)
Arthritis	21	(5)	29	(7)
Pathological Fracture	17	(4)	32	(8)
Nervous System				
Dizziness	41	(10)	35	(9)
Paresthesia	31	(8)	40	(10)
Insomnia	27	(7)	39	(10)
Anxiety	20	(5)	9	(2)
Depression	16	(4)	33	(8)
Respiratory System				
Dyspnea	51	(13)	32	(8)
Cough Increased	33	(8)	24	(6)
Pharyngitis	32	(8)	23	(6)
Bronchitis	24	(6)	22	(3)
Pneumonia	18	(4)	19	(5)
Rhinitis	15	(4)	22	(5)
Skin and Appendages				

Rash	35	(9)	30	(7)
Sweating	25	(6)	20	(5)
Urogenital				
Nocturia	49	(12)	55	(14)
Hematuria	48	(12)	26	(6)
Urinary Tract				
Infection	35	(9)	36	(9)
Gynecomastia	36	(9)	30	(7)
Impotence	27	(7)	35	(9)
Breast Pain	23	(6)	15	(4)
Urinary				
Frequency	23	(6)	29	(7)
Urinary				
Retention	20	(5)	14	(3)
Urinary				
Impaired	19	(5)	15	(4)
Urinary				
Incontinence	15	(4)	32	(8)

†Increased liver enzyme test includes increases in AST, ALT or both.

††Anemia includes anemia, hypochronic- and iron deficiency anemia.

Other adverse experiences (greater than or equal to 2%, but less than 5%) reported in the CASODEX-LHRH analogue treatment group are listed below by body system and are in order of decreasing frequency within each body system regardless of causality.

Body as a Whole: Neoplasm; Neck pain; Fever; Chills; Sepsis; Hernia; Cyst

Cardiovascular: Angina pectoris; Congestive heart failure; Myocardial infarct; Heart arrest; Coronary artery disorder; Syncope

Digestive: Melena; Rectal hemorrhage; Dry mouth; Dysphagia; Gastrointestinal disorder; Periodontal abscess; Gastrointestinal carcinoma

Metabolic and Nutritional: Edema; Bun increased; Creatinine increased; Dehydration; Gout; Hypercholesteremia

Musculoskeletal: Myalgia; Leg cramps

Nervous: Hypertonia; Confusion; Somnolence; Libido decreased; Neuropathy; Nervousness

Respiratory: Lung disorder; Asthma; Epistaxis; Sinusitis

Skin and Appendages: Dry skin; Alopecia; Pruritus; Herpes zoster; Skin carcinoma; Skin disorder

Special Senses: Cataract specified

Urogenital: Dysuria; Urinary urgency; Hydronephrosis; Urinary tract disorder

Abnormal Laboratory Test Values:

Laboratory abnormalities including elevated AST, ALT, bilirubin, BUN, and creatinine and decreased hemoglobin and white cell count have been reported in both CASODEX-LHRH analogue treated and flutamide-LHRH analogue treated patients.

Postmarketing Experience:

Rare cases of interstitial pneumonitis and pulmonary fibrosis have been reported with CASODEX.

OVERDOSAGE

Long-term clinical trials have been conducted with dosages up to 200 mg of CASODEX daily and these dosages have been well tolerated. A single dose of CASODEX that results in symptoms of an overdose considered to be life-threatening has not been established.

There is no specific antidote; treatment of an overdose should be symptomatic.

In the management of an overdose with CASODEX, vomiting may be induced if the patient is alert. It should be remembered that, in this patient population, multiple drugs may have been taken. Dialysis is not likely to be helpful since CASODEX is highly protein bound and is extensively metabolized. General supportive care, including frequent monitoring of vital signs and close observation of the patient, is indicated.

DOSAGE AND ADMINISTRATION

The recommended dose for CASODEX therapy in combination with an LHRH analogue is one 50 mg tablet once daily (morning or evening), with or without food. It is recommended that CASODEX be taken at the same time each day. Treatment with CASODEX should be started at the same time as treatment with an LHRH analogue.

Dosage Adjustment in Renal Impairment:

No dosage adjustment is necessary for patients with renal impairment (see CLINICAL PHARMACOLOGY, Special Populations, Renal Insufficiency).

Dosage Adjustment in Hepatic Impairment:

No dosage adjustment is necessary for patients with mild to moderate hepatic impairment. Although there is a 76% (5.9 and 10.4 days for normal and impaired patients, respectively) increase in the half-life of the active enantiomer of bicalutamide in patients with severe liver impairment (n=4), no dosage adjustment is necessary (see CLINICAL PHARMACOLOGY, Special Populations, Hepatic Impairment, PRECAUTIONS and WARNINGS sections).

HOW SUPPLIED**50 mg Tablets:**

(NDC 0310-0705) White, film-coated tablets (identified on one side with "CDX50" and on the reverse with the "CASODEX logo") are supplied in unit dose blisters of 30 tablets per carton (0310-0705-39), bottles of 30 tablets (0310-0705-30) and bottles of 100 tablets (0310-0705-10). Store at controlled room temperature, 20°-25°C (68°-77°F).

AstraZeneca

Manufactured for

AstraZeneca Pharmaceuticals LP

Wilmington, DE 19850

By: IPR Pharmaceuticals Inc.

Carolina, PR 00984

Made in USA

Rev 10-12-05

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/s/

Robert Justice
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