

NEW ZEALAND DATA SHEET

NAME OF MEDICINE

COSUDEX
Bicalutamide 50 mg tablets

PRESENTATION

COSUDEX 50 mg is a white film-coated tablet containing 50 mg bicalutamide and is impressed with CDX50 on one side and a logo on the other.

USES

ACTIONS

COSUDEX 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 COSUDEX can result in antiandrogen withdrawal syndrome in a subset of patients.

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

PHARMACOKINETICS

COSUDEX 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 COSUDEX, 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 µg/mL are observed during daily administration of 50 mg doses of COSUDEX. 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.

COSUDEX is highly protein bound (racemate 96%, R-bicalutamide 99.6%) 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 Cosudex 150 mg was 4.9 µg/mL. The amount of bicalutamide potentially delivered to a female partner during intercourse is low and equates to approximately 0.3 µg/kg. This is below that required to induce changes in offspring of laboratory animals.

INDICATIONS

Treatment of advanced prostate cancer in combination with GnRH (LHRH) agonist therapy or surgical castration.

Prevention of disease flare associated with the use of LHRH agonists.

DOSAGE AND ADMINISTRATION**AS COMBINATION THERAPY IN ADULT MALES INCLUDING THE ELDERLY**

One tablet (50 mg) once a day.

Treatment with COSUDEX should be started at the same time as treatment with a GnRH (LHRH) agonist or surgical castration.

CHILDREN

COSUDEX is contraindicated in children.

USE IN ADULT MALES WITH RENAL IMPAIRMENT

No dosage adjustment is necessary for patients with renal impairment.

USE IN ADULT MALES WITH 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).

CONTRAINDICATIONS

COSUDEX is contraindicated in females and children.

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

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, COSUDEX 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.

Severe hepatic changes and hepatic failure have been observed rarely with COSUDEX, and fatal outcomes have been reported (see ADVERSE EFFECTS). COSUDEX 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 COSUDEX in combination with LHRH agonists.

PREGNANCY AND LACTATION

COSUDEX is contraindicated in females and must not be given to pregnant women or nursing mothers.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

During treatment with COSUDEX, somnolence has been reported and those patients who experience this symptom should observe caution when driving or using machines.

ADVERSE EFFECTS

Unless specified, the following frequency categories were assigned based on the incidence of the adverse event in the 50 mg COSUDEX plus LHRH analogue arm of the pivotal LHRH combination study.

Frequency	System Organ Class	Event
Very common (≥10%)	Blood and Lymphatic	Anaemia
	Nervous System Disorders	Dizziness
	Vascular disorders	Hot flush
	Gastrointestinal disorders	Abdominal pain, constipation, nausea
	Renal and urinary disorders	Haematuria
	Very common (continued)	Reproductive system and breast disorders
	General disorders and administration site conditions	Asthenia, oedema
Common (≥1% and <10%)	Metabolism and nutrition disorders	Decreased appetite
	Psychiatric disorders	Decreased libido, depression
	Nervous System Disorders	Somnolence
	Cardiac disorders	Myocardial infarction (fatal outcomes have been reported) ^e , Cardiac failure ^e
	Gastrointestinal disorders	Dyspepsia, flatulence,
	Hepatobiliary disorders	Hepatotoxicity, jaundice, hypertransaminasaemia ^b
	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

Frequency	System Organ Class	Event
Uncommon (≥0.1% and <1%)	Immune system disorders	Hypersensitivity, angioedema, and urticaria
	Respiratory, thoracic and mediastinal disorders	Interstitial lung disease ^c . Fatal outcomes have been reported.
Rare (≥0.01% and <0.1%)	Hepatobiliary disorders	Hepatic failure ^d . Fatal outcomes have been reported.

^a May be reduced by concomitant castration.

^b Hepatic changes are rarely severe and were frequently transient, resolving or improving with continued therapy or following cessation of therapy.

^c 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.

^d Listed as an adverse drug reaction following review of post-marketed data. Frequency has been determined from the incidence of reported adverse events of hepatic failure in patients receiving treatment in the open-label COSUDEX arm of the 150 mg EPC studies.

^e 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 COSUDEX 50 mg was used in combination with LHRH agonists.

INTERACTIONS

There is no evidence of any pharmacodynamic or pharmacokinetic interactions between COSUDEX and GnRH analogues.

In vitro studies have shown that R-bicalutamide is an inhibitor of CYP3A4, with lesser inhibitory effects on CYP 2C9, 2C19 and 2D6 activity.

Although *in vitro* studies have suggested the potential for COSUDEX to inhibit cytochrome 3A4, a number of clinical studies show the magnitude of any inhibition is unlikely to be of clinical significance.

In vitro studies have shown that COSUDEX can displace the coumarin anticoagulant, warfarin, from its protein binding sites. It is therefore recommended that if COSUDEX is started in patients who are already receiving coumarin anticoagulants, prothrombin time should be closely monitored.

Although there is no evidence of any pharmacodynamic or pharmacokinetic interactions between COSUDEX 50 mg and LHRH agonists at steady state, COSUDEX 50 mg may prevent the harmful clinical consequences of flare associated with the start of LHRH agonist therapy.

OVERDOSAGE

There is no human experience of overdose. There is no specific antidote; treatment should be symptomatic. Dialysis may not be helpful, since COSUDEX is highly protein bound and is not recovered unchanged in the urine. General supportive care, including frequent monitoring of vital signs, is indicated.

PHARMACEUTICAL PRECAUTIONS**INSTRUCTIONS FOR USE/HANDLING**

No special precautions required.

INCOMPATIBILITIES

None known.

SHELF LIFE

5 years

SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C.

MEDICINE CLASSIFICATION

Prescription Medicine.

PACKAGE QUANTITIES

COSUDEX 50 mg tablets, blister pack 28 tablets.

FURTHER INFORMATION**PRECLINICAL INFORMATION**

Bicalutamide is a potent antiandrogen and a mixed function oxidase enzyme inducer in animals. Target organ changes, including tumour induction and minor clinical pathology changes, are related to these activities. Enzyme induction and minor cardiac changes seen in dogs have not been observed in man. There are no preclinical findings that preclude the administration of COSUDEX to prostate cancer patients.

LIST OF EXCIPIENTS

- Lactose monohydrate
- Sodium Starch Glycollate
- Povidone
- Magnesium Stearate
- Hypromellose
- Macrogol 300
- Titanium Dioxide

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