Drug Monograph

Drug Name | Mechanism of Action and Pharmacokinetics | Indications and Status | Adverse Effects | Dosing | Administration Guidelines | Special Precautions | Interactions | Recommended Clinical Monitoring | Supplementary Public Funding | References | Disclaimer

A - Drug Name

bicalutamide

COMMON TRADE NAME(S): Casodex® (multiple brands available)

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B - Mechanism of Action and Pharmacokinetics

Bicalutamide is a selective, non-steroidal antiandrogen. It binds to the androgen receptors in target tissue and competitively inhibits the action of androgen, resulting in regression of prostatic tumours. Bicalutamide is a racemate and the (R)-enantiomer is primarily responsible for its anti-androgenic activity.

Absorption	Oral: Well absorbed. Food does not appear to affect the rate or extent of absorption.	
Distribution	The (R)-enantiomer accumulates about 10-fold with daily administration.	
	Cross blood brain barrier?	Probably poor penetration
	PPB	> 96 %
Metabolism	Bicalutamide undergoes stereospecific metabolism, with hepatic biotransformation via glucuronidation and oxidation. The (S)-enantiomer is very rapidly cleared relative to the (R)-enantiomer.	
	Active metabolites	R-enantiomer
Elimination	Metabolites are eliminated equally via renal and biliary routes.	

Feces	43 % over 9 days
Urine	36 % over 9 days
Half-life	1 week

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C - Indications and Status

Health Canada Approvals:

For use in combination with LHRH analogue or surgical castration in the treatment of metastatic (stage D2) prostate cancer.

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D - Adverse Effects

Emetogenic Potential: Not applicable

Extravasation Potential: Not applicable

The following adverse effects were observed in metastatic prostate cancer patients, in combination with a LHRH agonist.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Arrhythmia (<5%)	D
	Arterial thromboembolism (<5%)	E D
	Cardiotoxicity (4%)	D
	Hypertension (8%)	D
	Venous thromboembolism (<5%)	E D
Dermatological	Alopecia (4%)	E
	Hirsutism (2%)	D
	Photosensitivity (rare)	E
	Rash (9%)	E
Gastrointestinal	Abdominal pain (11%)	E
	Anorexia (6%)	E

	Constipation (22%)	E
	Diarrhea (12%)	I
	Dyspepsia (7%)	E
	GI hemorrhage (<5%)	E
	GI obstruction (<5%)	E
	Nausea, vomiting (14%)	I
	Weight changes (7%)	D
General	Edema (13%)	D
	Fatigue (22%)	E
Hematological	Anemia (13%)	D
Hepatobiliary	↑ LFTs (7%) (may be severe)	D
Hypersensitivity	Hypersensitivity (1%) (angioedema, urticaria)	I
Infection	Infection (18%)	D
Metabolic / Endocrine	↑ Ca (<5%)	D
	↑ Cholesterol (<5%)	D
	Hyperglycemia (7%)	D
Musculoskeletal	Musculoskeletal pain (35%)	E
	Osteoporosis (4%) /Fractures	D
Nervous System	Anxiety (5%)	E
	Cognitive disturbance (<5%)	E
	Depression (4%)	E
	Dizziness (10%)	I E
	Headache (7%)	E
	Insomnia (7%)	I E
	Neuropathy (8%)	E
Ophthalmic	Cataract (<5%)	E D
	Conjunctivitis (<5%)	E D
Renal	Creatinine increased (<5%)	E
Reproductive and breast disorders	Androgen deprivation symptoms (53%)	D
Respiratory	Cough, dyspnea (13%)	D
	Pneumonitis (rare)	D
Urinary	Urinary symptoms (12%)	E

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.

"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.
Dose-limiting side effects are underlined.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

Bicalutamide is well-tolerated in general, with expected adverse effects including hot flashes, breast tenderness and gynecomastia, which may be reduced by concomitant surgical or medical castration. Bicalutamide may also be associated with occurrence of diarrhea, nausea, vomiting and fatigue. **Fluid retention** may occur.

In the pivotal trial comparing bicalutamide to flutamide, an imbalance in cardiac deaths was noted (18 patients vs. 9 patients receiving flutamide). The combined use of anti-androgen plus LHRH analogue / surgical castration increases risk of **cardiovascular** disease and osteoporosis or the potential of QT prolongation. **(**especially in patients with risk factors). Assess benefit-risk ratio in these patients before starting treatment. Use bicalutamide with caution in patients with cardiac disease as well as in patients at risk for prolonged QTc.

Bone loss may occur during the hypoandrogenic state caused by long-term combined androgen blockade. Risk factors such as older patients, pre-existing osteopenia, family history of osteoporosis, chronic use of corticosteroids or anticonvulsants, or chronic alcohol/tobacco abuse should be carefully considered before starting treatment. **Reduction of glucose tolerance** has also been observed in patients receiving combined androgen blockade.

Severe, sometimes fatal **hepatic** failure and hepatic changes have been observed rarely. Hepatotoxicity generally occurs within the first 3-4 months of treatment. **Interstitial lung disease (ILD)**, including fatal reports, has been reported rarely, especially at doses of over 50mg.

In some patients, antiandrogens may increase rather than inhibit growth of prostate cancer; patients with increasing PSA or worsening symptoms should discontinue bicalutamide and be assessed for 6-8 weeks for an antiandrogen withdrawal response.

Photosensitivity reactions have been reported rarely. If the reaction is persistent and/or severe, appropriate symptomatic treatment should be given.

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E - Dosing

Refer to protocol by which patient is being treated. Bicalutamide should be started at the same time as the LHRH analogue for patients who have not had surgical castration. Bicalutamide doses of 150 mg/day **should not** be used as this increases mortality (phase III localized prostate trials).

Patients should be advised to avoid direct exposure to excessive sunlight and may consider the use of sunscreens.

Adults:

Oral: 50 mg daily

Dosage with Toxicity:

Toxicity	Action
Myelosuppression	No adjustment required
Pneumonitis	Hold; investigate. If confirmed, discontinue.
Cardiac failure, arterial or venous thromboembolism	Discontinue
Grade 3 or 4 LFT increases	Discontinue

Dosage with Hepatic Impairment:

No adjustment required in the presence of mild hepatic impairment. Caution should be exercised in moderate to severe hepatic impairment, as bicalutamide is extensively metabolized in the liver. Elimination is lower in subjects with severe hepatic impairment, leading to increased accumulation.

Dosage with Renal Impairment:

No adjustment required.

Dosage in the elderly:

No adjustment required.

Children:

CONTRAINDICATED in children

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F - Administration Guidelines

- Outpatient prescription for home administration
- May be taken with or without food

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G - Special Precautions

Contraindications:

- in patients with hypersensitivity to the drug or any of its components
- in localized prostate cancer undergoing ”watchful waiting”
- in females and children

Other Warnings/Precautions:

- contains lactose; use should be carefully considered in patients with hereditary galactose intolerance, severe lactase deficiency or glucose-galactose malabsorption
- results in fluid retention and should be used with caution in patients with cardiac disease as well as in patients at risk for prolonged QTc

Pregnancy and Lactation:

- Genotoxicity: No
- Fetotoxicity: Yes
  Bicalutamide is **CONTRAINDICATED** in pregnancy and breastfeeding. Patients and their partners should use adequate contraception for at least 130 days after the last dose.
- Fertility effects: Probable
  Male fertility impairment may be reversible.

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H - Interactions

No drug/drug interactions were observed with LHRH analogues.

AGENT	EFFECT	MECHANISM	MANAGEMENT
Drugs metabolized by CYP3A4	Bicalutamide (R-enantiomer) inhibits CYP3A4 (and 2C9, 2C19, 2D6 to a lesser extent)	↑ levels of drugs	Caution when using with drugs with narrow therapeutic index
warfarin	↑ PT/INR	Increased anticoagulant effect and risk of bleeding; bicalutamide displaces warfarin from protein binding	Monitor PT/INR closely; warfarin dose may require adjustment
Drugs that may prolong QT interval	Potential risk in ↑ QT interval	Additive effects when combined with LHRH analogue and anti-androgen	Caution and monitor

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I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
Liver function tests	baseline and regular
Electrolytes	baseline, also during treatment for patients at risk of electrolyte abnormality and QT prolongation
Blood glucose	especially in diabetic patients; baseline and regular
ECG	baseline; also during treatment for patients at risk of QT prolongation
Bone density	as clinically indicated
INR, for patients on warfarin	as clinically indicated
Clinical assessment for fluid retention, pneumonitis, androgen withdrawal effects, cardiovascular, hepatic effects and thromboembolism	at each visit

Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

Suggested Clinical Monitoring

Monitor Type	Monitor Frequency
Hemoglobin	baseline and as clinically indicated

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J - Supplementary Public Funding

ODB - General Benefit (
ODB Formulary
)

- bicalutamide ()

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K - References

Prescribing Information: Casodex® (bicalutamide). AstraZeneca US Inc., December 2008.

Product Monograph: Casodex® (bicalutamide). AstraZeneca Canada Inc., July 13, 2017.

November 2017 modified contraception, interactions and monitoring sections

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L - Disclaimer

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

The information set out in the drug monographs, regimen monographs, appendices and symptom management

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