DRUG NAME: Bicalutamide

SYNONYM(S): ICI 176,334

COMMON TRADE NAME(S): CASODEX®

CLASSIFICATION: hormonal agent

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:

Bicalutamide is a non-steroidal androgen receptor inhibitor. It is a racemate with the R-isomer being primarily responsible for the anti-androgenic activity. Prostate cancer is known to be androgen sensitive and responsive to treatment that counteracts the effects of androgen. By binding to cytosol androgen receptors in the target tissue, bicalutamide competitively inhibits the action of androgens. Bicalutamide does not suppress androgen production and may increase serum androgen concentrations.[1,2]

PHARMACOKINETICS:

Oral Absorption	extensively absorbed and unaffected by food	
Distribution	highly protein-bound	
	cross blood brain barrier?	no information found
	volume of distribution	no information found
	plasma protein binding	96%
Metabolism	extensive metabolism via both oxidation and glucuronidation	
	active metabolite(s)	no information found
	inactive metabolite(s)	hydroxybicalutamide, glucuronide conjugate
Excretion	urinary and fecal excretion	
	urine	36% over 9 days
	feces	43% over 9 days
	terminal half life	one week (R-isomer)
	clearance	no information found
Elderly	pharmacokinetics of the R-isomer are unaffected by age	
Children	pharmacokinetics of the R-isomer are unaffected by age	

Adapted from standard reference[1,3,4] unless specified otherwise.

USES:

Primary uses:

*Prostate cancer[1]

Other uses:

*Health Canada approved indication

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SPECIAL PRECAUTIONS:

Contraindications:
- not indicated for use in women[1]

Caution:
- ***high-dose bicalutamide*** (e.g., 150 mg daily) is not routinely recommended in patients with localized prostate cancer who would otherwise undergo watchful waiting or active surveillance as this dose has been associated with increased mortality; refer to protocol by which patient is being treated[1,4,5]
- patients with history of ***heart disease***, cardiovascular risk factors, long QT syndrome, electrolyte abnormalities, CHF, or concurrent administration with other QT prolonging drugs may be at increased risk for cardiovascular side effects[1]
- ***reduced glucose tolerance*** and/or glycated hemoglobin (HbA1c) may occur with combined androgen deprivation therapy in patients with or without pre-existing diabetes; assess blood glucose and/or HbA1c prior to starting treatment[1]
- ***anemia*** occurs with testosterone suppression; assess anemia risk prior to starting treatment[1]
- risk of ***osteoporosis*** and ***skeletal fractures*** increases with long-term combined androgen deprivation therapy; assess benefit of treatment in patients with significant risk factors for decreased bone mineral content and/or bone mass[1]

Carcinogenicity: Based on animal studies, there is no carcinogenic potential in humans.[1,4]

Mutagenicity: not mutagenic in Ames test or mammalian *in vivo* and *in vitro* mutation tests[1,4]

Fertility: In animal studies, testicular atrophy and inhibition of spermatogenesis occurred at exposures higher than those seen following human clinical exposure. The precoital interval and time to successful mating was also increased in animal subjects, but no effects on fertility following successful mating were observed. These effects were reversible by 7 weeks following the last dose. Based on these effects, a period of subfertility or infertility should be assumed in treated human males. In female test animals, estrous cycle irregularity occurred at exposures higher than those seen following human clinical exposure, but no effects on female fertility were observed.[1,4]

Pregnancy: In animal studies, impotency, reduced anogenital distance, and feminization leading to hypospadias were observed in male offspring of treated females at exposures lower than those seen following human clinical exposure. Reduced pregnancy rates were observed in female offspring of treated females. Based on these effects, male patients with female partners of childbearing potential should use effective contraception during treatment and for 130 days following the last dose.[1,4]

Breastfeeding is not recommended due to the potential secretion into breast milk. In animal studies, bicalutamide was detected in breast milk.[1]

SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important.[6] **Incidence data in the Side Effect table is only based on combination therapy with an LHRH analogue unless otherwise indicated.**

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia	anemia (11-13%)
	ecchymosis (<5%)
	thrombocytopenia (<5%)
cardiac see paragraph following **Side Effects** table	***cardiac failure*** (4%)
	myocardial infarction (3%); fatal events reported
endocrine	diabetes mellitus (<5%)
eye	abnormal vision (<5%)
	cataract (<5%)
	conjunctivitis (<5%)
gastrointestinal	*emetogenic potential:* minimal (rare)[7]
	abdominal pain (11%)
	constipation (22% with 50 mg dose in combination therapy, 9% with 150 mg dose in monotherapy)[8]
	diarrhea (12%)
	dyspepsia (7%)
	flatulence (6-7%)
	gastrointestinal disorder (including dysphagia, gastritis, melena, periodontal abscess, and dry mouth) (<5%)
	intestinal obstruction (<5%)
	nausea (14-15%)
	rectal disorder (including rectal hemorrhage) (<5%)
	vomiting (4-6%)
general disorders and administration site conditions	allergic reaction (<5%)
	asthenia (22% with 50 mg dose in combination therapy, 11% with 150 mg dose in monotherapy)[8]
	chills (<5%)
	cyst (<5%)
	edema, face (<5%)
	edema, peripheral (13%)
	fever (<5%)
	flu syndrome (7%)
	pain, chest (8%)
	pain, general (35%)
hepatobiliary	***hepatic failure*** (1%); fatal events reported, hepatotoxicity generally occurs within the first 3 to 4 months of treatment
immune system	hypersensitivity, including angioedema and urticaria (1%)

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infections and infestations	bronchitis (6%)
	herpes zoster (<5%)
	infection (18%)
	pharyngitis (8% with 50 mg dose in combination therapy, 11% with 150 mg dose in monotherapy)[8]
	pneumonia (4%)
	sepsis (<5%)
	sinusitis (<5%)
	urinary tract infection (9%)
injury, poisoning, and procedural complications	hernia (<5%)
	pathological fracture (4%)
investigations	alkaline phosphatase increase (5%)
	BUN increase (<5%)
	creatinine increase (<5%)
	hypercalcemia (<5%)
	liver enzyme test increase (7%)
	weight increase (5%)
	weight loss (7%)
metabolism and nutrition	appetite decrease (6%)
	dehydration (<5%)
	gout (<5%)
	hypercholesterolemia (<5%)
	hyperglycemia (6-7%)
	hypoglycemia (<5%)
musculoskeletal and connective tissue	arthritis (5%)
	arthralgia (9% with 150 mg dose in monotherapy)[8]
	back pain (25% with 50 mg dose in combination therapy, 10% with 150 mg dose in monotherapy)[8]
	bone disorders (<5%)
	bone pain (9%)
	leg cramps (<5%)
	myalgia (<5%)
	neck pain (<5%)
	neck rigidity (<5%)
neoplasms	gastrointestinal carcinoma (<5%)
	neoplasm (<5%)
	skin carcinoma (<5%)
nervous system	confusion (<5%)
	dizziness (10%)

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	headache (7%)
	hypertonia (<5%)
	myasthenia (7%)
	nervousness (<5%)
	neuropathy (<5%)
	paresthesia (8%)
	somnolence (3%)
psychiatric	anxiety (5%)
	decreased libido (2%)
	depression (4%)
	insomnia (7%)
renal and urinary	balanitis (<5%)
	bladder stenosis (<5%)
	dysuria (<5%)
	hematuria (12%)
	hydronephrosis (<5%)
	kidney calculus (<5%)
	nocturia (12%)
	prostatic disorder (<5%)
	urinary tract disorder (including urinary frequency (6%), urinary incontinence (4%), urinary retention (4%), and urinary urgency (2-5%))
reproductive system and breast disorders see paragraph after **Side Effects** table	***breast pain/tenderness*** (6% with 50 mg dose in combination therapy; 39-74% with 150 mg dose in monotherapy)[8]
	erectile dysfunction (7%)
	gynecomastia (9% with 50 mg dose in combination therapy; 38-70% with 150 mg dose in monotherapy)[8,9]; see paragraph after **Side Effects** table
	impotence (9% with 150 mg dose in monotherapy)[8]
	pelvic pain (21%)
respiratory, thoracic and mediastinal	asthma (<5%)
	cough (8%)
	dyspnea (13%)
	epistaxis (<5%)
	interstitial lung disease (ILD) (<5%); fatal events reported, see paragraph after **Side Effects** table
	lung disorder (<5%)
	pleural effusion (<5%)
	rhinitis (4%)
	voice alteration (<5%)
skin and subcutaneous tissue	alopecia (4%)
	hirsutism (2%)

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	photosensitivity reaction (<5%)
	pruritus (3%)
	rash (9% with 50 mg dose in combination therapy, 10% with 150 mg dose in monotherapy)[8]
	skin disorder (including dry skin, skin hypertrophy and skin ulcer) (<5%)
	sweating (6%)
vascular	***hot flashes*** (53% with 50 mg dose in combination therapy, 9-17% with 150 mg dose in monotherapy)[8,9]
	hypertension (8%)

Adapted from standard reference[1,4] unless specified otherwise.

Gynecomastia and breast pain/tenderness are more common with 150 mg/day dosing in monotherapy than with 50 mg/day dosing in combination therapy. These effects are related to the unopposed action of circulating estrogen during monotherapy, in contrast to the reduced circulating levels of testosterone and estrogen in combination therapy.[1,8,10]

Interstitial lung disease (ILD), including interstitial pneumonitis and pulmonary fibrosis, may rarely occur. Fatal events have been reported. ILD is associated more often with daily doses greater than 50 mg. Withhold bicalutamide for worsening respiratory symptoms such as dyspnea, cough and fever and promptly investigate. Permanently discontinue bicalutamide if ILD is confirmed.[1,4]

A possibly increased risk of ***myocardial infarction, sudden cardiac death, and stroke*** has been associated with androgen deprivation therapy in men, possibly due to its effects on traditional cardiovascular risk factors, including serum lipoproteins, insulin sensitivity, and obesity. Monitor for signs and symptoms suggestive of cardiovascular disease and manage as indicated. Androgen deprivation therapy also has the potential to ***prolong QT/QTc interval*** on ECG; therefore, concurrent therapy with other QT prolonging drugs may increase the risk of potentially fatal arrhythmias. Assess patients with long QT syndrome, electrolyte abnormalities, or CHF for increased cardiovascular risk.[1]

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
warfarin[1]	increased risk of bleeding	displacement of warfarin from binding sites	monitor INR with increased frequency when bicalutamide is started or discontinued; adjust warfarin dose as needed

In vitro, the R-enantiomer of bicalutamide is an ***inhibitor*** of ***CYP 3A4***, with lesser inhibitory effects on CYP 2C9, CYP 2C19, and CYP 2D6. Based on clinical studies, the magnitude of this inhibition is considered unlikely to be clinically significant for most substrates of cytochrome P450. Monitor for increased toxicity of coadministered CYP 3A4 substrates with a narrow therapeutic index.[1]

SUPPLY AND STORAGE:

Oral: AstraZeneca Canada Inc. and Teva Canada Limited supply bicalutamide as 50 mg film-coated tablets. Tablets contain lactose. Store at room temperature.[1]

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DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response, and concomitant therapy.

***Adults*:**

BC Cancer usual dose noted in ***bold, italics***

Oral:	***50 mg (range 50-150 mg) PO once daily***[1,4,5,8,9,11] Administer with food or on an empty stomach
Concurrent radiation:	no information found
Dosage in renal failure:	no adjustment required[1,4]
Dosage in hepatic failure:	mild hepatic impairment: no adjustment required[1,4] moderate/severe hepatic impairment: no information found; monitor for increased toxicity as increased accumulation may occur[1,4]
Dosage in dialysis:	no information found

Children: safety and efficacy has not been established

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