DRUG NAME: Bicalutamide

SYNONYM(S): ICI 176,334

COMMON TRADE NAME(S): CASODEX®

CLASSIFICATION: Endocrine antihormone

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

MECHANISM OF ACTION:

Bicalutamide is a nonsteroidal antiandrogen devoid of other endocrine activity which competes with androgen for the binding of androgen receptors.[1] It does not suppress androgen production and may increase serum androgen concentrations.[2] Bicalutamide is a racemate with the R-isomer primarily responsible for the antiandrogenic activity. Prostate cancer is mostly androgen-dependent and can be treated with surgical or chemical castration. To date, antiandrogen monotherapy has not consistently been shown to be equivalent to castration,[3-5] although it may be considered for patients who want to maintain sexual potency.[2,6] Antiandrogens are often used in combination with luteinizing hormone releasing hormone agonists (LHRHa), either for 2-4 weeks at the initiation of LHRHa to prevent or minimize temporary worsening of symptoms ("flare" reaction),[1]or sometimes to inhibit the effects of testicular and adrenal androgens (maximum androgen blockade).[3] Antiandrogen withdrawal may lead to a paradoxical decrease in serum prostate-specific antigen level in some patients.[7] In animal studies, bicalutamide has a fourfold greater affinity for the prostate androgen receptor than 2-hydroxyflutamide, the active metabolite of flutamide.[8] Bicalutamide and flutamide are not completely cross-resistant.[6]

PHARMACOKINETICS:

Interpatient variability	wide range of interpatient variability[9]	
Oral Absorption	Extensively absorbed and unaffected by food.[10] Absolute bioavailability is not known.[11]	
	time to peak plasma concentration	up to 48 h,[12] approaching steady state at one month[9]
Distribution	no information found	
	cross blood brain barrier?	no information found
	volume of distribution	no information found
	plasma protein binding	96%
Metabolism	Extensive, hepatic; R-isomer oxidized to an inactive metabolite for further glucuronidation[1]	
	active metabolite(s)	none
	inactive metabolite(s)	hydroxybicalutamide, glucuronide conjugate[11]
Excretion	urinary and fecal excretion	
	urine	36% over 9 days
	feces	43% over 9 days
	terminal half life	one week for R-isomer
	clearance	no information found
Elderly	no clinically significant difference	

Adapted from reference[10] unless specified otherwise.

USES:

Primary uses:
* Prostate cancer[13]

∗ Health Canada Therapeutic Products Programme approved indication

No pediatric indications.

SPECIAL PRECAUTIONS:

Contraindicated in females.[10]

Bicalutamide 150 mg should NOT be administered to patients with localized disease who would otherwise undergo watchful waiting as treatment at this dose is associated with increased mortality.[14,15]

Hepatic impairment: Use with caution in patients with moderate to severe hepatic impairment. Metabolism may be delayed, resulting in prolonged elimination half-life and increased risk of toxicity.[10]

Cardiac disease: Use with caution in patients with cardiac disease. Elevated plasma testosterone and estradiol levels may occur, and could cause fluid retention.[10]

Carcinogenicity: Animal studies showed no carcinogenic potential in humans.[2,10]

Mutagenicity: Not mutagenic in Ames test and mammalian *in vitro* mutation tests, and not clastogenic in mammalian *in vitro* and *in vivo* chromosome tests.[10]

Fertility: May inhibit spermatogenesis.[1]

Pregnancy: FDA Pregnancy Category X.[1] Studies in animals or human beings have shown fetal abnormalities, or there is evidence of fetal risk based on human experience, or both, and the risk of the use of the drug in pregnant women clearly outweighs any possible benefit. The drug is contraindicated in women who are or may become pregnant.

Breastfeeding is not recommended due to the potential secretion into breast milk.

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. When placebo-controlled trials are available, adverse events are included if the incidence is >5% higher in the treatment group.

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood/bone marrow febrile neutropenia	anemia (7%)
	neutropenia (1-5%)
cardiovascular (general)	hypertension (5%)
	peripheral edema (8%)
constitutional symptoms	fatigue (15%)
	sweating (6%)
	weight gain (1-5%)
	weight loss (4%)
dermatology/skin	alopecia (1-5%)

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	rash (6%)
endocrine	breast tenderness (4%; 39%*)[2]
	gynecomastia (6%; 38%*)[2]
	hot flashes (51%; 12%*)[2]
gastrointestinal	*emetogenic potential:* nonemetogenic
	anorexia (1-5%)
	constipation (17%)
	diarrhea (10%)
	dry mouth (1-5%)
	dyspepsia (1-5%)
	flatulence (5%)
	nausea (11%)
	vomiting (3%)
hepatic	increased bilirubin levels (1-5%)
	increased transaminase levels (6%)
infection	infection (10%)
	urinary tract infection (6%)
metabolic/laboratory	increased BUN (1-5%)
	hyperglycemia (5%)
neurology	dizziness (7%)
	insomnia (5%)
	neuropathy, sensory (6%)
	somnolence (1-5%)
pain	abdominal pain (8%)
	back pain (15%)
	bone pain (4%)
	chest pain (6%)
	headache (4%)
	pain (27%)
	pelvic pain (13%)
pulmonary	dyspnea (7%)
	pulmonary infiltrates and eosinophilia (rare)[16,17]
renal/genitourinary	increased creatinine (1-5%)
	hematuria (7%)
	nocturia (9%)
	urinary incontinence (2%)
sexual/reproductive function	impotence (5%)
	decreased libido (1-5%)
	reduced sperm count[1]
syndromes	flu-like symptoms (4%)

Adapted from reference[10] unless specified otherwise.
* Side effects and incidences were those of bicalutamide when used with LHRHa, unless marked with asterisk (*) when it is used as monotherapy 150 mg PO daily.

Diarrhea is less common with bicalutamide (10%) than with flutamide (24%). Withdrawal from clinical trials because of diarrhea was also less common with bicalutamide (0.5%) than with flutamide (6%).[8]

Fatigue: Bicalutamide monotherapy causes a slightly higher incidence of fatigue than surgical castration.[2]

Gynecomastia and breast tenderness: Gynecomastia is more common with bicalutamide 150 mg monotherapy (38%) than combination therapy with LHRHa (6%). Breast tenderness is also more common with monotherapy (39%) than combination therapy (4%).[2] Gynecomastia and breast tenderness are related to the unopposed action of circulating estrogen during monotherapy, in contrast to the reduced circulating levels of testosterone and estrogen during combination therapy.[3]

Hot flashes are less common with monotherapy (12%) than combination therapy with LHRHa (51%),[2] probably due to the hormonal changes described above.[3]

Erectile function is not significantly altered with bicalutamide monotherapy.[18]

Skin changes are uncommon (less than 5%) and due to reduced androgenic stimulation of sebaceous gland (eg, dry skin, pruritus and rash).[3]

Dose-related side effects: No dose-related increase in adverse events was reported over the range of 50 to 200 mg daily doses.[2,19]

Decreased bone mineral density has been seen with castration but not with bicalutamide. Thus, patients treated with bicalutamide monotherapy may be at less risk for osteoporotic fractures compared with castrated patients.[20]

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
LHRH analogues[21]	no interactions have been identified		
warfarin[10]	increased risk of bleeding	displacement of warfarin from protein binding sites	monitor INR with increased frequency when bicalutamide is being started or discontinued; adjust warfarin dose as needed.

In vitro studies have shown that the R-entantiomer of bicalutamide is an inhibitor of CYP 3A4, with lesser inhibitory effects on CYP 2c9, 2C19, and 2D6. Clinical studies, however, have shown that the magnitude of this inhibition is unlikely to be clinically significant for most substances metabolized by cytochrome P450. Clinical significance is unknown for those enzyme substrates having a narrow therapeutic index.[21]

SUPPLY AND STORAGE:

Oral: AstraZeneca Pharma and Novopharm Limited supply bicalutamide as 50 mg film-coated tablets. Select non-medicinal ingredients: lactose. Store at room temperature.[14,15]

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated.

Adults:

BCCA usual dose noted in ***bold, italics***

Oral: ***50 mg PO once daily***.[14,15]
Administer with food or on an empty stomach.[10]

Dosage in renal failure: no adjustment required[10]

BCCA usual dose noted in ***bold, italics***

Dosage in hepatic failure: No adjustment required for mild hepatic failure.
Elimination may be slower in patients with severe hepatic impairment, leading to accumulation of bicalutamide. Use with caution in patients with moderate to severe hepatic impairment.[10]

Dosage in dialysis: dialysis is not likely to remove significant quantities from the body because of extensive protein binding[1]

Children: no information found

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