DRUG NAME: Abiraterone

SYNONYM(S): abiraterone acetate [1]

COMMON TRADE NAME(S): ZYTIGA®

CLASSIFICATION: endocrine anti-hormone

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

MECHANISM OF ACTION:

Abiraterone acetate is converted, *in vivo,* to abiraterone, which selectively inhibits the CYP17 enzyme in testicular, adrenal and prostate tumour tissues. CYP17 enzyme inhibition reduces the conversion of pregnenolone and progesterone into testosterone precursors, DHEA and androstenedione. When used in addition to androgen deprivation therapies (luteinizing hormone releasing hormone [LHRH] agonists or orchiectomy), abiraterone further decreases androgen production to below castrate levels. [1,2]

PHARMACOKINETICS:

Oral Absorption	increased with food; time to peak plasma concentration 2 h	
Distribution	extensively distributed to peripheral tissues	
	cross blood brain barrier?	no information found
	volume of distribution	5630 L
	plasma protein binding	>99%
Metabolism	abiraterone acetate rapidly converted to abiraterone in the liver	
	active metabolite(s)	abiraterone (primary)
	inactive metabolite(s)	abiraterone sulphate; N-oxide abiraterone sulphate
Excretion	primarily in feces	
	urine	5%
	feces	88%; abiraterone acetate (55%); abiraterone (22%)
	terminal half life	12 h
	clearance	no information found
Elderly	no clinically significant difference	

Adapted from standard reference [1] unless specified otherwise.

USES:

Primary uses:

*Prostate cancer [1]

Other uses:

*Health Canada approved indication

SPECIAL PRECAUTIONS:

Contraindications:

- women who are or may become pregnant [1]

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Caution:

- use of ***radium 223 dichloride*** in combination with abiraterone plus prednisone has been associated with increased mortality and increased fracture rates; combination is not recommended outside clinical trials
- patients with ***underlying cardiovascular conditions*** might be compromised by effects of mineralocorticoid excess (hypertension, hypokalemia, fluid retention) occuring as a consequence of CYP17 inhibition; hypertension should be controlled and hypokalemia corrected prior to treatment[3]

Carcinogenicity: In animal studies, abiraterone was not carcinogenic in mice or female rats; however increased incidence of interstitial cell neoplasms in the testes of male rats were reported (clinical significance is unknown as this finding in male rats is believed related to pharmacological action of the drug). [4]

Mutagenicity: Not mutagenic in Ames test and mammalian *in vitro* mutation test. [1]

Fertility: Abiraterone reduced fertility in both male and female rats, although this was completely reversible 4-16 weeks after abiraterone was stopped. Reduced sperm counts, sperm motility, altered sperm morphology, and fertility were reported in males. Treated females experienced increased incidence of irregular or extended estrous cycles and pre-implantation loss. Untreated females mated with treated males experienced reduced corpora lutea, implantations, and live embryos, as well as increased pre-implantation loss. [4]

Pregnancy: In developmental studies in rats, abiraterone did not have teratogenic potential, but it did cause developmental toxicity throughout the period of organogenesis, including embryo-fetal lethality, fetal developmental delay, urogenital effects, and decreased fetal weight. Maternal use of abiraterone is expected to produce changes in hormone levels that could affect the development of the human fetus. [4] It is not known if abiraterone or its metabolites are present in semen. It is recommended that male patients taking abiraterone use a condom during sexual activity with a pregnant woman OR a condom plus another birth control method during sexual activity with a woman of child-bearing potential for the duration of treatment and for one week after the last dose. [4]

Breastfeeding is not recommended due to the potential secretion into 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. [5] 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***	
cardiac	angina (1-3%, severe <1%)
	arrhythmia (7%, severe 1%)
	cardiac failure (2%, severe 1-2%)
gastrointestinal	*emetogenic potential:* low [6]
	diarrhea (18-22%, severe <1%)
	dyspepsia (6-11%)
general disorders and administration site conditions	***peripheral edema*** (25%, severe 1%); see paragraph following **Side Effect** table
	fatigue (39%, severe 1%) [7]

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
infections and infestations	upper respiratory tract infection (5-13%)
	urinary tract infection (12%, severe 2%)
injury, poisoning, and procedural complications	fracture (6%, severe 1%)
investigations	ALT increase (11-41%, severe 1-6%); see paragraph following **Side Effect** table
	AST increase (30-36%, severe 2-3%); see paragraph following **Side Effect** table
	bilirubin increase (6-11%, severe <1%); see paragraph following **Side Effect** table
	cholesterol increase (55%, severe <1%)
	phosphorus decrease (23-26%, severe 5-7%)
	triglycerides increase (22-62%, severe <1%)
metabolism and nutrition	***hypokalemia*** (14-19%, severe 2-4%); see paragraph following **Side Effect** table
musculoskeletal and connective tissue	arthralgia [8] (27%, severe 4%)
	joint swelling, pain, or discomfort (31-32%, severe 2-5%)
	myopathy (36%, severe 5%)
renal and urinary	nocturia (6%)
	urinary frequency (7%, severe <1%)
	hematuria (10%, severe 1%) [7]
respiratory, thoracic and mediastinal	cough (11-17%)
skin and subcutaneous tissue	rash (8%) [7]
vascular	hot flush (19-23%, severe <1%)
	hypertension (9-22%, severe 1-4%); see paragraph following **Side Effect** table

Adapted from standard reference [1] unless specified otherwise.

The ***mineralocorticoid effects*** of abiraterone can occur due to the compensatory increase in ACTH. Therefore, pre-existing cardiovascular disease can be worsened with increased ***hypertension, hypokalemia*** and ***fluid retention***. Concomitant use of corticosteroids suppresses ACTH drive which reduces the incidence and severity of these reactions. If corticosteroids are withdrawn, monitor for adrenocortical insufficiency. If abiraterone is continued after corticosteroids are withdrawn, monitor for symptoms of mineralocorticoid excess. [4] Avoid choosing spironolactone as a potassium-sparing diuretic because it may stimulate the androgen receptor and cause disease progression. [1]

Hepatoxicity with marked increases in ***liver enzymes*** has been reported with abiraterone, with liver function abnormalities typically occurring during the first three months after starting treatment. Patients with elevated baseline ALT/AST may be more likely to experience liver function test elevations than normal baseline values. Regular monitoring of serum transaminases and bilirubin is recommended. Suggest treatment interruption for elevated ALT/AST (>5 X ULN) or bilirubin (>3 X ULN); continue treatment at a reduced dose after tests return to baseline. Patients developing severe hepatotoxicity (AST/ALT 20 X ULN) during treatment should not be retreated with abiraterone. [4]

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INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
dextromethorphan [1,9]	AUC of dextromethorphan increased by 200%; AUC of active metabolite increased by 33% [7]	inhibition of CYP 2D6 metabolism of dextromethorphan and its metabolite, dextrorphan by abiraterone	consider therapy modification; monitor for toxicity related to dextromethorphan [10]
ketoconazole[3]	no clinically meaningful effect on pharmacokinetics of abiraterone[3]	strong inhibition of CYP 3A4 by ketoconazole[3]	no action required
pioglitazone[3]	AUC of pioglitazone increased by 46%; AUC of active metabolites (M-III and M-IV) decreased by 10%[3]; severe hypoglycemia has been reported [11,12]	inhibition of CYP 2C8 by abiraterone[3]	monitor blood glucose[3]
rifampicin [7]	AUC of abiraterone decreased by 55% [7]	strong induction of CYP 3A4 by rifampicin [7]	avoid concurrent therapy [7]
theophylline[3]	no increase in systemic exposure of theophylline[3]	inhibition of CYP 1A2 by abiraterone[3]	no action required

Abiraterone is a **substrate** of CYP 3A4 *in vitro*. [7] Strong inhibitors or inducers of CYP 3A4 may result in an increase or decrease in the plasma concentration of abiraterone.

Abiraterone is a strong **inhibitor** of CYP 1A2, CYP 2D6, and CYP 2C8 *in vitro* and may also be a moderate **inhibitor** of CYP 2C9, CYP 2C19 and CYP 3A4/5. Plasma concentration of substrates of these enzymes may be increased when taken with abiraterone. If abiraterone is administered concurrently with a substrate of these enzymes, especially if the substrate has a narrow therapeutic index, dose reduction of the substrate should be considered. Monitor for toxicity of the substrate.[3]

Abiraterone acetate is an **inhibitor** of P-glycoprotein (P-gp) *in vitro*. [7] Plasma concentration of substrates of P-gp may be increased when taken with abiraterone.

SUPPLY AND STORAGE:

Oral: Janssen Inc. supplies abiraterone as uncoated 250 mg tablets and film-coated 500 mg tablets. Tablets contain lactose. Store at room temperature. [1]

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response, and concomitant therapy. Guidelines for dosing also include consideration of absolute neutrophil count (ANC). Dosage may be reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or with other toxicities.

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Revised: 1 April 2025

Adults:

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

Oral:	***1 g once daily*** [13] Administer on an empty stomach (one hour before or two hours after food). [1]
Dosage in renal failure:	no adjustment required [1]
Dosage in hepatic failure:	For baseline or pre-existing: • mild impairment [4]: no adjustment required • moderate impairment (Child-Pugh Class B) [5,14]: consider reduced starting dose of 250 mg • severe impairment (Child-Pugh Class C) [4,14]: avoid use
Dosage in dialysis:	no adjustment required [1]

Children: no information found

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