Drug Monograph

A - Drug Name

abiraterone

COMMON TRADE NAME(S): Zytiga®

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B - Mechanism of Action and Pharmacokinetics

Abiraterone acetate is converted *in vivo* to abiraterone, an androgen biosynthesis inhibitor, which inhibits 17α hydroxylase/C1, 20-lyase involved in androgen biosynthesis and mineralocorticoid production. Abiraterone also inhibits the formation of the testosterone precursors dehydroepiandrosterone (DHEA) and androstenedione.

Absorption	Pharmacokinetics are dose-proportional in the therapeutic range.	
	Effects with food	Administration with food increased C_{max} and AUC up to 17- and 10-fold respectively.
	Peak plasma levels	2 hours (fasting state). Accumulation is observed at steady state.
Distribution	Extensive distribution to peripheral tissues.	
	PPB	99.8%
Metabolism	Abiraterone acetate is rapidly hydrolyzed to abiraterone by esterases, then undergoes sulphation, hydroxylation and oxidation, mainly in the liver by CYP3A4 and SULT2A1, to inactive metabolites.	

	Active metabolites	Yes
	Inactive metabolites	Yes
Elimination	Half-life	~12 hours; prolonged in patients with mild and moderate hepatic impairment, ~18-19 hours
	Feces	88% of dose, 55% unchanged
	Urine	5%

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C - Indications and Status

Health Canada Approvals:

- Prostate cancer

Refer to the product monograph for a full list and details of approved indications.

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D - Adverse Effects

Emetogenic Potential: Not applicable

The following table contains side effects observed more frequently with abiraterone + prednisone compared to prednisone alone, in asymptomatic or mildly symptomatic patients with metastatic, castration-resistant prostate cancer (mCRPC) plus other potentially severe/life-threatening adverse events reported from other trials/sources.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Angina (3%)	E
	Arrhythmia (7%)	I
	Cardiotoxicity (2%)	D
	Hypertension (22%)	E
	QT interval prolonged (rare)	E

Dermatological	Other - Skin lesions (4%)	E
	Rash (8%)	E
Gastrointestinal	Constipation (23%)	E
	Diarrhea (22%)	E
	Dyspepsia (11%)	E
	Nausea, vomiting (13%)	E
General	Edema (25%)	E
	Fall (6%)	E
	Fatigue (39%)	E
Hematological	Anemia (11%)	E
	Lymphopenia (7%) (severe)	E
Hepatobiliary	↑ LFTs (41%) (6% severe)	E
Hypersensitivity	Hypersensitivity (rare, may be severe)	I
Infection	Infection (13%) (URTI, UTI)	E
Metabolic / Endocrine	Adrenal insufficiency (<2%)	E
	↑ Cholesterol (severe <1%) (in docetaxel pre-treated patients)	E
	Hypoglycemia (rare, with concurrent pioglitazone or repaglinide) (may be severe)	E
	↓ K (17%) , mineralocorticoid effects	E
	↑ Triglycerides (<2%)	E
Musculoskeletal	Fracture (6%)	D L
	Musculoskeletal pain (32%)	E
	Rhabdomyolysis (also myopathy; rare)	E
Nervous System	Confusion (13%)	E
	Depression (3%) (newly diagnosed patients)	E
	Insomnia (14%)	E
Renal	Creatinine increased (<2%)	E
Reproductive and breast disorders	Androgen deprivation symptoms (22%)	E
Respiratory	Cough, dyspnea (17%)	E
	Pneumonitis (allergic alveolitis; rare)	E
Urinary	Urinary symptoms (10%)	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.

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

The most common side effects for abiraterone include ↑ LFTs, fatigue, musculoskeletal pain, edema, constipation, androgen deprivation symptoms, diarrhea, hypertension, ↓ K, cough and dyspnea.

Severe **hepatotoxicity**, including acute liver failure and fulminant hepatitis (with fatal outcomes), has been reported and is more common in patients with abnormal LFTs at baseline. Across phase 3 clinical studies, hepatotoxicity grades 3 and 4 typically presented during the first three months after starting treatment. Most cases of hepatotoxicity appear to be reversible after discontinuation of abiraterone.

Cases of **myopathy** and **rhabdomyolysis** occurred generally within the first month of treatment and resolved following drug discontinuation. Some patients had rhabdomyolysis with renal failure.

Mineralocorticoid effects, which include hypertension, fluid retention and hypokalemia, are commonly reported. Patients on prednisone may require an increased dose of a corticosteroid before, during and after stressful conditions, such as surgery, trauma or severe infections.

There were slightly more **cardiac events** (mainly grades 1 or 2) reported in the abiraterone group (11-16%) than in the placebo group (7-14%). QT prolongation and torsades de pointes have been observed post marketing in patients who developed hypokalemia during abiraterone administration or have underlying cardiovascular conditions.

Isolated cases of **hypoglycemia** have been reported post marketing, particularly in patients receiving concomitant therapy with pioglitazone or repaglinide.

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E - Dosing

Refer to protocol by which patient is being treated.

Patients should continue to receive a GnRH agonist during abiraterone treatment unless they have had prior orchiectomy.

Control hypertension and correct hypokalemia before treatment.

Adults:

Metastatic castration-resistant prostate cancer (mCRPC)

Abiraterone: 1000 mg PO once daily, plus

Prednisone: 10 mg PO once daily

(Note: Prednisone 5 mg PO bid has been used in one of the phase III trials)

Newly diagnosed high-risk metastatic hormone-sensitive prostate cancer

Abiraterone: 1000 mg PO once daily, plus

Prednisone: 5 mg PO once daily

Dosage with Toxicity:

Refer to ABIRPRED regimen monograph for detailed prednisone dosing.

Toxicity	Abiraterone Dose
ALT or AST >5 x ULN OR Total bilirubin >3 x ULN	Hold; monitor liver function closely until recovery to baseline then restart at 500 mg once daily. Discontinue at recurrence.
ALT or AST >20 x ULN	Discontinue permanently.
ALT or AST >3 x ULN AND Total bilirubin >2 x ULN (in the absence of biliary obstruction or other causes)	
Myopathy/rhabdomyolysis	
Confirmed pneumonitis/allergic alveolitis	

Dosage with Hepatic Impairment:

Increased exposure and half-life have been observed in patients with hepatic impairment at baseline.

Hepatic Impairment (at baseline)	Abiraterone Dose
Mild (Child-Pugh Class A)	No dose adjustment required.
Moderate (Child-Pugh Class B)	Do not use abiraterone.
Severe (Child-Pugh Class C)	

Dosage with Renal Impairment:

No adjustment required.

Dosage in the elderly:

No overall differences in effectiveness or adverse effects were seen between elderly and younger patients.

Children:

Not indicated and has not been studied in children.

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F - Administration Guidelines

- Abiraterone must be taken on an empty stomach. No solid or liquid food should be eaten for at least 2 hours before and at least 1 hour after the dose.
- The tablets should be swallowed whole with a glass of water.
- If an abiraterone dose is missed, the dose should be skipped and the next dose taken as scheduled. Patients should not double the dose to make up for the missed one.
- Since abiraterone may harm the fetus, women who are pregnant or who may become pregnant should handle abiraterone with protection (e.g. gloves).
- Store at 15-30°C.

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G - Special Precautions

Contraindications:

- Patients who have a hypersensitivity to this drug or any of its components

Other Warnings/Precautions:

- Patients with pre-existing moderate or severe hepatic impairment should not receive abiraterone. Patients with moderate to severe hepatic impairment, active hepatitis, chronic liver disease or ascites were excluded from clinical trials.
- Use with caution in patients with cardiovascular disease as they were not included in clinical trials. Increased mineralocorticoid levels from CYP17 inhibition may cause hypertension, hypokalemia and fluid retention. Use with caution in patients whose underlying medical conditions may be affected by these effects.
- Caution is advised if patients need to be withdrawn from prednisone. Monitoring for adrenocortical insufficiency should occur.
- Adrenal insufficiency has been reported in patients taking abiraterone and prednisone. Increased corticosteroid dosage may be required before, during and after a stressful situation.
- Contains lactose and should not be used in patients with hereditary galactose intolerance, severe lactase deficiency or glucose-galactose malabsorption.
- Efficacy may be lower in patients who have been treated previously with ketoconazole for their prostate cancer.
- The safety and efficacy of combination abiraterone and cytotoxic chemotherapy use has not been established.

Other Drug Properties:

- Carcinogenicity: Documented in animals
  Increased incidence of testicular interstitial cell neoplasm was observed in male rats and is considered related to abiraterone's pharmacologic action. No information available in humans.

Pregnancy and Lactation:

- Genotoxicity: No
- Embryotoxicity: Yes
- Fetotoxicity: Yes
  Abiraterone is **contraindicated** in pregnancy and **not for use** in patients who can become pregnant. Adequate contraception should be used by patients and their partners during treatment, and for at least **1 week** after the last dose. Barrier contraception (including condoms) should be used.
- Excretion into breast milk: Unknown
  Breastfeeding is not recommended.
- Fertility effects:
  Observed in animal studies (may be reversible).

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H - Interactions

Abiraterone is mainly metabolized by CYP3A4 and SULT2A1. The drug moderately inhibits CYP2C9, 2C19, CYP3A4/5 and P-gp in vitro (may not be clinically significant). In vitro, abiraterone is a CYP1A2 (no observed increase in systemic theophylline exposure), CYP2D6 and CYP2C8 inhibitor.

Lower abiraterone response rates may be expected in patients previously treated with ketoconazole for prostate cancer.

AGENT	EFFECT	MECHANISM	MANAGEMENT
CYP2D6 substrates (e.g. beta-blockers, tramadol, nortriptyline, mirtazapine, serotonin-H3 antagonists)	↑ substrate exposure and/or toxicity (up to 200% with dextromethorphan)	Abiraterone is a strong CYP2D6 inhibitor.	Caution; avoid co-administration with CYP 2D6 substrates with narrow therapeutic range. If no alternative option, consider ↓ dose of the concomitant 2D6 substrate.
CYP3A4 inducers (i.e. phenytoin, rifampin, dexamethasone, carbamazepine, phenobarbital, St. John's Wort, etc)	↓ abiraterone concentration (rifampin ↓ AUC of single-dose abiraterone by 55%) and/or efficacy	↑ metabolism of abiraterone, a CYP3A4 substrate.	Avoid strong CYP3A4 inducers; caution and monitor efficacy if must co-administer.

Spironolactone	May stimulate disease progression.	Spironolactone may bind and activate the wild-type androgen receptor.	Avoid use with abiraterone.
P-glycoprotein substrates (i.e. verapamil, digoxin, morphine, ondansetron)	↑ substrate exposure and/or toxicity (theoretical)	Abiraterone is a P-gp inhibitor.	Caution and monitor.
OATP1B1 substrates (i.e. rosuvastatin)	↑ substrate exposure (no clinical data)	Abiraterone inhibits OATP1B1.	Caution and monitor.
CYP 2C8 substrates (i.e. paclitaxel, sorafenib, amiodarone, pioglitazone, repaglinide, enzalutamide)	↑ substrate exposure	Abiraterone inhibits CYP2C8.	Caution and monitor CYP2C8 substrates with narrow therapeutic range. (Isolated hypoglycemia has been reported in patients receiving pioglitazone or repaglinide).
Drugs that increase risk of myopathy (e.g. statins)	↑ risk of myopathy/rhabdomyolysis	Additive	Caution and monitor for myopathy/rhabdomyolysis.
Radium 223 dichloride	↑ risk of fractures and mortality	Unknown	Avoid use with abiraterone.

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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
Blood pressure, serum potassium, fluid retention	Baseline and monthly
Liver function tests, bilirubin	Baseline, every 2 weeks for the first 3 months and monthly thereafter, or as clinically indicated
Monitor for adrenal insufficiency	As clinically indicated when prednisone is withdrawn, or during periods of infection/stress
Monitor for mineralocorticoid excess	As clinically indicated if patient continues on abiraterone after stopping prednisone
Blood glucose levels in patients with pre-existing diabetes receiving concomitant pioglitazone or repaglinide	Baseline and as clinically indicated
Clinical toxicity assessment for infection, hot flashes, gastrointestinal, dermatological, musculoskeletal, urinary, cardiac and respiratory effects	At each visit

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

Suggested Clinical Monitoring

Monitor Type	Monitor Frequency
Cholesterol and triglycerides	Baseline, every 2 to 3 months and as clinically indicated

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J - Supplementary Public Funding

ODB - General Benefit (ODB Formulary)

- abiraterone

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K - References

de Bono JS, Logothetis CJ, Molina A, et al. Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med 2011;364:1995-2005.

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Ryan CJ, Smith MR, de Bono JS, et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. N Engl J Med 2013;368(2):138-48.

Salem M & Garcia JA. Abiraterone acetate, a novel adrenal inhibitor in metastatic castration-resistant prostate cancer. Curr Oncol Rep 2011;13:92–6.

August 2024 Updated abiraterone funding (ODB general benefit) and Dosing section

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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.

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