DRUG NAME: Apalutamide

SYNONYM(S): ARN-509, JNJ-56021927[1]

COMMON TRADE NAME(S): ERLEADA®

CLASSIFICATION: hormonal agent

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

MECHANISM OF ACTION:

Apalutamide is a nonsteroidal androgen receptor inhibitor which affects several steps in the androgen receptor signaling pathway. It inhibits nuclear translocation of activated androgen receptors, DNA binding, and receptor-mediated transcription. In xenograft models, apalutamide reduced tumour cell proliferation and induced apoptosis, which lead to decreased tumour volume. Apalutamide competitively inhibits binding of androgens to androgen receptors with more affinity than other antiandrogen agents. In contrast to conventional androgen receptor inhibitors, apalutamide lacks agonist activity in cells that overexpress androgen receptors.[1-4]

PHARMACOKINETICS:

Oral Absorption	bioavailability ~100%; time to peak: 2 h; steady state after 4 weeks	
Distribution	extensive extravascular distribution	
	cross blood brain barrier?	yes (based on animal studies)
	volume of distribution	276 L
	plasma protein binding	96% apalutamide; 95% N-desmethyl apalutamide
Metabolism	mainly by CYP 2C8 and CYP 3A4 (40% and 37%, respectively, at steady state)	
	active metabolite(s)	N-desmethyl apalutamide (44%)
	inactive metabolite(s)	carboxylic acid metabolite (3%)
Excretion	primarily by urinary excretion of inactive metabolites	
	urine	65% (1% unchanged apalutamide, 3% N-desmethyl apalutamide)
	feces	24% (2% unchanged apalutamide, 2% N-desmethyl apalutamide)
	terminal half life	~3 days at steady state
	clearance	2 L/h at steady state

Adapted from standard reference[2] unless specified otherwise.

USES:

Primary uses:

*Prostate cancer

*Health Canada approved indication

Other uses:

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SPECIAL PRECAUTIONS:

Contraindications:
- history of hypersensitivity reaction to apalutamide[2]
- women who are or may become pregnant[2]

Caution:
- do NOT ***donate semen*** while taking apalutamide and for at least three months after the last dose[4]
- numerous ***potential drug interactions*** are reported, particularly in regard to CYP 3A4, CYP 2C8, and CYP 2C19; dose adjustment may be required[2]
- ***QT interval prolongation*** has been reported; monitor ECG and electrolytes in patients with known history of QT prolongation, risk factors for torsades de pointes, or taking concurrent medications known to prolong the QT interval[2]
- ***ischemic cardiovascular events*** are reported; optimize management of ***cardiovascular risk factors*** such as hypertension, diabetes, and dyslipidemia in patients prior to starting apalutamide[5]
- to prevent ***clinical fractures***, risk of fracture and falls should be assessed prior to treatment; consider use of bone-targeted agents[5]

Special populations: Patients aged 65 or greater may experience increased frequency of grade 3 or 4 adverse reactions from apalutamide; dose adjustment may be required for toxicity.[2,3]

Carcinogenicity: no information found

Mutagenicity: Not mutagenic in Ames test. Apalutamide was not clastogenic in mammalian *in vitro* or *in vivo* chromosome tests.[2]

Fertility: In animal studies, decreased sperm concentration and motility, lower copulation and fertility rates, and reduced weights of secondary sex glands and epididymis were reported at doses equivalent to at least half that of human clinical exposure. These effects were reversible eight weeks after discontinuation of apalutamide.[2]

Pregnancy: In animal studies, increased pre- and post-implantation losses were observed in untreated females paired with treated males (at doses equivalent to at least half that of human clinical exposure). Male patients taking apalutamide should use a condom during sexual activity with a pregnant woman OR a condom plus another effective birth control method during sexual activity with a woman of child-bearing potential for the duration of treatment and at least three months after the last dose.[2,4]

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[6,7]. When placebo-controlled trials are available, adverse events will generally be included if the incidence is ≥5% higher in the treatment group.[8] **Side effects and incidence are those of apalutamide when used with surgical or medical castration.**

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile	anemia (17-70%, severe ≤4%)[2,9]
	leukopenia (47%, severe <1%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
neutropenia	lymphopenia (41%, severe 2%)
cardiac	heart failure (2%)
	ischemic heart disease (4%)
	myocardial infarction (severe <1%)
endocrine	***hypothyroidism*** (8-22%)[2,8,10]; see paragraph following **Side Effects** table
gastrointestinal	*emetogenic potential:* low[11]
	abdominal pain (18-30%, severe 2-3%)[9,10,12]
	constipation (15-23%, severe 4%)[9,12]
	diarrhea (20-43%, severe 1-2%)[2,8,10,12]
	flatulence (9%)[9]
	nausea (18-46%, severe 3%)[8,9,12]
	vomiting (≤17%, severe 2%)[8,9]
general disorders and administration site conditions	edema, peripheral (11-17%)[3,12]
	fatigue (30-61%, severe ≤4%)[2,8,10,12]
	pain (13%, severe 3%)[12]
infections and infestations	nasopharyngitis (16%)[10]
	pneumonia (severe 1%)
	sepsis (severe 1%)
	upper respiratory infection (11-16%)[9,10]
	urinary tract infection (severe 1%)
injury, poisoning, and procedural complications	***falls*** (16%, severe 2%)[2,8]; see paragraph following **Side Effects** table
	fracture (12%, severe 3%)[2,8]; see paragraph following **Side Effects** table
investigations	***hypercholesterolemia*** (76%, severe <1%)
	thyroid stimulating hormone increase (25%)[3]
	weight loss (16-18%, severe 1%)[2,8,10]
metabolism and nutrition	anorexia (12-20%)[3,9]
	hyperglycemia (70%, severe 2%)
	hyperkalemia (32%, severe 2%)
	hypertriglyceridemia (67%, severe 2%)
musculoskeletal and connective tissue	arthralgia (16-27%, severe 2-3%)[2,8,10,12]
	back pain (22-30%, severe 4%)[9,10,12]
	musculoskeletal chest pain (15%, severe 2%)[9]
	musculoskeletal pain (17%, severe 2%)[9,12]
	pain in extremity (17-20%, severe 2%)[10,12]

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
nervous system	cerebral hemorrhage (severe <1%)
	cerebrovascular accident (severe <1%)
	dizziness (13%)[9]
	dysgeusia (22%)[10]
	headache (15-20%)[9,12]
	peripheral sensory neuropathy (20%)[12]
	seizure (<1%)[2,8]; see paragraph following **Side Effects** table
psychiatric	insomnia (11%)[9]
renal and urinary	hematuria (16%)[10]
	pollakiuria (18%)[10]
	urinary tract hemorrhage (10%)[12]
respiratory, thoracic and mediastinal	cough (17-20%)[9,10]
	dyspnea (22-30%, severe 2%)[9,12]
skin and subcutaneous tissue	pruritus (6%)
	rash (15-24%, severe 5%)[2,8,9]; see paragraph following **Side Effects** table
vascular	hot flashes (11-20%)[2,9,10,12]
	hypertension (25%, severe 14%)[2,8]

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Falls and ***fractures*** are associated with apalutamide. These falls are unassociated with loss of consciousness or seizure; mechanism is unknown. Fractures mainly occur in weight bearing bones and may be serious and require hospitalization. Median time to fracture is approximately 10 months, but fractures have been reported within one month and up to 32 months after treatment initiation.[2,3]

Grade 1-2 ***hypothyroidism*** is reported in up to 22% of patients receiving apalutamide. Median onset is 4 months. Monitor TSH throughout treatment and initiate thyroid replacement as indicated. Apalutamide may decrease the efficacy of levothyroxine via induction of UDP-glucuronosyl transferase (UGT); therefore, dose adjustment of levothyroxine may be required.[2]

Rash is reported in approximately one quarter of patients receiving apalutamide. Some reactions are grade 3-4 severity. Rashes are usually macular or maculopapular in presentation and have a median onset within 3 months. Rash typically resolves after 2 months, but has been reported to recur in about half the patients re-challenged with apalutamide. Corticosteroids and antihistamines have been used to treat the rash. Apalutamide dose reduction, interruption, or discontinuation may also be required.[2,3]

Rarely, ***seizures*** have been observed in patients receiving apalutamide, with a reported onset of 12-16 months after treatment initiation. Both apalutamide and its active metabolite cross the blood brain barrier, where they inhibit the activity of the $GABA_A$-gated chloride channel (an off-target mechanism associated with the onset of seizure in animals). It is unclear if history of seizure or other predisposing factors increase seizure risk with apalutamide, and it is unknown if antiepileptic medications can prevent apalutamide-associated seizures; therefore, apalutamide should be used cautiously in this patient group. Apalutamide should be permanently discontinued if a seizure is experienced during treatment.[2,3]

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INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
abiraterone and prednisone[4]	no effect on apalutamide or abiraterone kinetics		
fexofenadine[2]	30% decrease in fexofenadine AUC	weak induction of P-glycoprotein by apalutamide	monitor for reduced control of allergy symptoms; adjust fexofenadine dose as required
gemfibrozil[2]	19-32% increase in C_{max} and 23-44% increase in AUC of apalutamide	strong CYP 2C8 inhibition by gemfibrozil	initial dose adjustment is unnecessary; consider apalutamide dose reduction based on tolerability
ketoconazole[2]	23-38% increase in C_{max} and 28-51% increase in AUC of apalutamide	strong CYP 3A4 inhibition by ketoconazole	initial dose adjustment is unnecessary; consider apalutamide dose reduction based on tolerability
midazolam[2]	77% decrease in C_{max} and 92% decrease in AUC of midazolam	strong induction of CYP 3A4 by apalutamide	avoid concurrent use; if unavoidable, midazolam dose adjustment may be required
omeprazole[2]	77% decrease in C_{max} and 85% decrease in AUC of omeprazole	strong induction of CYP 2C19 by apalutamide	avoid concurrent use; if unavoidable, omeprazole dose adjustment may be required
rifampin[2]	15-25% decrease in C_{max} and 19-34% decrease in AUC of apalutamide	strong CYP 3A4 and moderate CYP 2C8 induction by rifampin	no dose adjustment necessary
rosuvastatin[2]	41% decrease in AUC of rosuvastatin	weak induction of BCRP and OATP1B1 by apalutamide	monitor for worsening lipid panel results; adjust rosuvastatin dose as required
warfarin[2]	16% decrease in Cmax and 46% decrease in AUC of S-warfarin	weak induction of CYP 2C9 by apalutamide	avoid concurrent use; if unavoidable, monitor INR; warfarin dose adjustment may be required

Apalutamide is a minor ***substrate*** of ***CYP 2C8*** and ***CYP 3A4***. Concurrent administration of strong CYP 2C8 or CYP 3A4 ***inhibitors*** may increase exposure of apalutamide and its active metabolite. Monitor for apalutamide toxicity and reduce apalutamide dose if necessary. Mild or moderate CYP 2C8 and CYP 3A4 inhibitors are not expected to affect apalutamide exposure. Conversely, strong CYP 2C8 and CYP 3A4 ***inducers*** may decrease exposure of apalutamide and its active metabolites; however, no apalutamide dose adjustments are recommended.[2,3]

Apalutamide is a ***strong inducer*** of ***CYP 3A4*** and ***CYP 2C19*** and a ***weak inducer*** of ***CYP 2C9***. Concurrent administration of apalutamide with substrates of these enzymes may result in decreased exposure of the substrate. Avoid concurrent use. Monitor for loss of efficacy of substrate and adjust dose as indicated.[2,3]

Apalutamide is a weak ***inducer*** of UDP-glucuronosyl transferase ***(UGT)***, resulting in decreased exposure of UGT substrates; clinical significance is unknown.[2]

Apalutamide is a weak ***inducer*** of P-glycoprotein (***P-gp***), breast cancer resistance protein (***BCRP***), and organic anion transporting polypeptide 1B1 (***OATP1B1)***, resulting in decreased exposure of these transporter substrates; clinical significance is unknown.[2]

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SUPPLY AND STORAGE:

Oral: Janssen Inc. supplies apalutamide as 60 mg film-coated tablets. Store at room temperature. Keep in the original packaging to protect from light and moisture; do not remove desiccant.[2]

Additional information: Tablets are stable for 2 months at room temperature when dispensed in an amber vial and protected from light and moisture. Tablets remaining in the original commercial bottle should be stored with the desiccant and are stable for 3 months prior to subsequent dispensing. Tablets are stable for 10 days at room temperature when kept in a daily use pill box due to exposure to open air.[13]

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[5,14]: ***240 mg*** (range 120-240 mg) ***PO once daily***

Administer with food or on an empty stomach.

Concurrent radiation: no information found

Dosage in renal failure: CrCl ≥30 mL/min: no adjustment required[2]
CrCl <30 mL/min: no information found

$$\text{calculated creatinine clearance} = \frac{N^* \times (140 - \text{Age}) \times \text{weight in kg}}{\text{serum creatinine in micromol/L}}$$

* For males N=1.23; for females N=1.04

Dosage in hepatic failure: mild to moderate impairment (Child-Pugh A or B): no adjustment required[2]
severe hepatic impairment (Child-Pugh C): no information found

Dosage in dialysis: no information found

Children: no information found

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