Drug Monograph

A - Drug Name

apalutamide

COMMON TRADE NAME(S): Erleada®

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B - Mechanism of Action and Pharmacokinetics

Apalutamide is a nonsteroidal androgen receptor (AR) inhibitor that binds directly to the AR ligand-binding domain to inhibit nuclear translocation, DNA binding, and AR-mediated transcription. In mouse xenograft models of prostate cancer, apalutamide administration caused decreased tumour cell proliferation and increased apoptosis leading to decreased tumour volume.

Absorption	Bioavailability	100%. Apalutamide is completely absorbed after oral administration. Median t_{max} is 2 hours.
	Effects with food	Food administration has no significant effect on apalutamide exposure, however the median time to reach t_{max} was delayed approximately 2 hours with food. Administration of apalutamide 60 mg tablets as a dispersed mixture in applesauce resulted in comparable exposures and shorter t_{max} (shorter by 1 hour) compared to administration as whole tablets. Dissolution of apalutamide 240 mg tablets was comparable with or without food.
	Time to reach steady state	4 weeks; accumulates approximately 5x relative to a single dose.

Distribution	Cross blood brain barrier?	Apalutamide and N-desmethyl apalutamide (active metabolite) have been observed to cross the blood brain barrier in animal studies.
	PPB	96% Apalutamide; 95% N-desmethyl apalutamide
Metabolism	Apalutamide is primarily metabolized by CYP2C8 and CYP3A4.	
	Active metabolites	Yes. 44% N-desmethyl apalutamide
	Inactive metabolites	Yes
Elimination	Urine	65%; 1% as apalutamide and 3% as N-desmethyl apalutamide
	Feces	24%; 2% as apalutamide and 2% as N-desmethyl apalutamide
	Half-life	~ 3 days

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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 adverse effects were reported in ≥ 10% of patients with non-metastatic castration resistant prostate cancer (nmCRPC) in the phase III trial comparing apalutamide with androgen deprivation therapy (ADT) to placebo with ADT, where incidence was at least 2% or more compared to placebo. Severe adverse effects from other studies or post-marketing may also be included.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Arterial thromboembolism (4%)	E
	Cardiotoxicity (2%)	E
	Hypertension (25%) (14% severe)	E
	QT interval prolonged (rare)	E
Dermatological	Rash, pruritus (25%) (5% severe)	D
	Stevens-Johnson syndrome (rare)	E
	Toxic epidermal necrolysis (rare)	E
Gastrointestinal	Anorexia, weight loss (16%)	E
	Diarrhea (20%)	E
	Nausea (18%)	E
General	Edema (11%)	E
	Fall (16%)	E D
	Fatigue (39%)	E
Hematological	Anemia (<1%) (severe)	E D
	Myelosuppression (2%) (severe)	E
Hypersensitivity	DRESS syndrome (%)	E
Metabolic / Endocrine	↑ Cholesterol (6%) (or triglycerides)	E
	Hyperglycemia (2%) (severe; non-fasting)	E
	Hypothyroidism (8%)	E D
	↑ K (2%) (severe)	E
Musculoskeletal	Arthralgia (16%)	E
	Fracture (12%)	D
Nervous System	Seizure (<1%)	E
	Syncope (2%)	E
Reproductive and breast disorders	Androgen deprivation symptoms (14%)	E
Respiratory	Interstitial lung disease (rare)	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 apalutamide include fatigue, hypertension, rash, pruritus, diarrhea, nausea, anorexia, weight loss, arthralgia, fall, androgen deprivation symptoms and fracture.

Rash (usually macular or maculopapular) onset typically occurred at a median of 83 days with resolution within a median of 78 days in most patients. Rash was commonly managed with oral antihistamines and topical corticosteroids, though some patients required systemic corticosteroids. Rash recurred in approximately half of patients who were re-challenged with apalutamide.

Grade 1 or 2 **hypothyroidism** has been reported with apalutamide. Thyroid replacement therapy should be initiated or adjusted as clinically indicated as apalutamide may induce UDP-glucuronosyl transferase (UGT).

Fall and **fractures**, which were not associated with loss of consciousness or seizure, have been observed in patients receiving apalutamide. The median time to onset of fracture was approximately 10 months (range: 20 to 953 days). 40-50% of patients experienced a fall within 7 days before the fracture event. Most of the severe fractures occurred in the weight bearing bones.

Seizures were observed in patients receiving apalutamide, with a reported onset of 159 to 650 days after treatment initiation and may be related to off target effects on GABAA gated channels. It is unknown whether anti-epileptic medications will prevent apalutamide-associated seizures.

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E - Dosing

Refer to protocol by which patient is being treated.

Patients should also receive a gonadotropin-releasing hormone (GnRH) analog concurrently or should have had a bilateral orchiectomy.

Patients should be assessed for the risk of fracture and fall and managed according to guidelines with consideration given to the use of bone-targeted agents.

Patients with a cardiac or stroke history should be assessed before starting treatment. Manage patients optimally for risk factors such as hypertension, diabetes, or dyslipidemia.

Adults:

Oral: 240 mg (4 x 60mg tablets) Daily

Dosage with Toxicity:

Dose Level	Apalutamide Dose (mg/day)
0	240
-1	180
-2	120
-3	Discontinue

Toxicity	Action
Intolerable or ≥ Grade 3	Hold until recovery to ≤ grade 1, resume at the same dose or at ↓ 1 dose level. If the toxicity recurs at ≥ grade 3, ↓ 1 dose level.
Seizure	Discontinue.
Stevens-Johnson syndrome, Toxic epidermal necrolysis, or DRESS	Discontinue.

Dosage with Hepatic Impairment:

Hepatic Impairment at baseline	Action
Mild or moderate (Child-Pugh A or B)	No adjustment required
Severe (Child-Pugh C)	No data

Dosage with Renal Impairment:

Renal Impairment	Action
Mild to moderate (CrCL ≥ 30 mL/min)	No adjustment required
Severe (CrCL ≤ 29 mL/min)	No data

Dosage in the elderly:

No dose adjustment is necessary for elderly patients. Patients ≥ 75 years treated with apalutamide experienced higher incidence of grade 3 or 4 adverse events and lower tolerance. Monitor elderly patients more closely for toxicity and adjust dose when needed.

Dosage based on ethnicity:

No dose adjustments are necessary. There is no clinically relevant difference in exposure between White (Caucasian or Hispanic or Latino), Black (of African heritage or African American), Asian (non-Japanese), or Japanese patients. In clinical studies, the incidence of rash was more than 2-fold higher in the Japanese population compared with the entire study population.

Children:

Safety and effectiveness of apalutamide in pediatric patients have not been evaluated.

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F - Administration Guidelines

- Tablets should be swallowed whole with a glass of water.
- Tablets can be taken with or without food.
- Take the dose at around the same time each day.
- A missed dose should be taken as soon as possible on the same day with a return to the normal schedule on the following day. The patient should not take extra tablets to make up the missed dose.
- For patients who have difficulty swallowing **60 mg tablets**, the dose may be mixed in applesauce. Refer to product monograph for the most up-to-date instructions.
    - Mix whole 60 mg tablets in 120 mL of applesauce by stirring. Do not crush the tablets.
    - Wait 15 minutes, then stir the applesauce.
    - Wait another 15 minutes, then stir the applesauce until the tablets are well mixed with no chunks remaining.
    - Using a spoon, swallow the mixture right away.
    - Rinse the mixture container with 60 mL of water and drink this immediately.
    - Repeat the rinsing with another 60 mL of water, then drink this to ensure the entire dose is taken.
    - The mixture should be taken within 1 hour of preparation.
- For patients who have difficulty swallowing **240 mg tablets**, the dose may be dispersed in non-fizzy water, then mixed with non-fizzy beverages or soft foods. Refer to product monograph for the most up-to-date instructions.
    - Place whole 240 mg tablet in a cup. Do not crush or split the tablet.
    - Add about 10 mL of non-fizzy water. Wait 2 minutes for the tablet to disperse, then stir the mixture.
    - Add 30 mL of the following non-fizzy beverages or soft foods: orange juice, green tea, applesauce, or drinkable yogurt), then stir the mixture.
    - The mixture should be swallowed immediately.
    - Rinse the cup with enough water, then drink it immediately, to make sure the whole dose is taken.
- For **nasogastric (NG) tube** administration (8 French or greater), the **240 mg tablet** may be dispersed in 10 mL of non-carbonated water (in at least a 20 mL syringe). Wait 10 minutes and shake vigorously to disperse the tablet; then administer immediately through the NG tube. Flush the NG tube with non-carbonated water until no dispersed tablet is remaining in the syringe or the NG tube.
- Store tablets at 15°C to 30°C, in the original package to protect from light and moisture.
- If tablets are provided in a bottle, do not remove the silica gel desiccant from the bottle.

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G - Special Precautions

Contraindications:

- Patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container.
- Women who are or may become pregnant

Other Warnings/Precautions:

Exercise caution in patients with:

- Cardiac disorders. Patients with clinically significant cardiovascular disease in the past 6 months including severe/unstable angina, myocardial infarction, symptomatic congestive heart failure, arterial or venous thromboembolic events or clinically significant ventricular arrhythmias were excluded from clinically trials.
- Seizures. Patients with a history of seizures or predisposing factors for seizures were excluded from clinical studies; patients on medications known to lower seizure threshold were prohibited while receiving apalutamide.
- QT prolongation, risk factors for Torsade de pointes or on medications known to prolong QTc.
- nmCRPC at low risk of developing metastases. Apalutamide has not been studied in these patients and the benefit and risk profile is unknown.

Other Drug Properties:

- Carcinogenicity: Unknown

Pregnancy and Lactation:

- Abortifacient effects: Probable
- Genotoxicity: No
- Embryotoxicity: Likely
    - Apalutamide is **not indicated for use in females**. It may cause harm to a developing fetus or lead to loss of pregnancy. Adequate contraception should be used by patients and their partners who can become pregnant during treatment, and for at least **3 months** after the last dose.
    - Patients who produce sperm should use a condom and not donate sperm during treatment, and for **3 months** after the last dose.

- Breastfeeding: Unknown
  - Apalutamide is **not indicated for use in females**. There are no data on the presence of apalutamide or its metabolites in human milk.
- Fertility effects: Documented in animals

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H - Interactions

- In vitro studies showed that apalutamide and N-desmethyl apalutamide are moderate to strong CYP2B6 inducers, and moderate inhibitors of CYP2B6.
- Apalutamide did not cause clinically significant changes in exposure to the CYP2C8 substrate.
- Based on in vitro data, inhibition of organic cation transporter 2 (OCT2), organic anion transporter 3 (OAT3) and multidrug and toxin extrusions (MATEs) by apalutamide and its N-desmethyl apalutamide cannot be excluded.
- GABA inhibition is an off-target activity of both apalutamide and N-desmethyl apalutamide. This interaction is considered the mechanism for the seizures/convulsions observed in general toxicology studies at high doses in animals.
- Acid lowering agents (e.g., proton pump inhibitor, H2-receptor antagonist, antacid) are not expected to affect the solubility and bioavailability of apalutamide.

AGENT	EFFECT	MECHANISM	MANAGEMENT
CYP 2C8 strong inhibitors (i.e. gemfibrozil)	↑ apalutamide concentration	↓ metabolism of apalutamide	Caution; consider dose adjustment for apalutamide based on tolerability.
CYP 3A4 strong inhibitors (i.e. itraconazole, clarithromycin, ritonavir, nelfinavir, etc.)	↑ apalutamide concentration	↓ metabolism of apalutamide	Caution; consider dose adjustment for apalutamide based on tolerability.
CYP 3A4 strong inducers (i.e. phenytoin, rifampin, carbamazepine, phenobarbital, St. John's Wort, etc.)	↓ apalutamide concentration	↑ metabolism of apalutamide	Caution, no adjustment needed.

CYP3A4 substrates (e.g. cyclosporine, pimozide, tacrolimus, triazolo-benzodiazepines, dihydropyridine calcium-channel blockers, certain HMG-CoA reductase inhibitors)	↓ substrate concentration and/or efficacy	↑ metabolism of substrate (apalutamide is a strong inducer of CYP 3A4)	Avoid or substitute if possible. Evaluate for loss of efficacy if medication is continued.
CYP 2C19 substrates (e.g. omeprazole)	↓ substrate concentration and/or efficacy	↑ metabolism of substrate (apalutamide is a strong inducer of CYP 2C19)	Avoid or substitute if possible. Evaluate for loss of efficacy if medication is continued.
CYP 2C9 substrates (e.g. warfarin, meloxicam, fluvastatin)	↓ substrate concentration and/or efficacy	↑ metabolism of substrate (apalutamide is a weak inducer of CYP 2C9)	Avoid or substitute if possible. Evaluate for loss of efficacy (e.g. INR) if medication is continued.
P-glycoprotein substrates (i.e. verapamil, digoxin, fexofenadine)	↓ substrate concentration and/or efficacy	↑ metabolism of substrate (apalutamide is a weak inducer of Pgp)	Caution; evaluate for loss of efficacy if medication is continued.
BCRP substrates (i.e. topotecan)	↓ substrate concentration and/or efficacy	↑ metabolism of substrate (apalutamide is a weak inducer of BCRP)	Caution; evaluate for loss of efficacy if medication is continued.
OATP1B1 substrates (i.e. rosuvastatin)	↓ substrate concentration and/or efficacy	↑ metabolism of substrate (apalutamide is a weak inducer of OATP1B1)	Caution; evaluate for loss of efficacy if medication is continued.
UGT substrates (i.e. estradiol, irinotecan, levothyroxine, thyroxine)	↓ substrate concentration and/or efficacy	↑ metabolism of substrate	Caution; evaluate for loss of efficacy if medication is continued.
Drugs that may prolong QT (i.e. amiodarone,	↑ risk of QT prolongation and arrhythmias	Additive	Caution.

procainamide,
sotalol,
venlafaxine,
amitriptyline,
sunitinib,
methadone,
chloroquine,
clarithromycin,
haloperidol,
fluconazole,
moxifloxacin,
domperidone,
ondansetron, etc.)

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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
TSH	Baseline and as clinically indicated
ECG	Baseline and as clinically indicated; more frequent in patients at risk of QTc increase or taking medications known to prolong QT interval
INR	If warfarin cannot be discontinued; baseline and during apalutamide treatment
PSA and radiographic disease progression	Baseline and as clinically indicated
Clinical toxicity assessment for androgen deprivation symptoms, hypertension, fatigue, infection, seizure, cardiac, stroke, gastrointestinal, respiratory or dermatologic effects, and risk of fracture and falls	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	As clinically indicated
Blood glucose	As clinically indicated

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J - Supplementary Public Funding

Exceptional Access Program (EAP Website)

- apalutamide - For the treatment of non-metastatic castration resistant prostate cancer (nmCRPC) according to clinical criteria
- apalutamide - For the treatment of metastatic castration sensitive prostate cancer (mCSPC), according to clinical criteria

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K - References

Prescribing Information: Erleada® (apalutamide). Janssen Ortho LLC. November 2020.

Product Monograph: Erleada® (apalutamide). Janssen Inc. July 2023.

Smith MR, Saad F, Chowdhury S, et al. Apalutamide Treatment and Metastasis-free Survival in Prostate Cancer. N Engl J Med 2018;378:1408-18.

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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.

The information set out in the drug monographs, regimen monographs, appendices and symptom management information (for health professionals) contained in the Drug Formulary (the "Formulary") is intended for healthcare providers and is to be used for informational purposes only. The information is not intended to cover all possible uses, directions, precautions, drug interactions or adverse effects of a particular drug, nor should it be construed to indicate that use of a particular drug is safe, appropriate or effective for a given condition. The information in the Formulary is not intended to constitute or be a substitute for medical advice and should not be relied upon in any such regard. All uses of the Formulary are subject to clinical judgment and actual prescribing patterns may not follow the information provided in the Formulary.

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