Drug Monograph

A - Drug Name

darolutamide

COMMON TRADE NAME(S): Nubeqa®

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B - Mechanism of Action and Pharmacokinetics

Darolutamide is a non-steroidal androgen receptor (AR) inhibitor that competitively inhibits androgen binding, AR nuclear translocation, and AR mediated transcription. AR inhibition decreased prostate cancer cell proliferation in vitro and tumour growth in animal models.

Absorption	Linear in a nearly dose-related manner in the dose range of 100 to 700 mg (after single dose and at steady state). No significant increase in exposure was observed > 700 mg twice daily.	
	Bioavailability	30% (fasted condition)
	Effects with food	Food ↑ bioavailability by 2 to 2.5-fold.
	Peak plasma levels	4 hours
	Time to reach steady state	2 to 5 days after repeated twice-daily dosing with food, with a 2.9-fold accumulation
Distribution	PPB	92% (darolutamide); 99.8% (active metabolite: keto-darolutamide), mainly to albumin
	Cross blood brain barrier?	2-4.5% of plasma exposure in animals

Metabolism	Darolutamide is metabolized primarily via oxidation by CYP3A4, and also through glucoronidation by UGT1A9 and UGT1A1.	
	Active metabolites	Yes
Elimination	Feces	63% (7% unchanged)
	Urine	32% (30% unchanged)
	Half-life	20 hours

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C - Indications and Status

Health Canada Approvals:

- Prostate cancer

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

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D - Adverse Effects

Emetogenic Potential: Not applicable

The following adverse effects were reported with incidences of 2% or greater than placebo in a Phase III trial of patients with non-metastatic castration resistant prostate cancer (nmCRPC). Severe and life-threatening adverse effects may also be included.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Cardiac ischemia (3%) (2% severe)	E
	Heart failure (2%) (may be severe)	E
	Hypertension (7%) (3% severe)	E
	Thromboembolism (<1%)	E
Dermatological	Rash (3%)	E

General	Fatigue (16%)	E
Hepatobiliary	Drug-induced liver injury (rare)	E D
	↑ LFTs (23%) (↑ bilirubin, ↑ AST; < 1% severe)	E
Musculoskeletal	Fracture (6%)	D
	Musculoskeletal pain (6%)	E
Nervous System	Seizure (<1%)	D
Urinary	Urinary retention (2%) , hematuria	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)

Serious adverse reactions in ≥ 1 % of patients included **urinary retention, pneumonia** and **hematuria**.

The most frequent adverse reactions requiring dosage interruption included **hypertension, diarrhea,** and **pneumonia** (< 1% in each).

The most frequent adverse reactions requiring dosage reduction included **fatigue, hypertension,** and **nausea** (< 1% in each).

Ischemic heart disease, including fatal cases, occurred in patients treated with darolutamide.

In clinical trials, **drug-induced liver injury** (with ≥ Grade 3 ALT and AST elevations, including with concomitant bilirubin ≥ 2 x ULN) has been reported with an onset of 1 to 12 months after treatment initiation. ALT and AST elevations were reversible upon discontinuation of darolutamide.

Seizures have been reported in patients (without a history of seizures).

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E - Dosing

Refer to protocol by which the patient is being treated.

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

Optimize management of cardiovascular risk factors (e.g., hypertension, diabetes, or dyslipidemia).

Adults:

Oral: 600 mg BID

Dosage with Toxicity:

Dose Level	Darolutamide Dose
0	600 mg BID
-1	300 mg BID
-2	Discontinue

Toxicity	Action
Intolerable or ≥ grade 3	Hold or ↓ 1 dose level until symptoms improve. Then may resume at previous dose.
Drug-induced liver injury (DILI)	Discontinue.
Seizure	Consider discontinuing.

Dosage with Hepatic Impairment:

During a pharmacokinetic (PK) study, patients with moderate hepatic impairment had a 1.9-fold higher darolutamide exposure.

Hepatic Impairment	Darolutamide Dose
Mild (Child-Pugh class A)	No dose adjustment necessary
Moderate (Child-Pugh class B)	300 mg BID
Severe (Child-Pugh class C)	Not studied

Dosage with Renal Impairment:

During PK studies, patients with mild, moderate and severe renal impairment had a 1.1-,1.3- and 1.5-fold higher darolutamide exposure, respectively.

Creatinine Clearance (mL/min)	Darolutamide Dose
≥ 30	No dose adjustment necessary
15 - 29*	300 mg BID (limited data)
< 15**	Not studied

*Not on hemodialysis
**Including patients with ESRD on dialysis

Dosage in the elderly:

No clinically relevant differences in safety or efficacy in patients ≥ 65 years of age. Compared to patients < 65 years of age, patients > 85 years of age had a 1.6-fold higher darolutamide exposure without associated greater toxicity.

Dosage based on gender:

Safety and efficacy in females have not been established. Darolutamide is not indicated for use in females.

Dosage based on ethnicity:

During a PK study, Japanese patients had a 1.4-fold higher darolutamide exposure without associated greater toxicity.

Children:

Safety and efficacy in children and adolescents < 18 years of age have not been studied. Darolutamide is not indicated for use in pediatrics.

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F - Administration Guidelines

- Administer darolutamide with food.
- Tablets should be swallowed whole.
- If a dose is missed, patient may take as soon as possible. If it is close to the next dose, patient should not double the dose to make up for the missed dose.
- Store at room temperature (15°C to 30°C). Keep bottle tightly closed after opening. Once bottle is opened, darolutamide is stable for 3 months.

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G - Special Precautions

Contraindications:

- Patients who are hypersensitive to this drug or any of its components.

Other Warnings/Precautions:

- Patients with uncontrolled hypertension, recent stroke, myocardial infarction, severe/unstable angina pectoris, coronary/peripheral artery bypass graft or CHF NYHA Class III or IV were excluded in clinical trials.
- Tablets contain lactose; carefully consider use in patients with hereditary galactose intolerance, severe lactase deficiency or glucose-galactose malabsorption.

Other Drug Properties:

- Carcinogenicity: Unknown

Pregnancy and Lactation:

- Genotoxicity: No
- Clastogenicity: Yes
- Abortifacient effects: Probable
- Fetotoxicity: Probable
  - Darolutamide 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 both patients and their partners during treatment, and for **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.
- Excretion into breast milk: Unknown
  - Darolutamide is **not indicated for use in females**. There are no data on the presence of darolutamide or its metabolites in human milk.
- Fertility effects: Probable
  - Atrophy and hypospermia in the male reproductive system were reported in animal studies.

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H - Interactions

Darolutamide is primarily metabolized by CYP3A4 and is also a substrate of P-gp and BCRP.

In vitro, darolutamide is an inhibitor of BCRP and may also inhibit OATP1B1, OATP1B3, OAT3, MATE1, MATE2K and intestinal MRP2.

Darolutamide may be given concomitantly with P-gp substrates.

Administration of darolutamide in combination with docetaxel did not result in clinically significant pharmacokinetic changes in either of these drugs in metastatic castration-sensitive prostate cancer patients (mCSPC).

Agent	Effect	Mechanism	Management
Combined P-gp and strong CYP3A4 inducers (i.e. rifampin)	↓ darolutamide exposure (up to 72%), concentration and/or efficacy	↑ metabolism of darolutamide	Avoid when possible.
Combined P-gp, BCRP, and strong CYP3A4 inhibitors (i.e. itraconazole)	↑ darolutamide concentration and/or toxicity	↓ metabolism of darolutamide	Consider an alternative with less inhibition. If co-administered, monitor closely for toxicity.
BCRP substrates (i.e. rosuvastatin)	↑ substrate exposure (up to 5-fold), concentration and/or toxicity	↓ metabolism of substrate	Avoid when possible. If co-administered, monitor closely for toxicity; consider substrate dose reduction.
OATP1B1 or OATP1B3 substrates (i.e. rosuvastatin)	↑ substrate exposure concentration and/or toxicity	↓ metabolism of substrate	Caution; monitor for toxicity. Consider substrate dose reduction.
St. John's Wort	↓ darolutamide concentration and/or efficacy (theoretical)	↑ metabolism of darolutamide	Avoid when possible.

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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
CBC	Baseline and as clinically indicated
Liver function tests	Baseline and as clinically indicated
Renal function tests	Baseline and as clinically indicated
PSA and radiographic disease progression	Baseline and as clinically indicated
Clinical toxicity assessment for fatigue, seizures, musculoskeletal, dermatologic, GI and cardiovascular effects	At each visit

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

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J - Supplementary Public Funding

Exceptional Access Program (EAP Website)

- darolutamide - For the treatment of high risk non-metastatic castration resistant prostate cancer (nmCRPC) according to clinical criteria
- darolutamide - For the treatment of patients with metastatic castration-sensitive prostate cancer (mCSPC) in combination with docetaxel

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K - References

Fizazi K, Shore N, Tammela TL, et al. Darolutamide in Nonmetastatic, Castration-Resistant Prostate Cancer. *N Engl J Med*. 2019;380(13):1235-1246.

Fizazi K, Shore N, Tammela TL, et al. Nonmetastatic, Castration-Resistant Prostate Cancer and

Survival with Darolutamide. N Engl J Med. 2020 Sep 10;383(11):1040-1049.

Prescribing Information: Nubeqa (darolutamide). Bayer HealthCare Pharmaceuticals Inc. January 2021 and October 2023.

Product Monograph: Nubeqa (darolutamide). Bayer Inc. November 2023.

March 2024 Updated Dose modifications and Supplementary public funding sections

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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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