DRUG NAME: Darolutamide

SYNONYM(S): ODM-201, BAY-1841788[1]

COMMON TRADE NAME(S): NUBEQA®

CLASSIFICATION: hormonal agent

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

MECHANISM OF ACTION:

Darolutamide 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 androgen receptor-mediated gene transcription. In xenograft models, darolutamide reduced tumour cell proliferation, which led to decreased tumour volume. Darolutamide competitively inhibits binding of androgens to androgen receptors. Unlike conventional androgen receptor inhibitors, darolutamide lacks agonist activity in cells that overexpress androgen receptors. Darolutamide has demonstrated inhibition in both wild-type and mutant androgen receptors.[2-4]

PHARMACOKINETICS:

Oral Absorption	C_{max}: 4 hours; bioavailability ~30% (fasted state); 2-2.5 fold increase in bioavailability when administered with food	
Distribution	primarily bound to serum albumin	
	cross blood brain barrier?	low penetration based on animal studies; likelihood of clinical relevance in humans is low
	volume of distribution	119 L
	plasma protein binding	92% darolutamide; 99.8% keto-darolutamide
Metabolism	primarily metabolized by CYP 3A4	
	active metabolite(s)	keto-darolutamide (2-fold higher total plasma exposure compared to darolutamide)
	inactive metabolite(s)	no information found
Excretion	primarily by urinary excretion	
	urine	63.4% (~7% unchanged)
	feces	32.4% (~30% unchanged)
	terminal half life	20 h
	clearance	116 mL/min
Elderly	no clinically significant difference	
Ethnicity	no clinically significant difference	

Adapted from standard reference[1-3] unless specified otherwise.

USES:

Primary uses:

*Prostate cancer

Other uses:

*Health Canada approved indication

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SPECIAL PRECAUTIONS:

Caution:
- not indicated for use in ***women***[2]
- patients should not ***donate semen*** while taking darolutamide and for three months following the last dose[2]

Carcinogenicity: no information found[2]

Mutagenicity: Not mutagenic in Ames test and mammalian *in vivo* mutation test. Darolutamide is clastogenic in mammalian *in vitro* chromosome test.[2,3]

Fertility: In animal studies, hypospermia, tubular dilation of testes, and atrophy of the male reproductive tract (e.g., seminal vesicles, testes, prostate gland, and epididymides) were observed. Effects were seen at exposures equal to or below those seen following human clinical exposure. Changes reversed or partially resolved following 4- to 8-week recovery periods.[2,3]

Pregnancy: Reproductive studies have not been conducted. Based on its mechanism of action, however, darolutamide may cause fetal harm or fetal loss if there is exposure during pregnancy. Patients with pregnant female partners should use a condom during treatment and for at least one week, and up to three months, following the last dose. Patients with female partners of childbearing potential should use highly effective contraception during treatment and for at least one week, and up to three months, following the last dose.[2,3]

Breastfeeding is not recommended due to the potential secretion into breast milk. Darolutamide is not intended for use in women.[2]

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.[5,6]
In the clinical trial setting, some adverse events occurred more frequently in the placebo group than the treatment group. These adverse events have been included in the Side Effect table below and are indicated with an asterisk (*).[7-9]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia	anemia (6%, severe <1%)
cardiac	***cardiac arrest*** (severe <1%); fatal events reported
	cardiac failure (2%, severe <1%); fatal events reported
	ischemic heart disease (3-4%, severe 2%)
endocrine	hypothyroidism (<1%)
gastrointestinal	*emetogenic potential:* minimal (rare)[10]
	constipation (6%)
	diarrhea (7%)
	nausea* (5%, severe <1%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
general disorders and administration site conditions	***fatigue*** (16%, severe <1%)
	general physical health deterioration (severe <1%)
injury, poisoning, and procedural complications	bone fracture (4%, severe <1%)
investigations	AST increase (23%, severe <1%)
	bilirubin increase (16%, severe <1%)
	weight decrease (4%)
musculoskeletal and connective tissue	pain in extremity (6%)
nervous system	cognitive disorder (<1%)
	dizziness (5%, severe <1%)
	seizure (<1%)
renal and urinary	***hematuria**** (5%, severe 1%)[8]
	urinary retention* (4%, severe 2%) [8]
respiratory, thoracic and mediastinal	***pneumonia**** (severe <1%); fatal events reported[8]
skin and subcutaneous tissue	***rash*** (3%, severe <1%)
vascular	hot flashes (5%)
	hypertension (7%, severe 3%)
	pulmonary embolism (severe <1%); fatal events reported

Adapted from standard reference[2,3,7] unless specified otherwise.

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
rifampin[2,3]	72% decrease in AUC and 52% decrease in C_{max} of darolutamide	strong induction of CYP 3A4 and induction of P-gp by rifampin	avoid concurrent use
itraconazole[2,3]	1.7-fold increase in AUC and 1.4-fold increase in C_{max} of darolutamide	strong inhibition of CYP 3A4 and inhibition of P-gp and BCRP by itraconazole	avoid concurrent use; if coadministration cannot be avoided, monitor for darolutamide toxicity
rosuvastatin[2,3]	5-fold increase in AUC and C_{max} of rosuvastatin	inhibition of BCRP by darolutamide	avoid concurrent use; if coadministration cannot be avoided, monitor for rosuvastatin toxicity

Darolutamide is a ***substrate*** of ***CYP 3A4,*** P-glycoprotein ***(P-gp)***, and Breast Cancer Resistance Protein ***(BCRP)***. Drugs that are ***combined*** P-gp and moderate or strong CYP 3A4 ***inducers*** may decrease darolutamide plasma levels and reduce treatment efficacy; avoid concurrent use. Drugs that are ***combined*** P-gp, BCRP and strong CYP 3A4 ***inhibitors*** may increase darolutamide

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plasma levels; avoid concurrent use. If coadministration cannot be avoided, monitor for darolutamide toxicity. Grapefruit and grapefruit juice may inhibit CYP 3A4 metabolism of darolutamide in the intestinal wall and, theoretically, may increase darolutamide plasma levels; clinical significance is unknown.[2,3,11]

Darolutamide is an ***inhibitor*** of ***BCRP*** and ***P-gp*** *in vitro*. Coadministration with a ***BCRP substrate*** may increase BCRP substrate-related toxicities; avoid concurrent use. Coadministration of darolutamide with a ***P-gp substrate*** is not considered to result in a clinically significant drug interaction.[2,3]

Darolutamide is an ***inhibitor*** of ***OATP1B1*** and ***OATP1B3*** *in vitro*; coadministration with OATP1B1 and OATP1B3 substrates may increase OATP1B1 and OATP1B3 substrate toxicity. Clinical significance is unknown; dose modification of the substrate may be required.[12]

Darolutamide is a weak ***inducer*** of ***CYP 3A4***. Coadministration of darolutamide with a CYP 3A4 substrate is not considered to result in a clinically significant interaction.[2]

Darolutamide is an inhibitor of OAT3, MATE1, MATE2K and intestinal MRP2 *in vitro;* clinical significance is unknown.[2]

SUPPLY AND STORAGE:

Oral: Bayer Inc. supplies darolutamide as 300 mg film-coated tablets. Tablets contain lactose. Store at room temperature.[2]

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[2,3,13]:

600 mg (range 300 – 600 mg) ***PO given twice daily***

Administer with food[2]

Concurrent radiation:

no information found

Dosage in renal failure:

Creatinine clearance (mL/min)	Dose
>30	no adjustment required[2]
15-29	300 mg PO BID[2,3]
<15	no information found

calculated creatinine clearance = N* x (140 - Age) x weight in kg / serum creatinine in micromol/L

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

Dosage in hepatic failure:

mild hepatic impairment (Child-Pugh class A): no adjustment required[2]
moderate hepatic impairment (Child-Pugh class B): 300 mg PO BID[2,3]
severe hepatic impairment (Child-Pugh class C): no information found

Dosage in dialysis:

no information found

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Children: safety and efficacy have not been established[2]

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