DRUG NAME: Nivolumab-relatlimab

SYNONYM(S): L01XY03

COMMON TRADE NAME(S): OPDUALAG®

CLASSIFICATION: immunotherapy

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

MECHANISM OF ACTION:

Nivolumab-relatlimab is a fixed-dose combination of two fully humanized IgG4 monoclonal antibodies: nivolumab (a programmed cell death 1 (PD-1) immune checkpoint inhibitor) and relatlimab (a lymphocyte-activation gene 3 (LAG-3) immune checkpoint inhibitor). The PD-1 pathway is an immune system checkpoint that may be exploited by tumour cells to escape active T-cell surveillance. By blocking the binding of the PD-1 receptor to PD-1 and PD-2 ligands, nivolumab reactivates tumour-specific cytotoxic T-lymphocytes in the tumour microenvironment and restimulates anti-tumour activity. Similarly, LAG-3 is an immune checkpoint receptor protein which has a major role in negatively regulating T-cell function and providing tumours with an immune escape in the tumour microenvironment. By binding to the LAG-3 T-cell receptor and blocking its interaction with ligands, relatlimab reduces LAG-3 pathway inhibition of the immune response and promotes T-cell proliferation and cytokine secretion. The combination of nivolumab and relatlimab results in increased T-cell activation compared to the activity of either antibody alone.[1-4]

PHARMACOKINETICS:

Distribution	nivolumab: tissue penetration or distribution is not known; relatlimab: steady-state concentrations by 16 weeks	
	cross blood brain barrier?	no information found
	volume of distribution	nivolumab: 6.65 L relatlimab: 6.65 L
	plasma protein binding	no information found
Metabolism	expected to degrade to small peptides and individual amino acids	
	active metabolite(s)	no information found
	inactive metabolite(s)	no information found
Excretion	steady-state clearance is 21.1% lower (nivolumab) and 9.7% lower (relatlimab) than clearance after the first dose	
	urine	no information found
	feces	no information found
	terminal half life	nivolumab: 26.5 d relatlimab: 26.2 d
	clearance	nivolumab: 7.57 mL/h relatlimab: 5.48 mL/h
Children	reported clearance and volume of distribution of nivolumab in pediatric patients are 36% and 16% lower respectively than in adults; however, no clinically relevant differences in the exposure of nivolumab and relatlimab are expected between adults and pediatric patients ≥12 years of age weighing at least 40 kg	
Sex	no clinically relevant difference	

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

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USES:

Primary uses:
*Melanoma

Other uses:

*Health Canada approved indication

SPECIAL PRECAUTIONS:

Caution:
- avoid ***systemic corticosteroids or immunosuppressants*** prior to starting nivolumab-relatlimab due to potential interference with its efficacy; corticosteroids or immunosuppressants may be used during treatment with nivolumab-relatlimab in the management of immune-mediated adverse reactions[1]
- ***solid organ transplant rejection*** has been reported in patients treated with PD-1 inhibitors[1]
- serious ***transplant-related complications*** (e.g., graft-versus-host disease) have been reported in patients receiving allogeneic HSCT before or after treatment with a PD-1/PDL1 blocking antibody[1,2]
- the safety and efficacy of ***vaccination*** in patients receiving immunotherapy is currently being investigated[5-8]
- nivolumab-relatlimab is ***NOT interchangeable*** with nivolumab and should not be substituted[2]

Carcinogenicity: no information found

Mutagenicity: no information found

Fertility: In animal studies with nivolumab-relatlimab, inflammation of the reproductive tract was observed in a male test subject. However, most test subjects were not sexually mature. Clinical significance is unknown. In human clinical trials with nivolumab-relatlimab, azoospermia has been reported in <1% of patients.[1]

Pregnancy: Nivolumab-relatlimab has not been studied in pregnant women. Human IgG4 is known to cross the placental barrier; therefore, as a combination of human IgG4 antibodies, nivolumab-relatlimab is expected to be transmitted from mother to fetus. The effects of nivolumab-relatlimab are expected to be greater during the second and third trimesters of pregnancy. In animal reproductive studies with nivolumab, non-dose-related spontaneous abortion and neonatal death were increased. In females of childbearing potential, pregnancy tests are recommended prior to starting treatment and contraception is recommended during treatment and for five months after the last dose.[1,2]

Breastfeeding is not recommended due to the potential secretion into breast milk. Because of the potential for serious adverse reactions in breastfed infants, women should not breastfeed during treatment and for five months after the last dose.[1,2]

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[9,10].

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia	anemia (37-41%, severe 3-4%)
	eosinophilia (3%)
	hemolytic anemia (<1%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	leukopenia (13%)
	lymphopenia (32-35%, severe 3%)
	neutropenia (13%)
cardiac	acute myocardial infarction (1%)
	myocarditis (1-2%, severe <1%)
	pericardial effusion (<1%)
endocrine	***adrenal insufficiency*** (4-5%, severe 1%)
	hyperthyroidism (6-7%)
	hypogonadism (<1%)
	hypophysitis (1-3%, severe <1%)
	hypopituitarism (<1%)
	hypothyroidism (16-17%)
	thyroiditis (3%)
eye	dry eye (2%)
	increased lacrimation (1%)
	ocular hyperaemia (<1%)
	uveitis (1%)
	visual impairment (2%)
	Vogt-Koyanagi-Harada disease (<1%)
gastrointestinal	*emetogenic potential:* low[11,12]
	abdominal pain (14%, severe <1%)
	colitis (3-7%, severe 1%)
	constipation (11%, severe <1%)
	diarrhea (24-26%, severe 2%)
	dry mouth (9%)
	dysphagia (2%)
	esophagitis (<1%)
	gastritis (3%, severe <1%)
	nausea (17-19%, severe <1%)
	pancreatitis (1%)
	stomatitis (3%)
	vomiting (10%, severe <1%)
	extravasation hazard: none[13]
	chills (4%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
general disorders and administration site conditions	edema (9%, severe <1%)
	fatigue (39-41%, severe 2%)
	influenza-like illness (5%)
	multi-organ failure (severe <1%); fatal events reported
	pyrexia (12%)
hepatobiliary	cholangitis (<1%)
	hepatitis (1-6%, severe 1%)
immune system (see paragraph following **Side Effects** table)	***hemophagocytic lymphohistiocytosis*** (severe <1%); fatal events reported
	immune-mediated adrenal insufficiency (4-5%, severe 1%); median time to onset = 13 weeks
	immune-mediated diabetes mellitus (severe <1%); median time to onset = 13 weeks
	immune-mediated gastrointestinal adverse reactions including diarrhea, colitis (7-16%, severe ≤2%); median time to onset = 14 weeks
	immune-mediated hepatic adverse reactions (6-13%, severe 4%); median time to onset = 11 weeks
	immune-mediated myocarditis (1-2%, severe <1%); median time to onset = 4.1 weeks
	immune-mediated pituitary disorders including hypophysitis (3%, severe <1%); median time to onset = 13 weeks
	immune-mediated pulmonary adverse reactions including pneumonitis, interstitial lung disease (5%, severe <1%); median time to onset = 28 weeks
	immune-mediated renal adverse reactions (2-5%, severe 1%); median time to onset = 21 weeks
	immune-mediated skin adverse reactions (9-45%, severe 1%); median time to onset = 8 weeks
	immune-mediated thyroid disorders (21-26%); median time to onset = 13 weeks
infections and infestations	folliculitis (<1%)
	pneumonia (1%)
	upper respiratory tract infection (9%)
	urinary tract infection (11%, severe 1%)
injury, poisoning, and procedural complications	***infusion-related reaction*** (7%); see paragraph following **Side Effects** table
investigations	alkaline phosphatase increase (19-22%, severe <1%)
	ALT increase (26-30%, severe 3-4%)
	AST increase (30-34%, severe 2-3%)
	c-reactive protein increase (<1%)
	creatinine increase (19-24%, severe <1%)
	hypercalcemia (12%, severe <1%)
	hyperkalemia (16%, severe 2%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	hypocalcemia (17%, severe <1%)
	hypokalemia (10%, severe <1%)
	hypomagnesemia (16%, severe <1%)
	hyponatremia (24-27%, severe <2%)
	weight loss (9%, severe 1%)
metabolism and nutrition	appetite decrease (15-16%, severe <1%)
	dehydration (1%, severe <1%)
	diabetes mellitus (1%, severe <1%)
	hyperuricemia (3%)
	hypoalbuminemia (2%)
musculoskeletal and connective tissue	***arthralgia*** (26%, severe 2%)
	arthritis (6%, severe <1%)
	back pain (severe 1%)
	muscle spasms (3%)
	muscular weakness (3%, severe <1%)
	musculoskeletal pain (32-45%, severe 2-4%)
	myositis (<1%)
	polymyalgia rheumatica (<1%)
	rheumatoid arthritis (<1%)
	Sjogren's Syndrome (<1%)
	systemic lupus erythematosus (<1%)
nervous system	dizziness (10%)
	dysgeusia (2%)
	encephalitis (<1%)
	Guillain-Barré syndrome (<1%)
	headache (18-20%, severe <1%)
	optic neuritis (<1%)
	peripheral neuropathy (6%)
psychiatric	confusional state (2%, severe <1%)
renal and urinary	***nephritis*** (<2%)
	proteinuria (1%)
	renal failure (2%, severe 1%)
reproductive system and breast disorders	azoospermia (<1%)
	acute lung edema (severe <1%); fatal events reported

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
respiratory, thoracic and mediastinal	asthma (<1%)
	cough (15-16%, severe <1%)
	dyspnea (10%, severe 1%)
	nasal congestion (3%)
	pneumonitis (4-5%, severe 1%); fatal events reported
skin and subcutaneous tissue	***alopecia*** (2%)
	dry skin (4%)
	lichenoid keratosis (1%)
	pemphigoid (<1%)
	photosensitivity reaction (1%)
	pruritus (25-26%)
	psoriasis (<1%)
	rash (9-29%, severe <2%)
	urticaria (<1%)
	vitiligo (13%)
vascular	phlebitis (1%)

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

Immune-mediated adverse reactions, some of which may be severe or fatal, have been reported with nivolumab-relatlimab. Immune-mediated adverse reactions can affect any organ system and reactions affecting more than one organ system can occur simultaneously. Early identification and management are essential to the safe use of nivolumab-relatlimab. While immune-mediated adverse reactions usually occur *during* treatment, they may also manifest after treatment has been discontinued. Patients should be monitored at least up to five months after treatment has ended. When corticosteroids are administered to treat an adverse reaction, dose tapering over at least one month is recommended following the resolution of symptoms because rapid tapering may lead to worsening or recurrence of the adverse reaction. Permanently discontinue nivolumab-relatlimab for any life-threatening immune-mediated adverse reaction or for any severe immune-mediated adverse reaction that recurs.[1,2] For further information on management of immune-mediated adverse reactions, see BC Cancer Protocol SCIMMUNE ***Management of Immune-Mediated Adverse Reactions to Checkpoint Inhibitors Immunotherapy***.

Infusion-related reactions are reported in up to 7% of patients and, in rare cases, can be severe. Median time to onset is 4.1 weeks (range: 0.1 to 57.6 weeks).[14] Depending on severity, reactions are usually managed by interrupting or slowing the rate of infusion, although permanent discontinuation of nivolumab-relatlimab may be required.[1,2] For management of infusion-related reactions, see BC Cancer Protocol SCDRUGRX ***Management of Infusion-Related Reactions to Systemic Therapy Agents***.

INTERACTIONS: Nivolumab and relatlimab are not metabolized by cytochrome P450 or other drug metabolizing enzymes**;** therefore, inhibition or induction of these enzymes by co-administered agents is not anticipated to affect the pharmacokinetics of nivolumab or relatlimab.[1]

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SUPPLY AND STORAGE:

***Injection*:** Bristol-Myers Squibb Canada supplies nivolumab-relatlimab as single-use vials (preservative free) containing 240 mg nivolumab (in a concentration of 12 mg/mL) and 80 mg relatlimab (in a concentration of 4 mg/mL) per vial. Refrigerate. Keep in original carton to protect from light. Do not shake.[1]

For basic information on the current brand used at BC Cancer, see Chemotherapy Preparation and Stability Chart in Appendix.

SOLUTION PREPARATION AND COMPATIBILITY:

For basic information on the current brand used at BC Cancer, see Chemotherapy Preparation and Stability Chart in Appendix.

Additional information:
- can be administered undiluted or diluted with NS or D5W[1,2]
- a few translucent-to-white particles may be present; discard if solution is cloudy, discoloured, or extraneous particulates are present[1,2]
- in adult patients weighing <40 kg: maximum infusion volume of 4 mL/kg is intended to prevent exceeding endotoxin limit[1,2,15]

Compatibility: consult detailed reference

PARENTERAL ADMINISTRATION:

BC Cancer administration guideline noted in ***bold***, ***italics***

Subcutaneous	no information found
Intramuscular	no information found
Direct intravenous[1]	do NOT use
Intermittent infusion[1,2]	over 30 minutes; administer using a 0.2-1.2 micron in-line filter
Continuous infusion	no information found
Intraperitoneal	no information found
Intrapleural	no information found
Intrathecal	no information found
Intra-arterial	no information found
Intravesical	no information found

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated.

***Adults*:**

BC Cancer usual dose noted in ***bold, italics***

	Cycle Length:	
Intravenous[1,2,4]*:*	4 weeks:	nivolumab 480 mg and relatlimab 160 mg IV for one dose on day 1 (total dose per cycle nivolumab 480 mg and relatlimab 160 mg) Dose reductions are not recommended[1,2].

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Concurrent radiation:	no information found
Dosage in myelosuppression:	modify according to protocol by which patient is being treated
Dosage in renal failure[1]*:*	CrCl ≥30 mL/min: no adjustment required CrCl <30 mL/min: 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[1]*:*	mild/moderate impairment (bilirubin ≤3 x ULN): no adjustment required severe hepatic impairment: no information found
Dosage in dialysis:	no information found

Children: safety and efficacy has not been established in patients <12 years of age OR patients ≥12 years of age weighing <40 kg[1]

Intravenous[1,2]*:*	Cycle Length: 4 weeks:	in patients ≥12 years of age and ≥40 kg: nivolumab 480 mg and relatlimab 160 mg IV for one dose on day 1 (total dose per cycle nivolumab 480 mg and relatlimab 160 mg)

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