DRUG NAME: Dostarlimab

SYNONYM(S): TSR-042 [1]

COMMON TRADE NAME(S): JEMPERLI®

CLASSIFICATION: immunotherapy

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

MECHANISM OF ACTION:

Dostarlimab is a humanized IgG4 monoclonal antibody immune checkpoint inhibitor that binds to programmed death receptor-1 (PD-1) on T cells and blocks the interaction with its ligands, PD-L1 and PD-L2. Blocking PD-L1 and PD-L2 releases the inhibition of the PD-1 pathway-mediated immune response, including the anti-tumour immune response, and results in decreased tumour growth. [2]

PHARMACOKINETICS:

Absorption	immediately and completely bioavailable after IV administration[3]; peak concentrations are observed shortly after the end of the 30 minute infusion[4]	
Distribution	small volume of distribution; distribution largely in the systemic circulation and interstitial spaces[4]	
	cross blood brain barrier?	no information found
	volume of distribution	5.81 L[3]
	plasma protein binding	no information found
Metabolism	not characterized; expected to be degraded into small peptides and amino acids via catabolic non-specific pathways in the same manner as endogenous IgG[3]	
	active metabolite(s)	no information found
	inactive metabolite(s)	no information found
Excretion	time-dependent linear elimination; essentially excluded from glomerular filtration due to its molecular size and there is no evidence for renal tubular secretion of IgG antibodies[4]	
	urine	no information found
	feces	no information found
	terminal half life	23.2 days[3]
	clearance	6.81 mL/h at steady state[3]
Sex	no effect on pharmacokinetic parameters[3]	
Elderly	no effect on pharmacokinetic parameters[3]	
Ethnicity	no effect on pharmacokinetic parameters[3]	

Adapted from standard reference[3,4] unless specified otherwise.

USES:

Primary uses:

*Endometrial cancer

Other uses:

*Health Canada approved indication

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SPECIAL PRECAUTIONS:

Caution:
- the safety and efficacy of ***vaccination*** in patients receiving immunotherapy is currently being investigated [5-8]
- ***solid organ transplant rejection*** has been reported in patients treated with PD-1 inhibitors [2]
- 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/PD-L1 blocking antibody [2]
- avoid ***systemic corticosteroids*** or ***immunosuppressants*** prior to starting dostarlimab due to potential interference with its efficacy; corticosteroids or immunosuppressants may be used during treatment with dostarlimab in the management of immune-mediated adverse reactions [2]

Carcinogenicity: no information found

Mutagenicity: no information found

Fertility: In animal toxicology studies, there were no notable effects in male or female reproductive organs. However, these results are not considered to be representative of the potential clinical risks because of the immaturity of the reproductive systems in the study subjects. Therefore, fertility toxicity remains unknown.[3]

Pregnancy: Inhibition of the PD-1/PD-L1 pathway has been shown in animal studies to disrupt tolerance to the fetus and result in increased fetal loss. Human IgG4 immunoglobulins are known to cross the placental barrier so dostarlimab has the potential to be transmitted from mother to fetus. Therefore, based on its mechanism of action, dostarlimab may cause fetal harm, including increased rates of abortion and stillbirth if administered during pregnancy. Female patients of childbearing potential should use contraception during treatment with dostarlimab and for 4 months after the last dose of dostarlimab.[3]

Breastfeeding is not recommended due to the potential secretion into breast milk. Because of the potential for serious adverse reactions in breastfed children, breastfeeding should be avoided during treatment and for at least 4 months after the last dose of dostarlimab.[3]

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. When placebo-controlled trials are available, adverse events will generally be included if the incidence is ≥5% higher in the treatment group.

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia	anemia (33-50%, severe 17-18%)
	leukocyte count decrease (20%, severe 5%)
	lymphocyte count decrease (45%, severe 14%)
	neutrophil count decrease (17%, severe 3%)
gastrointestinal	*emetogenic potential:* low [9]
	constipation (16-23%)[10]
	diarrhea (29%, severe 3%)
	gastritis (3%, severe 1%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	nausea (33%, severe 1%)
	pancreatitis, acute (<1%)
	vomiting (22%, severe 1%)
general disorders and administration site conditions	*extravasation hazard:* none [11]
	chills (7%)
	fatigue, asthenia (42-49%)[10]
	pyrexia (14%)
hepatobiliary	hepatic cytolysis (<1%)
immune system (see paragraph following **Side Effects** table)	***immune-mediated adrenal insufficiency*** (1%)
	immune-mediated arthritis (<1%)
	immune-mediated colitis (2%, severe 1%)
	immune-mediated enterocolitis (<1%)
	immune-mediated hepatitis (severe <1%)
	immune-mediated hyperthyroidism (5%, severe <1%)
	immune-mediated hypophysitis (<1%)
	immune-mediated hypothyroidism (12%)
	immune-mediated myositis (<1%)
	immune-mediated nephritis, tubulointerstitial nephritis (<1%)
	immune-mediated pancreatitis (<1%)
	immune-mediated pneumonitis, interstitial lung disease (4%, severe 1%)
	immune-mediated rash, skin toxicity (17%, severe 2%); median time to onset 57 days
	immune-mediated thyroiditis (<1%)
	immune-mediated uveitis, iridocyclitis (<1%)
infections and infestations	encephalitis (<1%)
	sepsis[10] (3%)
	urinary tract infection[10] (19%)
injury, poisoning, and procedural complications	***infusion-related reactions*** (1%, severe <1%); see paragraph following **Side Effects** table
investigations	albumin decrease (35%, severe 3%)
	alkaline phosphatase increase (30%, severe 3%)
	ALT increase (9-25%, severe 3-5%)
	AST increase (9-31%, severe 1-2%)
	creatinine increase (32%, severe 3%)
	hypercalcemia (7%, severe 2%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	hypokalemia (22%, severe 2%)
	hypomagnesemia (27%, severe 2%)
	hyponatremia (29%, severe 6%)
metabolism and nutrition	appetite decrease (21%, severe <1%)
musculoskeletal and connective tissue	***arthralgia*** (22%, severe 2%)
	myalgia (11%)
skin and subcutaneous tissue	erythema (4%)
	pruritus (19%, severe 1%)

Adapted from standard reference [2] unless specified otherwise.

Immune-mediated adverse reactions, sometimes fatal, can involve any organ system. Onset usually occurs during the treatment period, but symptoms can manifest after discontinuation of treatment. Early diagnosis and appropriate management are necessary to minimize life-threatening complications. Prompt use of corticosteroids may be required to manage symptoms. Based on the severity of the reaction, dostarlimab may be withheld or permanently discontinued. Permanent discontinuation is recommended for grade 4 and recurrent grade 3 immune-mediated reactions. Endocrinopathies may require specialist consultation but may be controlled with replacement hormones as indicated. 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 rarely reported but may be severe. Depending on severity, reactions may be managed by interrupting or slowing the rate of infusion, although permanent discontinuation of dostarlimab may be required. For management of infusion-related reactions, see BC Cancer Protocol SCDRUGRX ***Management of Infusion-Related Reactions to Systemic Therapy Agents***.

INTERACTIONS: No information found. Dostarlimab is considered to have low potential to affect the pharmacokinetics of other drugs due to a lack of effect on cytokines, cytochrome P450, and active substance transporters. [3]

SUPPLY AND STORAGE:

Injection: GlaxoSmithKline Inc. supplies dostarlimab as 500 mg single-use (preservative free) vials in a concentration of 50 mg/mL. Refrigerate. Store in original carton to protect from light. [2]

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: Discard if visible particles are present. [2]

Compatibility: consult detailed reference

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PARENTERAL ADMINISTRATION:

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

Subcutaneous	no information found
Intramuscular	no information found
Direct intravenous [2]	do NOT use
Intermittent infusion [2,12,13]	***over 30 minutes***; administer using 0.2 or 0.22 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***

Intravenous:

Cycle Length:

3 weeks [2,12,13]: ***500 mg IV for one dose on day 1***
(total dose per cycle 500 mg)

6 weeks [2,12,13]: ***1000 mg IV for one dose on day 1***
(total dose per cycle 1000 mg)

Dose reduction is not recommended. Dose delays or drug discontinuation may be required based on tolerability. [2]

Concurrent radiation: no information found

Dosage in myelosuppression: modify according to protocol by which patient is being treated; if no guidelines available, refer to Appendix "Dosage Modification for Myelosuppression"

Dosage in renal failure[3]*:* mild to moderate impairment (eGFR ≥30 mL/min/1.73 m^2): no adjustment required
severe impairment (eGFR <30 mL/min/1.73 m^2): no information found

Dosage in hepatic failure[3]*:* mild impairment (bilirubin ≤1.5 x ULN and any AST): no adjustment required
moderate to severe impairment (bilirubin >1.5 ULN and any AST): no information found

Dosage in dialysis[3]*:* no information found

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Children: safety and efficacy has not been established

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