DRUG NAME: Cemiplimab

SYNONYM(S): cemiplimab-rwlc [1,2], REGN-2810 [3]

COMMON TRADE NAME(S): LIBTAYO®

CLASSIFICATION: immunotherapy

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

MECHANISM OF ACTION:

Cemiplimab is a recombinant human IgG monoclonal antibody known as a programmed cell death 1 (PD-1) 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. Cemiplimab binds to PD-1 on T cells and blocks the interaction with its ligands, PD-L1 and PD-L2. Inhibition of the receptor/ligand signaling restores the anti-tumour immune response. [2,4]

PHARMACOKINETICS:

Absorption	immediately and completely available when administered IV	
Distribution	primarily distributed in the vascular system [5]; steady state after 4 months of treatment	
	cross blood brain barrier?	no information found
	volume of distribution	5.9 L
	plasma protein binding	no information found
Metabolism	entirely metabolized by proteolysis; expected to degrade to small peptides and individual amino acids [2,4,6]	
	active metabolite(s)	none
	inactive metabolite(s)	no information found
Excretion	linear and dose proportional pharmacokinetics	
	urine	no information found
	feces	no information found
	terminal half life	22 days (estimate) at steady state
	clearance	0.22 L/day at steady state

Adapted from standard reference [7] unless specified otherwise.

USES:

Primary uses:

*Cervical cancer
*Lung cancer, non-small cell
*Skin cancer, basal cell
*Skin cancer, squamous cell

Other uses:

*Health Canada approved indication

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SPECIAL PRECAUTIONS:

Caution:
- ***solid organ transplant rejection*** has been reported; risk of rejection in transplant recipients may increase [4]
- patients receiving ***allogeneic stem cell transplantation*** before or after treatment with a PD-1/PD-L1 inhibitor may experience serious or fatal complications such as graft-versus-host disease or hepatic veno-occlusive disease [8,9]
- avoid systemic ***corticosteroids*** or ***immunosuppressants*** prior to starting cemiplimab due to potential interference with the efficacy of cemiplimab; corticosteroids or immunosuppressants may be used during treatment with cemiplimab in the management of immune-mediated adverse reactions [6,10,11]
- the safety and efficacy of ***vaccination*** in patients receiving immunotherapy is currently being investigated [12-15]

Special populations: No overall differences in efficacy are observed between ***older*** and younger patients; however, there is a trend towards a higher frequency of serious adverse events in patients 65 years and older. [7]

Carcinogenicity: no information found

Mutagenicity: no information found

Fertility: In animal studies, no effects were observed on fertility parameters or male and female reproductive organs. [2,4]

Pregnancy: Cemiplimab has not been studied in pregnant women. Human IgG4 is known to cross the placental barrier; therefore, as a human IgG4 antibody, cemiplimab is expected to be transmitted from mother to fetus. In murine models, blocking PD-L1 signaling disrupted tolerance to the fetus and resulted in an increase in fetal loss. Women of reproductive potential should use effective contraception while on cemiplimab and for at least four months following the last dose. [2,4]

Breastfeeding is not recommended due to the potential secretion into breast milk. Antibodies, including IgG4, are known to be secreted into human breast milk. Avoid breastfeeding during treatment and for at least four months following the last dose. [2,4,16]

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. [17,18] 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 (11%, severe 2-5%)
	immune-mediated thrombocytopenic purpura (<1%)
	lymphopenia (severe 7-9%)
cardiac	***immune-mediated myocarditis*** (<1%, severe <1%)
	immune-mediated pericarditis (<1%)
endocrine	***adrenal insufficiency, immune-mediated adrenal insufficiency*** (<1%, severe <1%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	immune-mediated type I diabetes mellitus (1%, severe 1%); may present with ketoacidosis
	hyperthyroidism, immune-mediated hyperthyroidism (2%, severe <1%)
	hypophysitis, immune-mediated hypophysitis (<1%, severe <1%)
	hypothyroidism, immune-mediated hypothyroidism (6-10%, severe <1%)
eye (see paragraph following **Side Effects** table)	***immune-mediated iritis*** (<1%)
	immune-mediated ocular inflammation (<1%)
	immune-mediated uveitis (<1%)
gastrointestinal	*emetogenic potential:* low [19]
	constipation (12-13%, severe 1%)
	diarrhea (12-25%, severe 1%)
	immune-mediated colitis (1%, severe <1%)
	immune-mediated pancreatitis (<1%)
	nausea (19-21%)
	vomiting (10%, severe <1%)
general disorders and administration site conditions	*extravasation hazard:* none [20]
	fatigue (21-34%, severe 1-3%)
hepatobiliary	***hepatitis, immune-mediated hepatitis*** (2%, severe 2%); sometimes fatal
immune system	refer to organ site; see paragraph following **Side Effects** table
	Sjogren's syndrome (<1%)
infections and infestations	***cellulitis*** (severe ≥2%)
	pneumonia (severe ≥2%)
	sepsis (severe ≥2%)
	skin infection (severe ≥2%)
	urinary tract infection (severe ≥2%)
injury, poisoning, and procedural complications	infusion-related reactions (4-9%, severe <1%); see paragraph following **Side Effects** table
investigations	alkaline phosphatase increase (2%)
	ALT increase (5%, severe 1%)
	AST increase (4%, severe 1-3%)
	INR increase (severe 2%)
	hypercalcemia (severe 2%)
	hyponatremia (severe 5%)
	hypophosphatemia (severe 4%)
	serum creatinine increase (2%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
metabolism and nutrition	appetite decrease (10%)
	hypoalbuminemia (severe 1%)
musculoskeletal and connective tissue	arthritis (1%, severe 1%)
	arthralgia (11%, severe 1%)
	musculoskeletal pain (17-24%, severe 3%)
	myalgia (3%, severe 1%)
	myositis, immune-mediated myositis, rhabdomyolysis (<1%)
nervous system	chronic inflammatory demyelinating polyradiculoneuropathy (<1%)
	immune-mediated encephalitis (<1%, severe <1%)
	immune-mediated Guillain-Barre syndrome (<1%, severe <1%)
	immune-mediated myasthenia gravis (<1%)
	immune-mediated myelitis and demyelination (<1%)
	immune-mediated paraneoplastic encephalomyelitis (<1%, severe <1%); sometimes fatal
	meningitis, immune-mediated meningitis (<1%, severe <1%)
renal and urinary	***nephritis, immune-mediated nephritis*** (1%, severe <1%)
respiratory, thoracic and mediastinal	cough (14%)
	pneumonitis, immune-mediated pneumonitis (2-4%, severe 1%); sometimes fatal
skin and subcutaneous tissue	erythema multiforme and pemphigoid (2%, severe 1%)
	pruritis (10-18%)
	rash (20-31%, severe 1%)
	Stevens-Johnson syndrome (<1%); sometimes fatal
	toxic epidermal necrolysis (<1%); sometimes fatal
vascular	***hypertension*** (severe ≥2%)
	immune-mediated vasculitis (<1%)

Adapted from standard reference [1,2,4,8,9,21] unless specified otherwise.

Cemiplimab is a programmed death receptor-1 (PD-1) inhibitor, a class of drugs which, by its mechanism, removes the inhibition of the immune response. Therefore, ***immune-mediated adverse events*** can occur in any organ system or tissue and reactions may be severe or fatal. While immune-mediated reactions usually occur *during* the course of treatment, they may also manifest *after* the PD-1 inhibitor has been discontinued. Early identification and management of immune-mediated side effects are essential for safe use of cemiplimab. In general, cemiplimab is withheld for grade 3 or 4 reactions and some grade 2 reactions, and permanently discontinued for grade 4 reactions. Corticosteroids are administered until reactions improve to grade 1 or less, and then tapered over one month. Other systemic immunosuppressants may be required if reactions are not controlled with corticosteroids. For symptomatic endocrinopathies, appropriate hormone therapy may be required. ***Permanent discontinuation*** of cemiplimab should be considered for the following:

- grade 3-4: pneumonitis, hepatitis, nephritis, immune-related skin reaction, other immune-related adverse reactions including but not limited to neurologic adverse events, myelitis, myositis, rhabdomyolysis or

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myocarditis [18], immune-related adverse reactions in patients with prior treatment with idelalisib (excluding endocrinopathies)
- grade 4: colitis, skin adverse reactions or confirmed Stevens-Johnson syndrome/toxic epidermal necrolysis, immune-mediated adverse reactions involving a major organ
- recurrent or persistent immune-mediated adverse reactions. [2,16,18]

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 9% of patients and, in rare cases, can be severe. Depending on severity, reactions may be managed by interrupting or slowing the rate of infusion, although permanent discontinuation of cemiplimab may be required. [2,4] For management of infusion-related reactions, see BC Cancer Protocol SCDRUGRX ***Management of Infusion-Related Reactions to Systemic Therapy Agents***.

Uveitis, iritis, and other immune-mediated ***ocular toxicities*** are rare but in some cases have been associated with retinal detachment. Varying degrees of visual impairment, including blindness, can occur. Consider a diagnosis of Vogt-Koyanagi-Harada-like syndrome if uveitis occurs in combination with other immune-mediated reactions. Systemic corticosteroids may be required to reduce the risk of permanent vision loss. [2]

INTERACTIONS: no information found

SUPPLY AND STORAGE:

***Injection*:**

sanofi-aventis Canada Inc supplies cemiplimab as 250 mg and 350 mg ready to use, single-use (preservative free) vials in a concentration of 50 mg/mL. Refrigerate. Do not shake. Protect from light. [4]

Regeneron Canada Company supplies cemiplimab as 350 mg ready-to-use, single-use (preservative free) vials in a concentration of 50 mg/mL. Refrigerate. Protect from light. Do not shake. [7]

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:
- vials may contain trace amounts of translucent to white particles [7]

Compatibility: consult detailed reference

PARENTERAL ADMINISTRATION:

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

Subcutaneous	no information found
Intramuscular	no information found
Direct intravenous	no information found
Intermittent infusion	***over 30 minutes*** [4,16]; use a 0.2-5 micron in-line filter to administer [22]

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

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:	***3 weeks*** [8,9,22]:	***350 mg IV for one dose on day 1*** (total dose per cycle 350 mg) Dose reductions are not recommended
	2 weeks [8]:	3 mg/kg IV for one dose on day 1 (total dose per cycle 3 mg/kg) Dose reductions are not recommended
Concurrent radiation:	no information found	
Dosage in myelosuppression:	modify according to protocol by which patient is being treated	
Dosage in renal failure:	CrCl ≥30 mL/min: no adjustment required [4,8] CrCl <30 mL/min: no information found	
	calculated creatinine clearance = $\frac{N^* \times (140 - Age) \times \text{weight in kg}}{\text{serum creatinine in micromol/L}}$ * For males N=1.23; for females N=1.04	
Dosage in hepatic failure:	no information found	
Dosage in dialysis:	no information found	

Children: safety and efficacy have not been established [4]

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