DRUG NAME: Ipilimumab

SYNONYM(S): MDX-010[1]; BMS-734016[1]

COMMON TRADE NAME(S): YERVOY®

CLASSIFICATION: immunotherapy

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

MECHANISM OF ACTION:

Ipilimumab is a recombinant, fully human monoclonal antibody that binds to and blocks human cytotoxic T lymphocyte-associated antigen 4 (CTLA-4). Blocking CTLA-4 results in T-cell activation, proliferation, and lymphocyte infiltration into organ tissues and tumours, which leads to tumour cell death. Ipilimumab is an immune-potentiator and can cause inflammatory adverse reactions resulting from increased or excessive immune activity related to its mechanism of action.[2]

PHARMACOKINETICS:

Distribution	confined primarily to the extracellular fluid volume (consistent with its large molecular weight); steady state achieved by fourth dose	
	cross blood brain barrier?	ipilimumab is not believed to cross the blood brain barrier due to its molecular size; however, activated T-cells can[3]; shows activity against brain mets[3-5]
	volume of distribution[6,7]	7.21 L; increases with increasing body weight
	plasma protein binding	no information found
Metabolism	not metabolized by cytochrome p450 or other drug metabolizing enzymes	
	active metabolite(s)	no information found
	inactive metabolite(s)	no information found
Excretion	systemic clearance increases with increasing body weight[7]	
	urine	no information found
	feces	no information found
	terminal half life[2,6,7]	14.7-15.6 days
	clearance[6]	15.3 mL/h
Elderly	no reported differences in safety or efficacy	

Adapted from standard reference[2] unless specified otherwise.

USES:

Primary uses:

*Melanoma

*Health Canada approved indication

Other uses:

Developed: 1 January 2012
Revised: 1 December 2019

SPECIAL PRECAUTIONS:

Contraindications:
- patients with active, life-threatening autoimmune disease or with organ transplantation graft where further immune activation is potentially imminently life-threatening[2]

Caution:
- Ipilimumab can cause severe and fatal immune-mediated adverse reactions, including enterocolitis, intestinal perforation, hepatitis, dermatitis, neuropathy, endocrinopathy, etc. Onset usually occurs during the induction period, but may occur months after last dose.[2]
- Systemic immunosuppressants or corticosteroids may interfere with the pharmacodynamic activity of ipilimumab: therefore, except for the treatment of immune-mediated adverse reactions, systemic immunosuppressants or corticosteroids should be avoided during ipilimumab treatment.[2]

Carcinogenicity: not formally studied; however, no hyperplastic, preneoplastic, or neoplastic lesions were reported in peripheral blood or lymphoid tissues in monkeys in long-term toxicology studies using immunostimulatory doses of ipilimumab.[2]

Mutagenicity: not formally studied; it is not expected that ipilimumab (as a large recombinant protein) would interact directly with DNA or other chromosomal materials.[2]

Fertility: not formally studied. Ipilimumab bound specifically to connective tissue in monkey ovary; however no specific binding to human ovary was observed. No histopathologic changes in sperm or ovum morphology were attributed to ipilimumab in study animals. Decreased testicular weights were reported in monkeys, but no other changes in reproductive or endocrine organ weights or drug-related microscopic changes were reported in male or female study animals.[2]

Pregnancy: FDA Pregnancy Category C.[6] Studies in women and animals are not available. Ipilimumab should be given only if the potential benefit justifies the potential risk to the fetus. Human IgG is known to cross the placental barrier; therefore, ipilimumab has the potential to be transmitted from the mother to the fetus and cause harm to the developing fetus.[2]

Breastfeeding is not recommended due to the potential secretion into breast milk. Human IgG is known to be secreted in human breast milk, therefore, there is potential for ipilimumab to be passed from mother to nursing child.[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[8,9].

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia	anemia (2-12%, severe 3%)[2,10]
endocrine	adrenal insufficiency (2%)
	hyperthyroidism (2%)
	hypothyroidism (2%)

Developed: 1 January 2012
Revised: 1 December 2019

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	hypophysitis (2%, severe 2%)[10]
	hypopituitarism (2-4%, severe 2-3%)[2,10]
eye	blurred vision (2%)
	uveitis (2%)
gastrointestinal	*emetogenic potential:* low[11]
	abdominal pain (11-15%, severe 2%)[2,10]
	colitis (8%, severe 5%)[2,10]
	constipation (2-21%, severe 2%)[2,10]
	diarrhea (27-33%, severe 5%)[2,10]
	enterocolitis (35%, severe 7%); sometimes fatal
	gastrointestinal hemorrhage (2%)
	gastrointestinal perforation (<1%)
	gastroesophageal reflux disease (<1%)
	nausea (23-35%, severe 2%)[2,10]
	vomiting (12-24%, severe 2%)[2,10]
general disorders and administration site conditions	*extravasation hazard:* none[12]
	asthenia (5%, severe 2%)
	chills (5%)
	edema (4%, severe <1%)
	fatigue (24-42%, severe 5-7%)[2,10]
	injection site reactions (4%)
	pain (2%)
	pyrexia (8-12%)[2,10]
hepatobiliary	hepatitis (1%)[10]
immune system (see paragraphs following **Side Effects** table)	any ***immune-mediated reaction*** (15-61%, severe 15%)[2,10]
	dermatologic (44%, severe 2%)[2,10]
	endocrinopathy (4-8%, severe 4%)[2,10]
	gastrointestinal (29%, severe 8%)[10]
	hepatoxicity (1-4%)[6,10]
	infusion reaction (2-6%; severe <1%)[2,13]
	neuropathy (<1%)
	pulmonary sarcoid-like granulomatosis[14] (<1%)
investigations	ALT increase (2%)
	AST increase (1%)
	serum corticotrophin decrease (2%, severe 1%)[2,10]

Developed: 1 January 2012
Revised: 1 December 2019

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	serum thyrotropin increase (1%)[10]
	weight decrease (3%)
metabolism and nutrition	appetite decrease (11-27%, severe 2%)[2,10]
	dehydration (2%)
musculoskeletal and connective tissue	arthalgia (4%, severe <1%)
	musculoskeletal pain (5%)
	myalgia (4%)
neoplasms	tumour pain (2%)
nervous system	dizziness (1%)
	headache (5-15%, severe 2%)[2,10]
renal and urinary	renal failure (2%, severe <1%)
respiratory, thoracic and mediastinal	cough (3-16%)[2,10]
	dyspnea (2-15%, severe 4%)[2,10]
skin and subcutaneous tissue (see paragraph following **Side Effects** table)	alopecia (2%)
	erythema (5%)
	night sweats (2%)
	pruritus (24-26%)[2,10]
	rash (19-26%, severe 1%)[2,10]; predominantly maculopapular, can be intensely pruritic[1]
	Stevens-Johnson syndrome (<1%)[1]
	toxic epidermal necrolysis (<1%)[1]
	vitiligo (2-11%)[1,2,10]; may be irreversible[15]
vascular	flushing (5%)
	hypotension (3%, severe 2%)

Adapted from standard reference[2] unless specified otherwise.

Immune–mediated adverse reactions, sometimes fatal, can involve any organ system. The gastrointestinal tract, liver, skin, endocrine, and nervous systems are most commonly involved. Signs and symptoms suggestive of immune-related reactions may be nonspecific. ***Diarrhea, increased stool frequency, bloody stool, liver enzyme test elevations, rash, and endocrinopathies*** must be considered immune-mediated. Most reactions occur during the induction phase, however onset months after the last dose has also been reported. Early diagnosis and appropriate management are necessary to minimize life-threatening complications. Patients should be strongly advised not to self-treat any of these symptoms and the importance of reporting any worsening of symptoms should be emphasized. Due to the mechanism of the inflammatory reactions observed, management of severe reactions requires systemic high-dose corticosteroids with or without additional immunosuppressive therapy. Permanently discontinue ipilimumab for severe immune-mediated adverse reactions.[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***.

Immune-mediated ***dermatitis***, including Stevens-Johnson syndrome, toxic epidermal necrolysis, or rash complicated by full thickness dermal ulceration, or necrotic, bullous, or hemorrhagic manifestations has been reported. Signs of

Developed: 1 January 2012
Revised: 1 December 2019

dermatitis should be considered immune-mediated, unless an alternate etiology is identified. The median time to onset of moderate, severe, or life-threatening dermatitis is three weeks, but has ranged up to more than 17 weeks from the initiation of ipilimumab. The median number of doses received prior to onset is two. Withhold ipilimumab for moderate to severe symptoms. Permanently discontinue ipilimumab for Stevens-Johnson syndrome, toxic epidermal necrolysis, or complicated rash, and administer systemic corticosteroids. When dermatitis is controlled, corticosteroid tapering may be initiated and continued over at least one month. Mild to moderate dermatitis, such as localized rash and pruritus, may be treated symptomatically. Administer topical or systemic corticosteroids for symptoms which do not improve within one week.[1,2] Vitiligo may manifest as discrete scattered macules or widespread generalized patches of depigmentation and tends to be irreversible, even after ipilimumab is discontinued.[15] There is no known treatment for ipilimumab-induced vitiligo; prevention of sunburn in depigmented areas is important.[16] Sun avoidance and/or broad-spectrum sunscreen is recommended prophylactically for dermatologic toxicities.[17,18]

Immune-mediated ***endocrinopathies***, some requiring hospitalization or urgent medical intervention, have been reported, including hypopituitarism, adrenal insufficiency, hypogonadism, and hypothyroidism. Median time to onset of moderate to severe endocrinopathy is 11 weeks, ranging to over 19 weeks after initiation of ipilimumab. The median number of doses prior to onset is four. Monitor for clinical signs of hypophysitis, adrenal insufficiency (including adrenal crisis), and hyper- or hypothyroidism. Patients may present with fatigue, headache, mental status changes, abdominal pain, unusual bowel habits, and hypotension, or other non-specific symptoms resembling brain metastases or underlying disease. Thyroid function tests and clinical chemistries should be monitored prior to each treatment. Withhold ipilimumab in symptomatic patients, and initiate systemic corticosteroids and appropriate hormone replacement.[1,2]

Immune mediated ***enterocolitis*** can be severe or life-threatening; fatalities have been reported. Median time to onset is 6-8 weeks after initiation of treatment, and the median number of doses administered prior to onset is three. Monitor for diarrhea, abdominal pain, mucous or blood in stool, and the signs of bowel perforation. Fever may be present. Rule out infectious etiologies in symptomatic patients, and conduct further investigations for persistent or severe symptoms. For moderate enterocolitis, withhold ipilimumab and administer anti-diarrheal treatment. Systemic corticosteroids may be initiated for symptoms persisting beyond one week. For severe enterocolitis, ipilimumab should be permanently discontinued and systemic corticosteroids initiated. Upon improvement to grade 1 or less, corticosteroid tapering may be initiated, and then continued over at least one month. Rapid corticosteroid tapering may result in recurrence or worsening of symptoms. Patients with inadequate response to corticosteroids may also require immunosuppressive therapy. Infliximab has been used.[2]

Severe or life-threatening ***hepatotoxicity*** has been reported, including in some instances, immune-mediated hepatitis. Hepatoxicity is manifested by elevations of AST or ALT at least 2.5 times the upper limit of normal or total bilirubin at least 1.5 times the upper limit of normal. Fatalities have been reported. Monitor liver function (AST, ALT, and bilirubin) and assess for hepatotoxicity prior to each treatment. Rule out infectious and malignant etiologies in patients with hepatotoxicity. Withhold ipilimumab for grade 2 hepatoxicity. For grade 3 or higher hepatotoxicity, permanently discontinue ipilimumab and administer high dose corticosteroids. After sustained improvement or tests return to baseline, corticosteroid tapering may be initiated and continued over one month. Mycophenolate has been used for patients with persistent severe hepatitis despite high-dose corticosteroids.[2]

Immune-mediated ***neuropathies,*** such as ***Guillain-Barré syndrome, myasthenia gravis,*** and ***peripheral motor neuropathy,*** some fatal, have been reported. Monitor for symptoms of motor or sensory neuropathy such as unilateral or bilateral weakness, sensory alterations, or paresthesia. Withhold ipilimumab for moderate neuropathy not interfering with daily activities. For severe neuropathy interfering with daily activities, ipilimumab should be permanently discontinued. Systemic corticosteroids may be required.[2]

Ipilimumab has been ***infused over 30 minutes.*** A slightly greater frequency of infusion reaction was reported with the 30 minute infusion than with the standard 90-minute infusion (up to 6% *vs* 2%), however this difference was not statistically significant. Reactions occur with the second dose of ipilimumab which may indicate that the first dose of ipilimumab is sensitizing. Patients who experience infusion reactions with ipilimumab should receive appropriate premedication (antihistamine and/or corticosteroid) for subsequent infusions.[13] For management of hypersensitivity reactions, see BC Cancer Protocol SCDRUGRX ***Management of Hypersensitivity Reactions to Chemotherapeutic Agents.***

Developed: 1 January 2012
Revised: 1 December 2019

INTERACTIONS: none known[2]

SUPPLY AND STORAGE:

***Injection*:** Bristol-Myers Squibb Canada supplies ipilimumab as an aqueous solution in 50 mg and 200 mg preservative-free, single-use vials in a concentration of 5 mg/mL. Refrigerate. Do not freeze. 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:

Compatibility: consult detailed reference

PARENTERAL ADMINISTRATION:

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

Subcutaneous	no information found
Intramuscular	no information found
Direct intravenous	do NOT use[2]
Intermittent infusion[13,19]	***over 90 minutes;*** may reduce infusion time to 30 minutes in subsequent cycles if no reaction in cycle 2
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. Numerous dosing schedules exist and depend on disease, response, and concomitant therapy. Guidelines for dosing also include consideration of absolute neutrophil count (ANC). Dosage may be reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or with other toxicities.

***Adults*:**

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

Intravenous:	Cycle Length: 3 weeks:[2,10,20]	***3 mg/kg IV for one dose on day 1*** (total dose per cycle 3 mg/kg)

Developed: 1 January 2012
Revised: 1 December 2019

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

	Cycle Length:
Concurrent radiation:	no information found
Dosage in myelosuppression:	modify according to protocol by which patient is being treated
Dosage in renal failure:	no information found
Dosage in hepatic failure:	no information found
Dosage in dialysis:	no information found
Children:	no information found

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Developed: 1 January 2012
Revised: 1 December 2019