Drug Monograph

Drug Name | Mechanism of Action and Pharmacokinetics | Indications and Status | Adverse Effects | Dosing | Administration Guidelines | Special Precautions | Interactions | Recommended Clinical Monitoring | Supplementary Public Funding | References | Disclaimer

A - Drug Name

ipilimumab

COMMON TRADE NAME(S): Yervoy®

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B - Mechanism of Action and Pharmacokinetics

The cytotoxic T-lymphocyte antigen-4 (CTLA-4) is a negative regulator of T-cell activation. Ipilimumab is a recombinant, fully human monoclonal antibody (IgG1) which blocks the inhibitory effects of CTLA-4.

Absorption	Pharmacokinetics are linear within the dosing range of 0.3mg/kg to 10mg/kg as induction. When ipilimumab is given on a q3 week schedule, steady state is usually achieved by the fourth dose; minimal systemic accumulation was observed.
Distribution	Ipilimumab is confined mainly to the extracellular fluid.
Metabolism	Ipilimumab is not metabolized by CYP 450 or other drug-metabolizing enzymes.
Elimination	Clearance increased with body weight and with lactate dehydrogenase (LDH) at baseline, but no dose adjustment is required for elevated LDH or body weight with dosing on a mg/kg basis. Age (23-88 years) and gender have no significant effect on ipilimumab clearance. Half-life 15.4 days (terminal)

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C - Indications and Status

Health Canada Approvals:

- Melanoma
- Renal cell carcinoma
- Non-small cell lung cancer
- Pleural mesothelioma
- Colorectal cancer

(Includes conditional approvals)
Refer to the product monograph for a full list and details of approved indications.

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D - Adverse Effects

Emetogenic Potential: Minimal

Extravasation Potential: None

The following adverse effects were reported in at least 1% of patients treated in the monotherapy arm of the phase 3 advanced melanoma study (Hodi 2010). Serious side effects reported in other clinical studies may also be included.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Arrhythmia (<1%)	E
	Cardiomyopathy (rare)	D
	Hypotension (3%) (severe 2%)	E
	Myocarditis (<1%)	E
	Pericarditis (<1%)	E
Dermatological	Alopecia (2%)	D
	Erythema multiforme (<1%)	E
	Rash (26%) (also pruritus, erythema; may be severe)	E

	Skin hypopigmentation (2%) (vitiligo)	E
	Stevens-Johnson syndrome (<1%)	E
	Toxic epidermal necrolysis (<1%)	E
Gastrointestinal	Abdominal pain (11%)	E
	Anorexia, weight loss (11%)	E
	Constipation (2%)	E
	Diarrhea (27%) (8% colitis)	E
	GI hemorrhage (2%)	E
	GI perforation (<1%)	E D
	Mucositis (uncommon)	E
	Nausea, vomiting (23%)	E
General	Edema (4%)	E
	Fatigue (24%)	E
	Fever (8%) (systemic flare response)	E
	Pain (2%) (tumor pain)	E
	Sarcoidosis (<1%)	E
Hematological	Anemia (2%)	E
	Hemolytic anemia (<1%)	E
	Other - Polycythemia (rare)	E
Hepatobiliary	Hepatitis (<1%)	E
	↑ LFTs (2%) (immune-mediated)	E
	Pancreatitis (<1%) (rare)	E
Hypersensitivity	DRESS syndrome (very rare)	E
	Hypersensitivity (<1%) (may be severe)	I E
Immune	Graft-versus-host disease (GVHD) (rare) (ipilimumab given before or after allogenic HSCT, may be severe)	E
	Hemophagocytic lymphohistiocytosis (rare)	E
	Other - Solid organ transplant rejection (rare, may be severe)	D
Infection	Infection (<1%)	E
Injection site	Injection site reaction (4%)	I
Metabolic / Endocrine	Adrenal insufficiency (2%)	D
	Cushingoid (rare)	D
	Hyperglycemia (diabetes; class effect)	E D

	Hyperthyroidism (2%)	D
	Hypoparathyroidism (rare)	D
	Hypopituitarism (4%)	D
	Hypothyroidism (2%)	D
Musculoskeletal	Musculoskeletal pain (5%)	E
Nervous System	Dizziness (1%)	E
	Encephalitis / aseptic meningitis (rare)	E
	Guillain-Barre syndrome (<1%)	E D
	Headache (5%)	E
	Myositis (<1%)	E D
	Neuropathy (<1%) (cranial) (severe, including optic neuritis)	E
	Other - Myasthenia gravis (rare)	E D
	Peripheral neuropathy (<1%)	E
Ophthalmic	Blurred vision (2%)	E
	Other (<1%) - episcleritis, iritis	E
	Retinal detachment (serous - rare)	E
	Uveitis (2%)	E
	Vogt-Koyanagi-Harada syndrome (rare)	E
Renal	Nephritis (<1%)	E
	Nephrotoxicity (2%)	E
Reproductive and breast disorders	Hypogonadism (<1%)	E
Respiratory	Cough, dyspnea (3%)	E
	Pneumonitis (<1%)	E
Vascular	Arteritis (<1%)	E
	Flushing (5%) (flushing)	E
	Vasculitis (<1%)	E

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

The most common side effects for ipilimumab include diarrhea, rash, fatigue, nausea, vomiting, abdominal pain, and anorexia/ weight loss.

Refer to CCO's Immune Checkpoint Inhibitor Toxicity Management Guideline for detailed descriptions of Immune-related toxicities and their management.

Presentation of immune-mediated reactions may be different compared to other anti-cancer agents and early diagnosis and appropriate management is critical.

Immune-related reactions such as rash, pneumonitis, colitis, hepatitis, pancreatitis, nephritis, endocrinopathies, meningoencephalitis, and neuropathies were reported and may be severe or fatal. Onset may vary from days to many months.

Ipilimumab or ipilimumab in combination with nivolumab should be held if signs and symptoms of hemophagocytic lymphohistiocytosis (HLH) occur. Discontinue if HLH is confirmed.

Immune-mediated adverse effects are more common with combination therapy compared to nivolumab monotherapy (more than 60% were grade 3 or higher).

CMV infection/reactivation has been reported in patients with immune-related colitis, mostly in those who are refractory to corticosteroids. Addition of an alternative immunosuppressive agent or replacement of the corticosteroid therapy should be considered in corticosteroid-refractory immune-related colitis, if other causes are excluded (including CMV infection/reactivation, other viral, bacterial and parasitic etiology).

Less than 2% of patients with advanced melanoma developed antibodies against ipilimumab. Neutralizing antibodies were not detected. There was no clear association between antibody development and adverse reactions.

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E - Dosing

Refer to protocol by which patient is being treated.

Screen for hepatitis B virus in all cancer patients starting systemic treatment. Refer to the hepatitis B virus screening and management guideline.

Some treatment indications require a validated test to determine PD-L1 tumour status or MSI-H/dMMR status. Refer to the product monograph for details.

Avoid the use of corticosteroids or immunosuppressants before starting treatment.

Each 5 mg (=1 mL) of drug contains 2.3 mg (0.1 mmol) of sodium. The sodium content should be taken into consideration in patients on a controlled sodium diet.

Pre-medications (prophylaxis for infusion reaction):

- Consider an antipyretic and H1-receptor antagonist

Other Supportive Care:

For ipilimumab-related drug fever, premedicate with acetaminophen for subsequent doses. Consider repeating the antipyretic at 6-12 hours after the ipilimumab infusion.

Adults:

Monotherapy in unresectable or metastatic melanoma:

Intravenous: 3 mg/kg every 3 weeks for a total of 4 doses. All doses must be administered within 16 weeks of the initial dose.

Combination therapy:

Various dosing and schedules are used depending on the indication. Refer to the product monograph or related regimen monographs for details.

Dosage with Toxicity:

Healthcare professionals should also consult the most recent ipilimumab product monograph for additional information.

Summary of Principles of Management

- Immune-related adverse effects (irAEs) are different in their presentation, onset and duration compared to conventional chemotherapy. Patient and provider education is essential.
- Initial irAE presentation can occur months after completion of treatment and affect multiple organs.
- Dose escalation or reduction is not recommended.
- If no other cause can be identified (such as infection), any new symptom should be considered immune-related and prompt treatment initiated.
- Organ-specific system-based toxicity management is recommended.

Refer to CCO's Immune Checkpoint Inhibitor Toxicity Management Guideline for detailed descriptions of Immune-related toxicities and their management.

Management of Infusion-related reactions:

Also refer to the CCO guideline for detailed description of Management of Cancer Medication-Related Infusion Reactions.

Grade	Management	Re-challenge
1 or 2	• Stop or slow the infusion rate. • Manage the symptoms. **Restart:** • Once symptoms have resolved, the infusion may be restarted (ex. at 50% of the rate at which the IR occurred) with pre-medications and close monitoring.	• Re-challenge with a reduced infusion rate of 50% at which the IR occurred. • Consider an antipyretic and H1-receptor antagonist.
3 or 4	• Stop the infusion. • Aggressively manage symptoms.	• Discontinue permanently (do not re-challenge).

Dosage with Hepatic Impairment:

Safety and efficacy have not been studied in patients with hepatic impairment.

Refer to CCO's Immune Checkpoint Inhibitor Toxicity Management Guideline for management of immune-related hepatic toxicities.

Population pharmacokinetic data suggest the following for hepatic impairment:

Impairment	LFTs	Ipilimumab dose
Mild	Bilirubin >1 to 1.5 x ULN or AST > ULN	No dose adjustment necessary
Moderate	Bilirubin > 1.5 to 3 x ULN and any AST	Caution; no data
Severe	Bilirubin > 3 x ULN and any AST	Caution; no data

Dosage with Renal Impairment:

Safety and efficacy have not been studied in patients with renal impairment.

Refer to CCO's Immune Checkpoint Inhibitor Toxicity Management Guideline for management of immune-related renal toxicities.

Pharmacokinetic data suggest the following for pre-existing renal impairment:

Baseline Renal Impairment	Ipilimumab dose
Mild to moderate	No dose adjustment necessary
Severe	Caution; no data

Dosage in the elderly:

No dose adjustment required. No differences in efficacy or safety were reported in those ≥ age 65.

Children:

Safety and efficacy have not been established.

Some studies have shown higher incidences of severe (grade 3 or 4) adverse reactions and severe immune-mediated adverse reactions at certain dose levels, among children and adolescents ≥ age 12 than those in adults.

For additional information, consult the most recent ipilimumab product monograph.

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F - Administration Guidelines

- Do not administer as an IV push or bolus injection.
- Infuse IV over 30 minutes.
- Consider post-infusion monitoring for a short time after the infusion, as IRs have occurred up to 30 minutes after the infusion.
- A compatible low protein binding in-line filter and a separate infusion line must be used for infusing ipilimumab.
- Do not infuse with other medications.
- Must flush IV line with NS or D5W at the end of the infusion.
- Allow the vials to stand at room temperature for 5 minutes before withdrawing the drug to a compatible container.
- Ipilimumab may be administered without dilution after transferring to a compatible container.
- It may also be diluted in NS or D5W to a concentration between 1mg/mL to 4mg/mL.
- Do not shake the solution.
- Solution may contain translucent-to-white amorphous particles; discard if cloudy or discolored.
- Compatible with glass, PVC and non-PVC bags.
- Compatible with PVC IV extension or administration sets, polyethersulfone (0.2 and 1.2 micron) and nylon (0.2 micron) in-line filters.
- If given with nivolumab OR with nivolumab and chemotherapy, administer nivolumab first, followed on the same day by ipilimumab and then by chemotherapy. Use separate infusion bags and filters, if applicable, for each infusion.
- If a scheduled dose is missed, it should be administered as soon as possible. Adjust administration schedule to maintain the prescribed dosing interval.
- Refrigerate original vials (2 to 8°C) and protect them from light. Do not freeze.

Also refer to the CCO guideline for detailed description of Management of Cancer Medication-Related Infusion Reactions.

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G - Special Precautions

Contraindications:

- Patients who are hypersensitive to ipilimumab or any of its components
- Patients with active, life-threatening autoimmune disease, or with organ transplantation graft where further immune activation is potentially imminently life-threatening

Other Warnings/Precautions:

- Caution in patients who have previously experienced severe or life-threatening skin reactions to prior cancer immune-stimulating therapy
- Usage in patients with ocular melanoma or central nervous metastases has not been studied.
- Fatal or serious graft-versus-host disease (GVHD) can occur in patients who receive a CTLA-4 receptor blocking antibody (e.g. ipilimumab) either before or after allogeneic HSCT. Consider benefit versus risks of treatment with ipilimumab after allogeneic HSCT.

Other Drug Properties:

- Carcinogenicity: Unknown
  Fatal lymphoproliferative disorder has been observed in CTLA-4 knockout animals.

Pregnancy and Lactation:

- Fetotoxicity: Yes
- Teratogenicity: Yes
- Genotoxicity: Unknown
- Crosses placental barrier: Probable
  IgG1 is known to cross the placental barrier and may cause harm to the developing fetus. Effects are likely to be greater during the second and third trimesters. Ipilimumab is not recommended for use in pregnancy. Adequate contraception should be used by both sexes during treatment, and for at least **3 months** after the last dose.
- Breastfeeding:
  Ipilimumab is secreted into milk in animals. Also, human IgG1 is secreted into human breast milk. Breastfeeding should be avoided during treatment, and for at least **3 months** after the last dose.
- Fertility effects: Unlikely

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H - Interactions

Ipilimumab is not expected to have pharmacokinetic drug-drug interactions, since it is not metabolized by CYP450 or other drug metabolizing enzymes.

Use of systemic corticosteroids or immunosuppressants should be avoided prior to starting ipilimumab because of potential interference with efficacy. They can be used to treat immune-mediated reactions after starting the drug. Corticosteroids may be used as premedication (e.g. antiemetic) when given with chemotherapy.

Acetaminophen may affect the response to immune checkpoint inhibitors. Further clinical studies are needed to determine the exact mechanism and the appropriate clinical management (Bessede et al, 2022).

AGENT	EFFECT	MECHANISM	MANAGEMENT
Anticoagulants	↑ risk of GI hemorrhage	Additive	Monitor patients closely
Vemurafenib	Severe LFT increases reported in clinical trials in combination with ipilimumab	Unknown	Concurrent use with ipilimumab is not recommended

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I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Refer to the hepatitis B virus screening and management guideline for monitoring during and after treatment.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
CBC	Baseline and as clinically indicated
Liver function tests	Baseline, before each dose and as clinically indicated
Electrolytes	Baseline, before each dose and as clinically indicated
Thyroid function tests	Baseline, before each dose and as clinically indicated
ACTH (+ cortisol, sex hormone levels)	Baseline, before each dose and as clinically indicated

Renal function tests	Baseline and as clinically indicated
Monitor patients on anticoagulants carefully	Baseline and as clinically indicated
Clinical toxicity assessment for fatigue, infusion-related and immune-related reactions, including GI, skin, endocrine, pancreatitis, musculoskeletal, respiratory, ocular, cardiac, or neurologic effects	At each visit, and as clinically indicated

Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

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J - Supplementary Public Funding

New Drug Funding Program (NDFP Website)

- Ipilimumab - Previously Untreated Advanced Unresectable Melanoma
- Ipilimumab - Previously Treated Advanced Unresectable Melanoma
- Nivolumab plus Ipilimumab - Advanced Melanoma (Unresectable or Metastatic Melanoma)
- Nivolumab plus Ipilimumab - Metastatic Renal Cell Carcinoma
- Nivolumab plus Ipilimumab - Advanced Malignant Pleural Mesothelioma
- Nivolumab plus Ipilimumab - In Combination with Platinum Doublet Chemotherapy for First Line Metastatic or Recurrent Non-Small Cell Lung Cancer

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K - References

Assessment report for Yervoy®. European Medicines Agency. May 2011.

Bessede A, Marabelle A, Guegan JP, et al. Impact of acetaminophen on the efficacy of immunotherapy in cancer patients. Ann Oncol 2022;33(9):909-15.

Cameron C, Whiteside G, Perry C. Ipilimumab: first global approval. Drugs 2011; 71(8): 1093-104.

Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 2010;363:711-23.

Momtaz P, Park V, Panageas KS, Postow MA, Callahan M, Wolchok JD, Chapman PB. Safety of Infusing Ipilimumab Over 30 Minutes. J Clin Oncol. 2015 Jun 29.

Prescribing Information: Yervoy® (ipilimumab). Bristol-Myers Squibb (US), March 2011 and May 2022.

Product Monograph: Yervoy® (ipilimumab). Bristol-Myers Squibb Canada, November 24, 2022.

Summary of Product Characteristics: Yervoy® (ipilimumab). Bristol Myers Squibb Pharma (UK), July 2011.

March 2023 Updated Pharmacokinetics, Dosing, Warnings/Precautions, Pregnancy/lactation sections

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L - Disclaimer

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

The information set out in the drug monographs, regimen monographs, appendices and symptom management information (for health professionals) contained in the Drug Formulary (the "Formulary") is intended for healthcare providers and is to be used for informational purposes only. The information is not intended to cover all possible uses, directions, precautions, drug interactions or adverse effects of a particular drug, nor should it be construed to indicate that use of a particular drug is safe, appropriate or effective for a given condition. The information in the Formulary is not intended to constitute or be a substitute for medical advice and should not be relied upon in any such regard. All uses of the Formulary are subject to clinical judgment and actual prescribing patterns may not follow the information provided in the Formulary.

The format and content of the drug monographs, regimen monographs, appendices and symptom management information contained in the Formulary will change as they are reviewed and revised on a periodic basis. The date of last revision will be visible on each page of the monograph and regimen. Since standards of usage are constantly evolving, it is advised that the Formulary not be used as the sole source of information. It is strongly recommended that original references or product monograph be consulted prior to using a chemotherapy regimen for the first time.

Some Formulary documents, such as the medication information sheets, regimen information sheets and symptom management information (for patients), are intended for patients. Patients should always consult with their healthcare provider if they have questions regarding any information set out in the Formulary documents.

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