Drug Monograph

A - Drug Name

pembrolizumab

COMMON TRADE NAME(S): Keytruda®

back to top

B - Mechanism of Action and Pharmacokinetics

Pembrolizumab is a humanized monoclonal antibody that binds to the programmed death receptor-1 (PD-1), preventing PD-1 pathway-mediated inhibition of tumour immune surveillance by active T-cells and reactivating anti-tumor responses.

Distribution	AUC increases proportional to dose. Steady-state is reached by 16 weeks at q3w dosing. For patients aged 2-6 years, exposure is approximately 1.3 fold higher than in adults.	
	Distribution Sites	Confined to extracellular fluid; does not bind to plasma proteins.
Metabolism	Catabolized through non-specific pathways.	
Elimination	Half-life	22 days (terminal elimination)

back to top

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C - Indications and Status

Health Canada Approvals:

- Melanoma
- Non-small cell lung cancer (NSCLC)
- Renal cell carcinoma (RCC)
- Head and neck squamous cell carcinoma (HNSCC)
- Hodgkin lymphoma (HL)
- Primary mediastinal B-cell lymphoma (PMBCL)
- Urothelial / bladder carcinoma
- Colorectal cancer
- Esophagus or esophagogastric junction cancer
- Endometrial / cervical cancer
- Triple-negative breast cancer (TNBC)

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

back to top

D - Adverse Effects

Emetogenic Potential: Minimal

Extravasation Potential: None

The following drug related adverse effects were reported in ≥ 1% of patients in adjuvant melanoma who received pembrolizumab 200 mg q3 weeks. Incidences of some immune-related effects were based on pembrolizumab monotherapy clinical studies in various tumour types (marked with "^"). Rare, severe or life-threatening side effects from other trials or post-marketing are also included.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Myocarditis (<1%)	E D
Dermatological	Dry skin (4%)	E
	Rash, pruritus (17%) (may be severe)	E
	Skin hypopigmentation (5%) (including vitiligo)	E
	Stevens-Johnson syndrome (rare)	E
	Toxic epidermal necrolysis (rare)	E

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Gastrointestinal	Anorexia, weight loss (5%)	E
	Diarrhea (19%) (1% severe colitis)	E
	Mucositis (3%)	E
	Nausea, vomiting (11%)	I E
General	Fatigue (28%)	E
	Flu-like symptoms (3%)	I E
	Sarcoidosis (<1%)	E
Hematological	Anemia (6%)	E
	Hemolytic anemia (<1%)	E
	Myelosuppression ± infection, bleeding (18%; in PMBCL) (<10% in other indications; rarely fungal and viral re-activation)	E
Hepatobiliary	Cholangitis (rare)	E D
	↑ LFTs (5%) (<1% immune-mediated hepatitis^)	L
	Pancreatitis (<1%)	E
	Veno-occlusive disease (in HL patients who received allo HSCT after pembrolizumab)	D
Hypersensitivity	Infusion related reaction (<1%)	I E
Immune	Cytokine release syndrome (2%) (Hodgkin lymphoma)	I E
	Graft-versus-host disease (GVHD) (in HL patients who received allo HSCT before or after pembrolizumab)	D L
	Hemophagocytic lymphohistiocytosis (rare)	E
	Other (Graft loss - solid organ transplant recipients) (rare)	D
Metabolic / Endocrine	Adrenal insufficiency (<1%) ^	E
	Hyperglycemia (2%) (including type 1 DM <1%^)	E
	Hyperthyroidism (3%) ^	E
	Hypoparathyroidism (<1%)	E
	Hypopituitarism (<1%) (immune-mediated hypophysitis 1%^)	E
	Hypothyroidism (9%) ^	E
	↑ Triglycerides (2%)	E
Musculoskeletal	Musculoskeletal pain (10%) (rarely myositis, myasthenia)	E
Nervous System	Encephalitis (<1%)	E
	Guillain-Barre syndrome (<1%)	E
Ophthalmic	Eye disorders (2%) (includes visual impairment; rarely uveitis)	E

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	Vogt-Koyanagi-Harada syndrome (rare)	E D
Renal	Nephritis (<1%) (autoimmune)^	E
	Nephrotoxicity (<1%)	D
Respiratory	Cough, dyspnea (5%)	E
	Pneumonitis (3%) ^	E D
Vascular	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)

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

The most common side effects for pembrolizumab include fatigue, diarrhea, rash/pruritus, nausea/vomiting, and musculoskeletal pain.

Immune-mediated pneumonitis, colitis, hepatitis, hypophysitis, other endocrinopathies and nephritis were reported, may be severe and affect more than one body system simultaneously. Onset of immune-mediated reactions is variable and may occur after treatment has ended. Pneumonitis, including fatal cases had a median time to onset of 3.3 months and the median duration was 1.5 months. Pneumonitis occurred more frequently in patients with a history of prior thoracic radiation. Colitis occurred in 1-2% of patients with a median onset of 3.5 months and a median duration of 1.3 months. The median onset for hepatitis was 1.3 months with a median duration of 1.8 months. For nephritis, median onset was 5.1 months and the median duration was 3.3 months. The median onset of hypophysitis was 3.7 months.

Type 1 **diabetes mellitus**, including ketoacidosis has been reported.

Hyper or hypothyroidism has been reported at any time during treatment. The median onset for hyperthyroidism was 1.4 months and hypothyroidism was 3.5 months.

Severe **infusion-related reactions** are rare.

Severe **skin rashes**, including Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis have been reported, including fatal reactions.

Graft vs. host disease (GVHD) cases have been reported in patients who received pembrolizumab before or after an allogenic HSCT. Cases of **veno-occlusive disease (VOD)** have been observed in patients undergoing allogenic HSCT after previous pembrolizumab exposure. The benefit-risk of allogenic HSCT before or after pembrolizumab should be carefully considered.

Atypical treatment responses, including a transient increase in tumour size, followed by shrinkage have been observed.

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back to top

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.

Avoid the use of corticosteroids or immunosuppressants before starting treatment.

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.

Premedication (prophylaxis for infusion reactions):

- Routine pre-medication is not recommended.
- May consider antipyretic and H1-receptor antagonist in patients who experienced a grade 1-2 infusion reaction.

Adults:

200 mg† IV every 3 weeks

OR

400 mg† IV every 6 weeks

Note: As atypical responses have been reported, clinically stable patients should continue on treatment until progression is confirmed.

†Health Canada approved dosing. Pembrolizumab weight-based and corresponding fixed dosing have been studied in various cancers, and have been suggested to have similar effects. NDFP funding is available for weight-based dosing (refer to NDFP forms).

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Dosage with Toxicity:

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

There are no dose reductions for pembrolizumab. Doses are either delayed or discontinued with toxicity.

Summary of Principles of Management or immune-related adverse effects (iRAEs)

- 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.

HL and PMBCL specific dose modifications:

Toxicity	Action
Grade 4 Hematologic	Hold until resolved to ≤ grade 1.

RCC specific dose modifications (during treatment in combination with axitinib):

ALT or AST		Bilirubin	Action
≥ 3 to < 10 x ULN	And	< 2 X ULN	Hold pembrolizumab and axitinib until ≤ grade 1. Consider corticosteroids. After recovery, consider re-challenge with a single drug or sequentially with both drugs.

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> 3 x ULN	And	≥ 2 x ULN	Discontinue both. Consider corticosteroids.
≥ 10 x ULN	And	Any	

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. • Manage the symptoms. **Restart:** • No specific recommendations can be made at this time.	• Consider re-challenge with close monitoring and pre-medications (antipyretic and H1-receptor antagonist).
3 or 4	• Stop the infusion. • Aggressively manage symptoms.	• Discontinue permanently (do not re-challenge).

Dosage with Hepatic Impairment:

Refer to CCO's Immune Checkpoint Inhibitor Toxicity Management Guideline for detailed descriptions for immune-related hepatitis management.

Impairment	Pembrolizumab Dose
Mild (bilirubin 1 - 1.5 x ULN or AST > ULN)	No dose adjustment necessary
Moderate (bilirubin >1.5 - 3 x ULN and any AST) to severe (bilirubin > 3 x ULN and any AST)	Caution; no data

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Dosage with Renal Impairment:

Refer to CCO's Immune Checkpoint Inhibitor Toxicity Management Guideline for detailed descriptions for immune-related nephritis management.

CrCl (mL/min)	Pembrolizumab Dose
≥ 60	No dose adjustment necessary
30 to 59	No dose adjustment necessary
< 30	Caution; no data

Dosage in the elderly:

No dosage adjustment is required. No differences in safety or efficacy were reported between patients aged 65 and older and younger patients (very limited data for Hodgkin lymphoma).

Children:

Refer to the product monograph for comprehensive pre-medication and dosing information in this population. The safety and efficacy of pembrolizumab has not been established in pediatric patients with conditions other than relapsed or refractory PMBCL and Hodgkin lymphoma. Refer to the product monograph for dosing.

Efficacy in PMBCL and Hodgkin lymphoma was extrapolated from the results in the respective adult populations. The developmental effects of pembrolizumab on pediatric patients have not been established.

In a single phase I/II trial that enrolled pediatric patients, immune mediated reactions were similar to those seen in adult patients including pneumonitis, colitis, thyroid disorders (hyperthyroidism, hypothyroidism and thyroiditis) and skin reactions. Infusion reactions were also observed.

Adverse reactions that occurred more frequently among pediatric patients (>15% increased) in comparison to adult patients include pyrexia, vomiting, abdominal pain and hypertransaminasemia.

back to top

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F - Administration Guidelines

- Dilute in 0.9% sodium chloride or D5W to final concentration of 1 to 10 mg/mL; mix by gentle inversion.
- Administer over 30 minutes using sterile, non-pyrogenic, low protein-binding 0.2 to 5 micron in-line or add-on filter.
- If given with chemotherapy on the same day, administer pembrolizumab before chemotherapy.
- Do not co-administer other drugs through the same infusion line.
- If a planned dose is missed, administer as soon as possible. Adjust the schedule to maintain the prescribed dosing interval.
- Unopened vials should be stored under refrigeration (2 to 8^{o}C). Do not freeze.

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

back to top

G - Special Precautions

Contraindications:

- Patients who have a hypersensitivity to this drug or any of its components.

Other Warnings/Precautions:

- Patients with active infection, autoimmune disease, conditions that require systemic immunosuppressive therapy (i.e. transplant patients) and a history of pneumonitis, severe immune-mediated adverse reactions with ipilimumab or severe hypersensitivity to other monoclonal antibodies, etc. were excluded from clinical studies.
- Pembrolizumab may cause serious immune-mediated reactions affecting multiple organ systems, including GI, hepatic, renal, respiratory, endocrine and others. Use with caution and monitor closely in patients with pre-existing conditions such as colitis, hepatic impairment, respiratory or endocrine disorders, such as hypo or hyperthyroidism or diabetes mellitus.
- Patients with ECOG performance status ≥ 2 were excluded from clinical trials.
- Use of a PD-1 or PD-L1 blocking antibody with a thalidomide analogue plus dexamethasone is not recommended outside of controlled clinical trials, due to increased mortality reported.

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Other Drug Properties:

- Carcinogenicity: Unknown

Pregnancy and Lactation:

- Genotoxicity: Unknown
- Fetotoxicity: Probable
- Embryotoxicity: Probable
  Pembrolizumab is not recommended for use in pregnancy. Adequate contraception should be used by both sexes during treatment, and for at least **4 months** after the last dose.
- Excretion into breast milk: Unknown
  Breastfeeding is not recommended during treatment, and for at least **4 months** after the last dose.
- Fertility effects: Unknown

back to top

H - Interactions

Pembrolizumab is not expected to have pharmacokinetic drug-drug interactions as it is not metabolized by drug metabolizing enzymes. No pharmacokinetic drug interaction studies have been performed.

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
Systemic corticosteroids / immunosuppressants (e.g. mycophenolate, cyclosporine)	Possible ↓ in anti-tumour effect	↓ T-cell activation and T-cell mediated immune responses	Avoid, especially at baseline before starting pembrolizumab. Corticosteroids or other immunosuppressants may be used to treat immune reactions after starting pembrolizumab. Corticosteroids may be used as premedication (e.g. antiemetic) when given with chemotherapy.

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Thalidomide Analogues	↑ mortality	Unknown	Avoid combination with thalidomide analogues and dexamethasone.

back to top

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
Liver function tests	Baseline, before each dose and as clinically indicated; frequent with severe toxicity
Renal function tests	Baseline, before each dose and as clinically indicated; frequent with severe toxicity
Electrolytes	Baseline, before each dose and as clinically indicated
Blood glucose	Baseline, before each dose and as clinically indicated
Thyroid function tests	Baseline, before each dose and as clinically indicated
CBC	Baseline and as clinically indicated
Blood cortisol (for TNBC in neoadjuvant setting)	Baseline, prior to surgery, and as clinically indicated
Clinical toxicity assessment for infusion-related and immune-mediated reactions, fatigue, ocular, endocrine, skin, GI, neurologic, musculoskeletal, cardiac and respiratory effects	At each visit

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

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back to top

J - Supplementary Public Funding

New Drug Funding Program (NDFP Website)

- Pembrolizumab - Advanced Melanoma (Unresectable or Metastatic Melanoma) and Prior Ipilimumab
- Pembrolizumab - Advanced Melanoma (Unresectable or Metastatic Melanoma) and No Prior Ipilimumab
- Pembrolizumab - Advanced or Metastatic Non-Small Cell Lung Cancer (Second or Subsequent Line)
- Pembrolizumab - Previously Untreated Locally Advanced or Metastatic Non-Small Cell Lung Cancer
- Pembrolizumab - In Combination with Platinum and Pemetrexed for First Line Metastatic Non-Squamous Non-Small Cell Lung Cancer (NSCLC)
- Pembrolizumab - In Combination with Carboplatin and Paclitaxel for First-Line Metastatic Squamous Non-Small Cell Lung Cancer (NSCLC)
- Pembrolizumab - In Combination with Axitinib for First Line Advanced or Metastatic Renal Cell Carcinoma
- Pembrolizumab - Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck
- Pembrolizumab - Previously Treated Locally Advanced or Metastatic Urothelial Carcinoma
- Pembrolizumab - First Line Treatment of MSI-H/dMMR Metastatic Colorectal Cancer
- Pembrolizumab (Adult Who Failed Prior Brentuximab Vedotin) - Relapsed Classical Hodgkin Lymphoma Post-Autologous Stem Cell Transplant or ASCT Ineligible
- Pembrolizumab (Adult and Pediatric) - Relapsed Classical Hodgkin Lymphoma Post-Autologous Stem Cell Transplant or ASCT Ineligible
- Pembrolizumab - First-line Treatment of Advanced Esophageal and Esophagogastric Junction Carcinoma
- Pembrolizumab - Adjuvant Treatment for Completely Resected Stage III or IV Melanoma
- Pembrolizumab - Previously Untreated High-Risk Early-Stage Triple Negative Breast Cancer
- Pembrolizumab - Adjuvant Treatment for Renal Cell Carcinoma
- Pembrolizumab (Adult and Pediatric) - Adjuvant Treatment for Completely Resected Stage IIB or IIC Melanoma
- Pembrolizumab - Metastatic, Persistent, or Recurrent Carcinoma of the Cervix
- Pembrolizumab - Locally Recurrent Unresectable or Metastatic Triple Negative Breast Cancer
- Pembrolizumab - Previously Treated MSI-H/dMMR Advanced Endometrial Cancer
- Pembrolizumab - In Combination with Lenvatinib for First-Line Advanced or Metastatic Renal Cell Carcinoma
- Pembrolizumab - In Combination with Lenvatinib for Advanced Endometrial Cancer

back to top

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K - References

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.

CADTH technology review: Dosing and timing of immune-oncology drugs. November 2019.

Fay AP, Brandao Moreira R, Nunes Filho PRS, et al. The management of immune-related adverse events associated with immune checkpoint blockade. Expert Rev of Qual Life Cancer Care 2016;1(1):89-97.

Friedman CF, Proverbs-Singh TA, Postow MA. Treatment of the immune-related adverse effects of immune checkpoint inhibitors: a review. JAMA Oncol 2016;2(10):1346-53.

Haanen JBAG, Carbonnel F, Robert C, et al. Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2017 Jul 1;28(suppl_4):iv119-iv142.

Herbst RS, Baas P, Kim DW et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. Lancet. 2016 Apr 9;387(10027):1540-1550.

Pembrolizumab (Keytruda) product monograph, Merck Canada, December 29, 2022.

Pembrolizumab (Keytruda) prescribing information (U.S.), January 2015.

Reck M, Rodríguez-Abreu D, Robinson AG, et al. Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. N Engl J Med 2016;375(19):1823-33.

Robert C, Schachter J, Long GV, et al; KEYNOTE-006 investigators. Pembrolizumab versus Ipilimumab in Advanced Melanoma. N Engl J Med. 2015 Jun 25;372(26):2521-32.

Robert C, Ribas A, Wolchok JD, et al. Anti-programmed-death-receptor-1 treatment with pembrolizumab in ipilimumab-refractory advanced melanoma: a randomized dose-comparison cohort of a phase 1 trial. Lancet. 2014 Sep 20;384(9948):1109-17.

Villadolid J and Amin A. Immune checkpoint inhibitors in clinical practice: update on management of immune-related toxicities. Transl Lung Cancer Res 2015;4(5):560-75.

August 2023 Added new NDFP forms (2)

back to top

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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.

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back to top

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