Pembrolizumab: Drug information

(For additional information see "Pembrolizumab: Patient drug information" and see "Pembrolizumab: Pediatric drug information")

For abbreviations and symbols that may be used in Lexicomp (show table)

Special Alerts

Keytruda Safety Alert March 2017

Health Canada is reporting that cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), some with fatal outcomes, have been reported in patients treated with *Keytruda* (pembrolizumab). Health Canada is working with the manufacturer to update the Canadian product monograph to include this safety information.

Health care providers are advised to counsel patients about the benefits and risks of *Keytruda*, including the risk and early symptoms of SJS and TEN; to suspend *Keytruda* treatment and refer for immediate evaluation and treatment for any severe skin reaction or suspected SJS or TEN; and to permanently discontinue *Keytruda* if SJS or TEN is confirmed.

Further information can be found at http://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2017/62670a-eng.php.

Brand Names: US

Keytruda

Brand Names: Canada

Keytruda

Pharmacologic Category

Antineoplastic Agent, Anti-PD-1 Monoclonal Antibody; Antineoplastic Agent, Monoclonal Antibody

Dosing: Adult

Head and neck cancer, squamous cell, (recurrent or metastatic): IV: 200 **mg** once every 3 weeks until disease progression, unacceptable toxicity, or (in patients without disease progression) for up to 24 months.

Hodgkin lymphoma, classical (relapsed or refractory): IV: 200 **mg** once every 3 weeks until disease progression, unacceptable toxicity, or (in patients without disease progression) up to 24 months.

Melanoma (unresectable or metastatic): IV: 200 **mg** once every 3 weeks until disease progression or unacceptable toxicity.

Off-label dosing: 2 mg/kg once every 3 weeks until disease progression or unacceptable toxicity (Ribas 2015).

Microsatellite instability-high cancer (unresectable or metastatic): IV: 200 **mg** once every 3 weeks until disease progression, unacceptable toxicity, or (in patients without disease progression) for up to 24 months.

Non-small cell lung cancer (metastatic), single-agent therapy: IV: 200 **mg** once every 3 weeks until disease progression, unacceptable toxicity, or (in patients without disease progression) up to 24 months.

Off-label dosing (in patients with disease progression following platinum-containing chemotherapy): 2 mg/kg once every 3 weeks for 24 months or until disease progression or unacceptable toxicity (Herbst 2016).

Non-small cell lung cancer (metastatic, nonsquamous), combination therapy: IV: 200 **mg** once every 3 weeks (in combination with pemetrexed and carboplatin) for 4 cycles, followed by pembrolizumab monotherapy of 200 **mg** once every 3 weeks (with or without optional indefinite pemetrexed maintenance therapy) until disease progression, unacceptable toxicity, or (in patients without disease progression) up to 24 months (Langer 2016).

Urothelial carcinoma (locally advanced or metastatic): IV: 200 **mg** once every 3 weeks until disease progression, unacceptable toxicity, or (in patients without disease progression) for up to 24 months (Belmunt 2017).

Merkel cell carcinoma, advanced (off-label use): IV: 2 **mg/kg** once every 3 weeks for up to 2 years or until complete response, or until disease progression or unacceptable toxicity (Nghiem 2016).

Dosing: Pediatric

(For additional information see "Pembrolizumab: Pediatric drug information")

Hodgkin lymphoma, classical (relapsed or refractory): Children ≥2 years and Adolescents: IV: 2 **mg/kg** (maximum: 200 mg) once every 3 weeks until disease progression, unacceptable toxicity, or (in patients without disease progression) up to 24 months.

Microsatellite instability-high cancer (unresectable or metastatic): Children ≥2 years and Adolescents: IV: 2 **mg/kg** (maximum: 200 mg) once every 3 weeks until disease progression, unacceptable toxicity, or (in patients without disease progression) up to 24 months.

Dosing: Geriatric

Refer to adult dosing.

Dosing: Renal Impairment

No dosage adjustment necessary. In a pharmacokinetic study, no difference in clearance was noted for patients with eGFR ≥15 mL/minute/1.73 m^2.

Dosing: Hepatic Impairment

*Hepatic impairment **prior** to treatment initiation:*

Mild impairment (total bilirubin ≤ULN and AST >ULN or total bilirubin >1 to 1.5 times ULN and any AST): No dosage adjustment necessary.

Moderate (total bilirubin >1.5 to 3 times ULN and any AST) to severe (total bilirubin >3 times ULN

and any AST) impairment: There are no dosage adjustments provided in the manufacturer's labeling (has not been studied).

*Hepatotoxicity **during** treatment:* **Note:** For patients with baseline grade 2 ALT or AST abnormalities due to liver metastases, permanently discontinue if AST or ALT increases by ≥50% (relative to baseline) and persists at least 1 week.

AST or ALT >3 to 5 times ULN or total bilirubin >1.5 to 3 times ULN: Withhold treatment; may resume therapy upon recovery to grade 0 or 1 toxicity. Also administer corticosteroids (prednisone 0.5 to 1 mg/kg/day [or equivalent] followed by a taper).

AST or ALT >5 times ULN or total bilirubin >3 times ULN: Permanently discontinue. Also administer corticosteroids (prednisone 1 to 2 mg/kg/day [or equivalent] followed a taper).

Dosing: Adjustment for Toxicity

Withhold treatment for any of the following (may resume upon recovery to grade 0 or 1 toxicity):

Colitis, moderate (grade 2) or severe (grade 3); also administer corticosteroids (prednisone 1 to 2 mg/kg/day [or equivalent] followed by a taper).

Endocrinopathies:

Hyperglycemia, severe; also administer antihyperglycemics.

Hyperthyroidism, severe (grade 3) or life threatening (grade 4); manage with thionamides and beta-blockers as appropriate.

Hypophysitis, grade 2 (symptomatic); also administer corticosteroids (followed by a taper) and hormone replacement therapy if appropriate.

Hematologic toxicity, grade 4 (in patients with classical Hodgkin lymphoma)

Nephritis, grade 2; also administer corticosteroids (prednisone 1 to 2 mg/kg/day [or equivalent] followed by a taper).

Pneumonitis, moderate (grade 2); also administer corticosteroids (prednisone 1 to 2 mg/kg/day [or equivalent] followed by a taper).

Other treatment-related toxicity, severe or grade 3; may require corticosteroids (based on severity). Upon improvement to grade 0 or 1, initiate corticosteroid taper and continue to taper over at least 1 month. Restart pembrolizumab if the adverse reaction remains at grade 0 or 1 following corticosteroid taper. May consider other systemic immunosuppressants if not controlled by corticosteroids (based on limited data).

Withhold (may resume upon recovery to grade 0 or 1 toxicity) or discontinue for:

Hyperthyroidism, severe (grade 3) or life-threatening (grade 4); manage with thionamides and beta-blockers as appropriate.

Hypophysitis, severe (grade 3) or life-threatening (grade 4); also administer corticosteroids and hormone replacement as appropriate.

Permanently discontinue for:

Adverse reactions that are life-threatening (excluding endocrinopathies controlled with hormone replacement therapy, or hematologic toxicity [in patients with classical Hodgkin lymphoma]), persistent grade 2 or 3 adverse reaction (excluding endocrinopathies controlled with hormone replacement therapy) that does not recover to grade 0 or 1 within 12 weeks after the last pembrolizumab dose, or any recurrent severe or grade 3 treatment-related adverse reaction. Also administer corticosteroids (may consider other systemic immunosuppressants if not controlled by corticosteroids [based on limited data]).

Colitis, life-threatening (grade 4); also administer corticosteroids (prednisone 1 to 2 mg/kg/day [or equivalent] followed by a taper).

Immune mediated adverse reactions: Discontinue permanently if unable to reduce corticosteroid dose to prednisone ≤10 mg/day (or equivalent) within 12 weeks.

Infusion-related reaction, grade 3 or 4.

Nephritis, severe (grade 3) or life-threatening (grade 4); also administer corticosteroids (prednisone 1 to 2 mg/kg/day [or equivalent] followed by a taper).

Pneumonitis, severe (grade 3), life-threatening (grade 4), or moderate (grade 2) that recurs; also administer corticosteroids (prednisone 1 to 2 mg/kg/day [or equivalent] followed by a taper).

Dosage Forms

Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution, Intravenous [preservative free]:

Keytruda: 100 mg/4 mL (4 mL) [contains polysorbate 80]

Solution Reconstituted, Intravenous [preservative free]:

Keytruda: 50 mg (1 ea) [contains polysorbate 80]

Generic Equivalent Available (US)

No

Medication Guide and/or Vaccine Information Statement (VIS)

An FDA-approved patient medication guide, which is available with the product information and at https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125514s016lbl.pdf#page=34, must be dispensed with this medication.

Administration

IV: Infuse over 30 minutes through a 0.2 to 5 micron sterile, nonpyrogenic, low-protein binding inline or add-on filter. Do not infuse other medications through the same infusion line.

Non-small cell lung cancer (metastatic): When administered in combination with chemotherapy (pemetrexed and carboplatin), pembrolizumab should be administered prior to chemotherapy if scheduled to be administered on the same day.

Use

Head and neck cancer, squamous cell (recurrent or metastatic): Treatment of recurrent or metastatic squamous cell carcinoma of the head and neck in patients with disease progression on or after platinum-containing chemotherapy.

Hodgkin lymphoma, classical (relapsed or refractory): Treatment of adult and pediatric patients with refractory classical Hodgkin lymphoma or patients who have relapsed after 3 or more prior lines of therapy.

Melanoma (unresectable or metastatic): Treatment of unresectable or metastatic melanoma.

Microsatellite instability-high cancer (unresectable or metastatic):

Solid tumors: Treatment of unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient solid tumors in adult and pediatric patients that have progressed following prior treatment and have no satisfactory alternate treatment options.

Limitation of use: Safety and efficacy in pediatric patients with MSI-H central nervous system cancers have not been established.

Colorectal cancer: Treatment of unresectable or metastatic, MSI-H or mismatch repair deficient colorectal cancer in patients that have progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.

Non-small cell lung cancer (metastatic):

First-line, single-agent treatment of metastatic non-small cell lung cancer (NSCLC) in patients with tumors with high PD-L1 expression (tumor proportion score [TPS] ≥50%), as determined by an approved test, and with no EGFR or ALK genomic tumor aberrations.

First-line treatment (in combination with pemetrexed and carboplatin) of metastatic nonsquamous NSCLC

Single-agent treatment of metastatic NSCLC in patients with tumors with PD-L1 expression (TPS ≥1%), as determined by an approved test, and with disease progression on or following platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression (on approved EGFR- or ALK-directed therapy) prior to receiving pembrolizumab.

Urothelial carcinoma (locally advanced or metastatic):

Treatment of locally advanced or metastatic urothelial cancer in patients who are not eligible for cisplatin-containing treatment.

Treatment of locally advanced or metastatic urothelial cancer in patients with disease progression during or after platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy.

Use: Off-Label

Merkel cell carcinoma (advanced)

Medication Safety Issues

Sound-alike/look-alike issues:

Pembrolizumab may be confused with atezolizumab, nivolumab, palivizumab, panitumumab

High alert medication:

This medication is in a class the Institute for Safe Medication Practices (ISMP) includes among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Adverse Reactions

Incidence of adverse reactions include unapproved dosing regimens.

>10%:

Cardiovascular: Facial edema (10%)

Central nervous system: Fatigue (43%)

Dermatologic: Pruritus (28%), skin rash (24%; immune-mediated: 1%)

Endocrine & metabolic: Hyperglycemia (49%), hypoalbuminemia (37%), hyponatremia (37%), hypertriglyceridemia (33%), decreased serum bicarbonate (22%), hypocalcemia (21%)

Gastrointestinal: Constipation (22%), nausea (22%), decreased appetite (20%), diarrhea (20%), abdominal pain (13%), vomiting (13%)

Hematologic & oncologic: Anemia (44%; grades 3/4: 10%), lymphocytopenia (40%; grades 3/4: 9%)

Hepatic: Increased serum alkaline phosphatase (26%), increased serum AST (24%), increased serum ALT (21%)

Neuromuscular & skeletal: Arthralgia (14%)

Respiratory: Dyspnea (≥20%), cough (18%)

Miscellaneous: Fever (14%)

1% to 10%:

Central nervous system: Confusion (≥2%), peripheral neuropathy (2%)

Endocrine & metabolic: Hypothyroidism (immune-mediated; 9%), hyperthyroidism (immune-mediated; 3%)

Gastrointestinal: Colitis (immune-mediated; 2%)

Immunologic: Antibody development (2%)

Neuromuscular & skeletal: Weakness (10%), arthritis (immune-mediated; 2%)

Respiratory: Pneumonitis (3%), pleural effusion (≥2%), pneumonia (≥2%), respiratory failure (≥2%)

<1%, postmarketing, and/or case reports: Adrenocortical insufficiency (immune-mediated), bullous pemphigoid (immune-mediated), chronic inflammatory demyelinating polyradiculoneuropathy (Maleissye 2016), diabetic ketoacidosis, exfoliative dermatitis (immune-mediated), Guillain-Barré syndrome (immune-mediated), hemolytic anemia (immune-mediated), hepatitis (including autoimmune hepatitis), hypophysitis, infusion-related reaction, interstitial nephritis (with renal failure), myasthenia gravis (immune-mediated), myositis (immune-mediated), nephritis (autoimmune), pancreatitis (immune-mediated), partial epilepsy (immune-mediated; in a patient with inflammatory foci in brain parenchyma),

thyroiditis, type 1 diabetes mellitus, uveitis (immune-mediated), vasculitis (immune-mediated)

Contraindications

There are no contraindications listed in the manufacturer's US labeling.

Canadian labeling: Hypersensitivity to pembrolizumab or any component of the formulation.

Warnings/Precautions

Concerns related to adverse effects:

• Diabetes mellitus: Type 1 diabetes mellitus has occurred (including diabetic ketoacidosis). Monitor closely for hyperglycemia and other signs/symptoms of diabetes. Insulin therapy may be required; if severe hyperglycemia is observed, administer antihyperglycemics and withhold pembrolizumab treatment until glucose control has been accomplished.

• Gastrointestinal toxicity: Immune-mediated colitis has occurred, including cases of grade 2 to 4 colitis. The median time to onset of colitis was 3.5 months (range: 10 days to 16.2 months) and the median duration was 1.3 months (range: 1 day to over 8 months). In many patients, colitis was managed with high-dose systemic corticosteroids for a median duration of 7 days (range: 1 day to 5.3 months), followed by a corticosteroid taper. Most patients with colitis experienced resolution. May require treatment interruption, systemic corticosteroid therapy, and/or permanent discontinuation. Monitor for signs and symptoms of colitis; administer systemic corticosteroids for grade 2 or higher colitis.

• Hepatotoxicity: Immune-mediated hepatitis occurred (grades 2 to 4 hepatitis). The median onset for hepatitis was 1.3 months (range: 8 days to 21.4 months); the median duration was 1.8 months (range: 8 days to over 20 months). Hepatitis resolved in most patients. Administer corticosteroids (prednisone 0.5 to 1 mg/kg/day [or equivalent] for grade 2 hepatitis, and prednisone 1 to 2 mg/kg/day [or equivalent] for grade 3 or higher, each followed by a taper), and withhold or discontinue therapy based on the severity of liver enzyme elevations. Systemic corticosteroids were used to manage immune-mediated hepatitis in many patients; the median duration of high-dose corticosteroid therapy was 5 days (range: 1 to 26 days), followed by a taper. Monitor for liver function changes. May require treatment interruption, systemic corticosteroids (for grade 2 or higher toxicity), and/or permanent discontinuation.

• Hypersensitivity: Hypersensitivity and anaphylaxis have been observed (rare).

• Hypophysitis: Immune-mediated hypophysitis occurred (grades 2, 3, and 4). The median time to onset was 3.7 months (range: 1 day to 12 months) and the median duration was 4.7 months (range: 8 days to over 12 months). Most cases were managed with systemic corticosteroids. Nearly half of patients with hypophysitis experienced resolution. Monitor for signs/symptoms of hypophysitis (eg, hypopituitarism, adrenal insufficiency). May require treatment interruption, systemic corticosteroids and hormone replacement therapy (as clinically indicated), and/or permanent discontinuation.

• Infusion-related reactions: Infusion-related reactions (including severe and life-threatening cases) have occurred. Monitor for signs/symptoms of a reaction (eg, rigors, chills, wheezing, pruritus, flushing, rash, hypotension, hypoxemia, and fever). Interrupt infusion and permanently discontinue for severe (grade 3) or life-threatening (grade 4) infusion-related reactions.

• Nephrotoxicity: Immune-mediated nephritis has occurred. The onset for autoimmune nephritis was 5.1 months (range: 12 days to 12.8 months) and the median duration was 3.3 months (range: 12 days to over 9 months). Grade 2 or higher nephritis should be managed with systemic corticosteroids (prednisone initial dose of 1 to 2 mg/kg/day [or equivalent], followed by a taper). Most patients required systemic corticosteroids. The median duration of corticosteroid use was 15 days (range: 3 days to 4 months), followed by a taper. Nephritis resolved in over half of affected patients. Monitor for renal function changes. May require treatment interruption, systemic corticosteroids (for grade 2 or higher toxicity), and/or permanent discontinuation.

• Pulmonary toxicity: Immune-mediated pneumonitis has been observed, including fatal cases. The median time to development was 3.3 months (range: 2 days to ~19 months) and the median duration was 1.5 months (range: 1 day to over 17 months). Many patients required initial management with high-dose systemic corticosteroids; the median duration of initial corticosteroid therapy was 8 days (range: 1 day to ~10 months) followed by a corticosteroid taper. Pneumonitis resolved in half of the affected patients. May require treatment interruption, corticosteroid therapy (prednisone 1 to 2 mg/kg /day [or equivalent] followed by a taper, for grade 2 or higher pneumonitis), and/or permanent discontinuation. Monitor for signs and symptoms of pneumonitis; if pneumonitis is suspected, evaluate with radiographic imaging and administer systemic corticosteroids for grade 2 or higher pneumonitis. Pneumonitis occurred more frequently in patients with a history of prior thoracic radiation.

• Thyroid disorders: Immune-mediated hyperthyroidism, hypothyroidism, and thyroiditis have occurred. The median onset for hyperthyroidism was 1.4 months (range: 1 day to ~22 months) and the median duration was 2.1 months (range: 3 days to over 15 months). Hyperthyroidism resolved in nearly three-fourths of affected patients. Hypothyroidism occurred with a median onset of 3.5 months (range: 1 day to 19 months) and median duration was not reached (range: 2 days to over 27 months). Hypothyroidism resolved in one-fifth of affected patients. The incidence of new or worsening hypothyroidism was higher in patients with squamous cell cancer of the head and neck. Monitor for changes in thyroid function (at baseline, periodically during treatment, and as clinically indicated) and for signs/symptoms of thyroid disorders. Administer thionamides and beta-blockers for hyperthyroidism as appropriate; may require treatment interruption and/or permanent discontinuation. Isolated hypothyroidism may be managed with replacement therapy. Thyroiditis occurred with a median onset of 1.2 months (range 0.5 to 3.5 months).

• Other immune-mediated toxicities: Other clinically relevant immune-mediated disorders have been observed (may involve any organ system), including rash, exfoliative dermatitis, bullous pemphigoid, uveitis, arthritis, vasculitis, myositis, Guillain-Barré syndrome, pancreatitis, hemolytic anemia, serum sickness, myasthenia gravis, myelitis, myocarditis, and partial seizures (in a patient with inflammatory foci in brain parenchyma). If an immune-mediated adverse event is suspected, evaluate appropriately to confirm or exclude other causes; withhold treatment and administer systemic corticosteroids based on severity of reaction. Upon resolution to grade 0 or 1, initiate corticosteroid taper (continue tapering over at least 1 month). When reaction remains at grade 1 or less during taper may reinitiate pembrolizumab. Immune-mediated adverse reactions that do not resolve with systemic corticosteroids may be managed with other systemic immunosuppressants (based on limited data). Discontinue permanently for severe or grade 3 immune-mediated adverse event that is recurrent or life-threatening.

Disease-related concerns:

• Hematopoietic stem cell transplant: Patients who received allogeneic hematopoietic stem cell

transplant (HSCT) following discontinuation of pembrolizumab therapy experienced immune-mediated complications (some fatal) including graft versus host disease (GVHD) and severe sinusoidal obstructive syndrome (SOS; formerly called veno-occlusive disease) following reduced-intensity conditioning. Fatal hyperacute GVHD post HSCT has also been reported in lymphoma patients who received an anti PD-1 antibody prior to transplant. These complications may occur despite intervening therapy between pembrolizumab and HSCT. Monitor closely for early signs/symptoms of transplant-related complications (eg, hyperacute GVHD, severe [grade 3 to 4] acute GVHD, steroid-requiring febrile syndrome, SOS, and other immune-mediated adverse reactions) and manage promptly.

Metabolism/Transport Effects

None known.

Drug Interactions

(For additional information: Launch drug interactions program) Lexicomp®

There are no known significant interactions.

Pregnancy Implications

Animal reproduction studies have not been conducted. Immunoglobulins are known to cross the placenta; therefore fetal exposure to pembrolizumab is expected. Based on the mechanism of action, pembrolizumab may cause fetal harm if administered during pregnancy; an alteration in the immune response or immune mediated disorders may develop following in utero exposure. Women of reproductive potential should use highly effective contraception during therapy and for at least 4 months after treatment is complete.

Breast-Feeding Considerations

It is not known if pembrolizumab is present in breast milk. The manufacturer recommends that breastfeeding be discontinued during therapy and for 4 months following the final dose. Immunoglobulins are excreted in breast milk; therefore pembrolizumab may be expected to appear in breast milk.

Monitoring Parameters

PD-L1 expression status in patients with NSCLC (when used as single-agent therapy); liver function tests (AST, ALT, and total bilirubin); renal function; thyroid function (at baseline, periodically during treatment and as clinically indicated); glucose; CBC with differential (in patients with Hodgkin lymphoma); signs/symptoms of colitis, hypophysitis, thyroid disorders, pneumonitis, infusion reactions.

Mechanism of Action

Highly selective anti-PD-1 humanized monoclonal antibody which inhibits programmed cell death-1 (PD-1) activity by binding to the PD-1 receptor on T-cells to block PD-1 ligands (PD-L1 and PD-L2) from binding. Blocking the PD-1 pathway inhibits the negative immune regulation caused by PD-1 receptor signaling (Hamid 2013). Anti-PD-1 antibodies (including pembrolizumab) reverse T-cell suppression and induce antitumor responses (Robert 2014).

Pharmacodynamics/Kinetics

Note: Clearance is ~21% lower at steady state than with the first dose. With weight-based dosing (2 mg/kg), pembrolizumab concentrations in pediatric patients are comparable to those of adults (at the same dose).

Distribution: V_{dss}: 6 L

Half-life elimination: 22 days

Pricing: US

Solution (Keytruda Intravenous)

100 mg/4 mL (4 mL): $5415.84

Solution (reconstituted) (Keytruda Intravenous)

50 mg (1): $2628.44

Disclaimer: The pricing data provide a representative AWP and/or AAWP price from a single manufacturer of the brand and/or generic product, respectively. The pricing data should be used for benchmarking purposes only, and as such should not be used to set or adjudicate any prices for reimbursement or purchasing functions. Pricing data is updated monthly.

International Brand Names

Keytruda (AT, AU, CH, CY, CZ, DE, DK, EE, ES, FR, GB, HK, HR, HU, IL, IS, JP, KR, LT, LU, MY, NL, NO, NZ, PH, PL, PT, RO, SE, SG, SI, SK, TH)

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