These Clinical Guidelines have been created using resources that were current as of the "Reviewed" date noted at the beginning of the document. Clinicians should refer to the manufacturer's Prescribing Information (or equivalent) for the most up-to-date information. While CarepathRx has published these Clinical Guidelines after a close review of available literature and a clinical review process, given the evolving nature and complexity of modern pharmaceutical products, CarepathRx does not and cannot warrant or guarantee that these Clinical Guidelines reflect the objectively best or highest standard of care at any given time.

Nothing within these Clinical Guidelines is intended to supersede or interfere with any individual clinician's decision-making or professional judgment with respect to either (1) prescribing or dispensing the drug or product in question or (2) the overall treatment plan for an individual patient.

Pembrolizumab (Keytruda) Clinical Guideline for Home or Outpatient Intravenous Therapy

Section: Clinical Guideline
Policy ID: CG046
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I. BACKGROUND

Keytruda (pembrolizumab) is a 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. PD-1 has a major involvement in suppressing the immune system during the formation of the PD-1/PD-L1 pathway, which transmits an inhibitory signal to reduce T cell activity. PD-L1 is often expressed in various malignant tumors. Blocking the PD-1 pathway inhibits the negative immune regulation caused by PD-1 receptor signaling. Anti-PD-1 antibodies reverse T-cell suppression and induce antitumor responses. Pembrolizumab is indicated in the treatment of numerous types of cancer in both adult and pediatric patients. The following outlines the procedures for servicing patients in need of outpatient pembrolizumab infusions.

II. PATIENT ACCEPTANCE CRITERIA

A. All candidates for home care service must be evaluated by the clinician(s) and deemed appropriate to receive home care based upon the dispensing pharmacy's admission criteria.

B. The decision to administer a first dose in the home by a field nurse will be determined on a case-by-case basis and reviewed by nursing and pharmacy management. The following criteria will be evaluated:

   a. Prescriber preference
   b. Allergy profile
   c. Age
   d. Other relevant social and/or medical history

C. Physician orders for Pembrolizumab must include:

   a. Drug
   b. Dose (total dose and weight-based dose for certain pediatric indications)
   c. Patient weight
   d. Route of administration
   e. Frequency of administration
   f. Emergency medications
   g. Line Care Protocol
   h. Orders for pre-medications, if applicable
   i. Routine lab monitoring, if applicable

D. Baseline labs or tests recommended prior to starting therapy:

a. Liver function tests
b. Renal function (BUN, serum creatinine)
c. Baseline BMP and CBC with differential
d. Thyroid function tests
e. Baseline blood cortisol
f. Pregnancy status for female patients of child-bearing age

E. Dispensing pharmacy treatment protocol for anaphylaxis will be instituted unless a more comprehensive patient-specific orders are provided by physician. See Appendix A (Nursing CarepathRx policy on *Management of Allergic/Anaphylactic Reactions*).

III. PHARMACOLOGY OVERVIEW

Refer to manufacturer's full Prescribing Information for most up to date information

A. Indications, Dosing, and Duration

Indication (Monotherapy)	Recommended Dosage of Pembrolizumab	Duration Timing of Treatment
Adult patients with unresectable or metastatic melanoma	200 mg IV every 3 weeks or 400 mg IV every 6 weeks	Until disease progression or unacceptable toxicity
Adjuvant treatment of adult patients with melanoma, NSCLC, or RCC	200 mg IV every 3 weeks or 400 mg IV every 6 weeks	Until disease progression, unacceptable toxicity, or up to12 months
Adult patients with NSCLC, HNSCC, cHL, PMBCL, locally advanced or metastatic Urothelial Carcinoma, MSI-H or dMMR Carcinoma, MSI-H or dMMR Colorectal Cancer (CRC), MSI-H or dMMR Endometrial Carcinoma, Esophageal Cancer, Cervical Cancer, HCC, MCC, TMB-H Cancer, cSCC	200 mg IV every 3 weeks or 400 mg IV every 6 weeks	Until disease progression, unacceptable toxicity, or up to 24 months

Adult patients with high-risk BCG-unresponsive NMIBC	200 mg IV every 3 weeks or 400 mg IV every 6 weeks	Until persistent or recurrent high-risk NMIBC, disease progression, unacceptable toxicity, or up to 24 months
Pediatric patients with cHL, PMBCL, MSI-H or dMMR Cancer, MCC, or TMB-H Cancer	2 mg/kg IV every 3 weeks (up to max dose of 200 mg) *Dosing is based off of actual body weight	Until disease progression, unacceptable toxicity, or up to 24 months
Pediatric patients (12 years and older) for adjuvant treatment of melanoma	2 mg/kg IV every 3 weeks (up to max dose of 200 mg) *Dosing is based off of actual body weight	Until disease progression, unacceptable toxicity, or up to 12 months

*Key: Non-small Cell Lung Cancer (NSCLC), Renal Cell Carcinoma (RCC), Head and Neck Squamous Cell Cancer (HNSCC), Classical Hodgkin Lymphoma (cHL), Primary Mediastinal Large B-Cell Lymphoma (PMBCL), Microsatellite Instability-High (MSI-H), Mismatch Repair Deficient (dMMR), Colorectal Cancer (CRC), Hepatocellular Carcinoma(HCC), Merkel Cell Carcinoma (MCC), Tumor Mutational Burden-High (TMB-H) Cancer, Cutaneous Squamous Cell Carcinoma (cSCC), Non-muscle invasive bladder cancer (NMIBC),

Indication (Combination Therapy)	**Recommended Dosage of Pembrolizumab**	**Duration Timing of Treatment**
Adult patients with resectable NSCLC	200 mg IV every 3 weeks or 400 mg IV every 6 weeks Administer pembrolizumab prior to chemo when given on the same day.	Neoadjuvant treatment in combination with chemotherapy for 12 weeks or until disease progression that precludes definitive surgery or unacceptable toxicity, followed by adjuvant treatment with pembrolizumab as a single agent after surgery for 39 weeks or until disease recurrence or unacceptable toxicity.
Adult patients with NSCLC, MPM, HNSCC, HER2-negative Gastric Cancer, Esophageal Cancer, or BTC	200 mg IV every 3 weeks or 400 mg IV every 6 weeks Administer pembrolizumab prior to chemo when given on the same day.	Until disease progression, unacceptable toxicity, or up to 24 months

Adult patients with locally advanced or metastatic urothelial cancer	200 mg IV every 3 weeks or 400 mg IV every 6 weeks Administer pembrolizumab after enfortumab vedotin when given on the same day.	Until disease progression, unacceptable toxicity, or up to 24 months
Adult patients with locally advanced HNSCC	200 mg IV every 3 weeks or 400 mg IV every 6 weeks Administer pembrolizumab prior to cisplatin when given on the same day.	Neoadjuvant: • Administer pembrolizumab for 6 weeks or until disease progression that precludes definitive surgery or unacceptable toxicity. Adjuvant: • Administer pembrolizumab in combination with radiation with or without cisplatin. • Continue pembrolizumab as a single agent. • Continue pembrolizumab until disease recurrence or unacceptable toxicity or up to one year.
Adult patients with HER2-positive Gastric Cancer	200 mg IV every 3 weeks or 400 mg IV every 6 weeks Administer pembrolizumab prior to trastuzumab and chemotherapy when give on the same day.	Until disease progression, unacceptable toxicity, or up to 24 months
Adult patients with Cervical Cancer	200 mg IV every 3 weeks or 400 mg IV every 6 weeks Administer pembrolizumab prior to chemoradiotherapy or prior to chemotherapy with or without bevacizumab when given on the same day.	Until disease progression, unacceptable toxicity, or up to 24 months

Adult patients with RCC	200 mg IV every 3 weeks or 400 mg IV every 6 weeks Administer pembrolizumab in combination with axitinib 5 mg PO BID. Administer pembrolizumab in combination with Lenvatinib 20 mg PO once daily.	Until disease progression, unacceptable toxicity, or up to 24 months
Adult patients with Endometrial Carcinoma	200 mg IV every 3 weeks or 400 mg IV every 6 weeks Administer pembrolizumab prior to carboplatin and paclitaxel when given on the same day. or Administer pembrolizumab in combination with lenvatinib 20 mg PO once daily.	Until disease progression, unacceptable toxicity, or up to 24 months
Adult patients with high-risk early-stage TNBC	200 mg IV every 3 weeks or 400 mg IV every 6 weeks Administer pembrolizumab prior to chemotherapy when given on the same day.	Neoadjuvant treatment in combination with chemotherapy for 24 weeks (8 doses of 200 mg IV every 3 weeks or 4 doses of 400 mg IV every 6 weeks) or until disease progression or unacceptable toxicity, followed by adjuvant treatment with pembrolizumab as a single agent for up to 27 weeks (9 doses of 200 mg IV every 3 weeks or 5 doses of 400 mg IV every 6 weeks) or until disease recurrence or unacceptable toxicity.

Adult patients with locally recurrent unresectable or metastatic TNBC	200 mg IV every 3 weeks or 400 mg IV every 6 weeks Administer pembrolizumab prior to chemotherapy when given on the same day.	Until disease progression, unacceptable toxicity, or up to 24 months

*Key: Malignant Pleural Mesothelioma (MPM), Biliary Tract Cancer (BTC), Triple-Negative Breast Cancer (TNBC)

B. Dose Adjustments

a. Renal and hepatic impairment **prior** to treatment initiation: No dosage adjustments

2. Recommended dose modifications for adverse reactions:

Adverse Reaction	Severity	Pembrolizumab Dosage Modification
Pneumonitis	Grade 2	Withhold pembrolizumab treatment Resume pembrolizumab in patients with complete or partial resolution (Grades 0 to 1) after corticosteroid taper.
	Grade 3 or 4	Permanently discontinue pembrolizumab
Colitis	Grade 2 or 3	Withhold pembrolizumab treatment Resume pembrolizumab in patients with complete or partial resolution (Grades 0 to 1) after corticosteroid taper.
	Grade 4	Permanently discontinue pembrolizumab
Hepatitis without tumor involvement of the liver	AST or ALT >3 up to 8 times ULN (upper limit of normal) OR Total bilirubin >1.5 up to 3 times ULN	Withhold pembrolizumab treatment. Resume pembrolizumab treatment with complete or partial resolution (to grade 0 or 1) of hepatitis after corticosteroid taper.

	AST or ALT >8 times ULN OR Total bilirubin >3 times ULN	Permanently discontinue pembrolizumab
Liver enzyme elevations for pembrolizumab in combination with axitinib	ALT or AST ≥ 3 times but < 10 times ULN without concurrent total bilirubin at least 2 times ULN	Withhold both pemborlizumab and axitinib until resolution to Grades 0 or 1 Consider rechallenge with a single drug or sequential rechallenge with both drugs after recovery
	ALT or AST > 3 times ULN with concurrent total bilirubin at least 2 times ULN OR ALT or AST ≥10 times ULN	Permanently discontinue both pembrolizumab and axitinib
Hepatitis with tumor involvement of the liver (Note: If AST and ALT are ≤ ULN at baseline, follow recommendations for hepatitis without tumor involvement of the liver)	If baseline AST or ALT >1 up to 3 times ULN and increases to >5 up to 10 times ULN OR Baseline AST or ALT >3 up to 5 times ULN and increases to >8 up to 10 times ULN	Withhold pembrolizumab treatment. Resume pembrolizumab treatment with complete or partial resolution (to grade 0 or 1) of hepatitis after corticosteroid taper.
	AST or ALT increases to >10 times ULN OR Total bilirubin increases to >3 times ULN	Permanently discontinue pembrolizumab
Endocrinopathies	Grade 3 or 4	Withhold pembrolizumab until clinically stable or permanently discontinue depending on severity

Nephritis with renal dysfunction	Grade 2 or 3 increased blood creatinine	Withhold pembrolizumab treatment Resume pembrolizumab in patients with complete or partial resolution (Grades 0 to 1) after corticosteroid taper.
	Grade 4 increased blood creatinine	Permanently discontinue pembrolizumab
Exfoliative dermatologic conditions	Suspected Stevens Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), or Drug Rash with Eosinophilia and Systemic Symptoms (DRESS)	Withhold pembrolizumab treatment Resume pembrolizumab in patients with complete or partial resolution (Grades 0 to 1) after corticosteroid taper.
	Confirmed SJS, TEN, or DRESS	Permanently discontinue pembrolizumab
Myocarditis	Grade 2, 3, or 4	Permanently discontinue pembrolizumab
Neurological toxicities	Grade 2	Withhold pembrolizumab treatment Resume pembrolizumab in patients with complete or partial resolution (Grades 0 to 1) after corticosteroid taper.
	Grade 3 or 4	Permanently discontinue pembrolizumab
Hematologic toxicity in patients with cHL or PMBCL	Grade 4	Withhold pembrolizumab treatment until resolution to Grades 0 or 1
Infusion related reactions	Grade 1 or 2	Interrupt or slow the infusion
	Grade 3 or 4	Permanently discontinue pembrolizumab

C. Contraindications: None

D. Warnings and Precautions

1. **Immune mediated pneumonitis:** Immune-mediated pneumonitis has been observed, including grades 2 to 4, and fatal cases. Many patients required management with systemic corticosteroids. Pneumonitis resolved in over half of the affected patients. In cases where pembrolizumab was withheld for pneumonitis, all reinitiated pembrolizumab after symptom improvement. Pneumonitis recurred in 23% of patients. Pneumonitis occurred more frequently in patients with a history of prior thoracic radiation.
2. **Immune mediated colitis**: Immune-mediated colitis has occurred (may present with diarrhea), including cases of grade 2 to 4 colitis. Systemic corticosteroids were administered to the majority of patients for immune-mediated colitis. Additional immunosuppressant therapy was necessary in some patients. Most patients with colitis experienced resolution. In cases where pembrolizumab was withheld for colitis, all reinitiated treatment after symptom improvement. Colitis recurred in 23% of patients. Pancreatitis (including increased serum amylase and lipase levels), gastritis, and duodenitis have also been reported.
3. **Hepatotoxicity and Immune mediated hepatitis:** Immune-mediated hepatitis has occurred with pembrolizumab monotherapy (grades 2 to 4 hepatitis). Monitor patients for changes in liver function. Hepatitis has led to pembrolizumab treatment interruption or discontinuation. Systemic corticosteroids were used to manage immune-mediated hepatitis in many patients; additional immunosuppressants were necessary in some cases. Hepatitis resolved in a majority of patients. In cases where pembrolizumab was withheld for hepatitis, all reinitiated treatment after symptom improvement with no recurrence of hepatitis.
   Pembrolizumab in combination with axitinib can cause hepatic toxicity with higher than expected frequencies
   of Grades 3 and 4 ALT and AST elevations compared to monotherapy. Monitor liver enzymes before initiation of and periodically throughout treatment. Consider more frequent monitoring of liver enzymes compared to when the drugs are administered as single agents.
4. **Immune mediated endocrinopathies**:

   a. Adrenal insufficiency: Primary and secondary adrenal insufficiency have occurred, including cases of $\geq$ grade 2 adrenal insufficiency. Over 75% of cases were managed with systemic corticosteroids. The majority of patients remained on corticosteroid therapy. In cases where pembrolizumab was withheld for adrenal insufficiency, all reinitiated treatment after symptom improvement.
   b. Hypophysitis: Immune-mediated hypophysitis has occurred (grades 2, 3, and 4), and may present with acute mass effect symptoms (headache, photophobia, or visual field defects). Hypophysitis may lead to hypopituitarism. Most hypophysitis cases were managed with systemic corticosteroids. The majority of patients remained on corticosteroid therapy. In cases where pembrolizumab was withheld for hypophysitis, all reinitiated treatment after symptom improvement.
   c. Thyroid disorders: Thyroiditis may present with or without endocrinopathy. Thyroiditis occurred rarely, and did not result in permanent discontinuation, although treatment was interrupted occasionally. Hyperthyroidism occurred in a small percentage of patients, including grade 2 and 3 events. Discontinuation or treatment interruption due to hyperthyroidism were required in a small number of patients. In cases where pembrolizumab was withheld, all reinitiated treatment after symptom improvement. Hypothyroidism has occurred, including grade 2 and 3 cases. Hypothyroidism may follow hyperthyroidism. Discontinuation or treatment interruption due to hypothyroidism were required in a small number of patients; in cases where pembrolizumab was withheld, all reinitiated treatment. Most patients required long-term thyroid replacement therapy.

d. Diabetes mellitus: Type 1 diabetes mellitus has occurred in a small percentage of patients taking pembrolizumab. Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Initiate treatment with insulin as clinically indicated

5. **Immune mediated nephritis with renal dysfunction**: Immune-mediated nephritis with kidney dysfunction has occurred, including grade 2 to grade 4 cases. Monitor patients for changes in renal function. Most patients required systemic corticosteroids. In cases where pembrolizumab was withheld for nephritis, all reinitiated treatment after symptom improvement with no recurrence of nephritis. Nephritis resolved in over one-half of affected patients.
6. **Immune mediated dermatologic toxicity**: Immune-mediated rash or dermatitis may occur. Immune-mediated dermatologic adverse reactions (including grade 2 and 3 events) occurred with pembrolizumab. Exfoliative dermatitis, including Stevens-Johnson syndrome, drug rash with eosinophilia and systemic symptoms, and toxic epidermal necrolysis has occurred with anti-PD-1/PD-L1 monoclonal antibodies. Immune-mediated dermatologic reactions were treated with systemic corticosteroids in 40% of patients, and reactions resolved in ~80% of patients. In cases where pembrolizumab was withheld, all reinitiated treatment after symptom improvement. Immune-mediated dermatologic toxicity recurred in some patients.
7. **Other immune related reactions**: Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue in patients receiving pembrolizumab. While immune-mediated adverse reactions usually occur during treatment with PD-1/PD-L1 blocking antibodies, they may occur after discontinuation of treatment. For suspected immune-mediated adverse reactions, ensure adequate evaluation to confirm etiology or exclude other causes. The following clinically significant, immune-mediated adverse reactions occurred in patients treated with pembrolizumab: uveitis, myositis, Guillain Barré syndrome, myasthenia gravis, vasculitis, pancreatitis, hemolytic anemia, sarcoidosis, and encephalitis. In addition, myelitis and myocarditis were reported in other trials, including cHL, and post marketing use.
8. **Infusion-related reactions**: Infusion-related reactions (including severe and life-threatening cases) have occurred. Hypersensitivity and anaphylaxis are rare but have been reported in 0.2% of 2799 patients receiving pembrolizumab. Signs/symptoms of an infusion reaction include rigors, chills, wheezing, pruritus, flushing, rash, hypotension, hypoxemia, and fever.
9. **Complications of Allogeneic Hematopoietic Stem Cell Transplantation (HSCT):** Immune-mediated complications, including fatal events, occurred in patients who underwent allogeneic HSCT after being treated with pembrolizumab. These complications may occur despite intervening therapy between PD-1 blockade and allogeneic HSCT. In patients with a history of allogeneic HSCT, acute graft versus host disease (GVHD), including fatal GVHD, has been reported after treatment with pembrolizumab. Patients who experienced GVHD after their transplant procedure may be at increased risk for GVHD after treatment with pembrolizumab. Consider the benefit of treatment with pembrolizumab versus the risk of possible GVHD in patients with a history of allogeneic HSCT.
10. **Increased Mortality in Patients with Multiple Myeloma when pembrolizumab is Added to a Thalidomide Analogue and Dexamethasone:** In two randomized trials in patients with multiple myeloma, the addition of pembrolizumab to a thalidomide analogue plus dexamethasone, a use for which no PD-1 or PD-L1 blocking antibody is indicated, resulted in increased mortality. Treatment of patients with multiple myeloma with a PD-1 or PD-L1 blocking antibody in combination with a thalidomide analogue plus dexamethasone is not recommended outside of controlled trials.
11. **Embryo-Fetal Toxicity:** Based on its mechanism of action, pembrolizumab can cause fetal harm when administered to a pregnant woman. Animal models link the PD-1/PD-L1 signaling pathway with maintenance of pregnancy through induction of maternal immune tolerance to fetal tissue. Advise women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with pembrolizumab and for 4 months after the last dose.

12. **Lactation:** There is no data on the presence of pembrolizumab in either animal or human milk or its effects on the breastfed child or on milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment with pembrolizumab and for 4 months after the last dose.

E. Pharmacokinetics

a. Distribution: Vd: 6 L.
b. Metabolism: Pembrolizumab is broken down into small peptides and amino acids through general protein degradation routes throughout the body.
c. Half-life elimination: 22 days.

F. Adverse Reactions

1. Common adverse reactions:

a. Cardiovascular: Hypertension (24-67%)
b. Dermatologic: Alopecia (34-61%), pruritis (11-41%), rash (1.4 -71%
c. Endocrine metabolic: Hypercholesterolemia (Non-small cell lung cancer, 20%), hyperglycemia (40% to 48%), hypertriglyceridemia (23% to 25%) hypoalbuminemia (32-34%), hyponatremia (10-38%), decrease in weight (10-36%)
d. Gastrointestinal: Constipation (12% to 42%), decrease in appetite (16% to 44%) , diarrhea (12-62%), nausea (11-67%), vomiting (2% to 37%).
e. Hematologic: Leukopenia (24%), thrombocytopenia (12-73%)
f. Hepatic: Alkaline phosphatase elevations (Non-small cell lung cancer, 26%), Aspartate aminotransferase serum level elevations (20% to 24%).
g. Musculoskeletal: Arthralgia (10% to 31%), disorder of musculoskeletal system (53% to 58%), musculoskeletal pain (16-41%)
h. Neurologic: Asthenia (10-53%), neuropathy (1-67%)
i. Renal: Proteinuria (29-30%), UTI (11-35%)
j. Respiratory: Cough (11-26%), dyspnea (10-23%)
k. Other: Fatigue (2070%)

2. Serious adverse reactions:

a. Cardiovascular: Cardiac tamponade (2%), myocardial ischemia (2%), myocardial infarction (2%), myocarditis (0.5-1.4%), pericarditis (4%
b. Dermatologic: Drug reaction with eosinophilia and systemic symptoms, hand-foot syndrome due to cytotoxic therapy (23% to 28%), Stevens Johnson syndrome, Stevens Johnson syndrome and toxic epidermal necrolysis overlap, toxic epidermal necrolysis
c. Endocrine metabolic: Adrenal insufficiency (0.8%), hyperthyroidism (3-13%), hypoparathyroidism, hypophysitis (0.6%), hypothyroidism (8-67%), thyroiditis (0.6-2%), Type 1 diabetes mellitus (0.2%).
d. Gastrointestinal: Colitis (1.7%), diarrhea (12-62%), duodenitis, gastritis, gastrointestinal obstruction, gastrointestinal perforation, lower gastrointestinal hemorrhage, pancreatitis, stomatitis (27% to 48%).
e. Hematologic: Anemia all grades (12% to 75%), anemia, grade 3 or 4 (2% to 12%), Aplastic anemia, febrile neutropenia (1.4%), hemolytic anemia, hemorrhage (19% to 27%), hemophagocytic lymphohistiocytosis, Neutropenia, Grade 3 or 4 (1.4% to 62%), thrombocytopenia, grade 3 or 4 (1.4% to 19%).

f. Hepatic: Hepatitis (0.7% to 2.9%), hepatotoxicity (14% to 39%), veno-occlusive disease of the liver (9%)
g. Immunologic: Histiocytic necrotizing lymphadenitis, hypersensitivity reaction (4.1%), sarcoidosis, systemic inflammatory response syndrome, transplanted organ rejection, Vogt-Koyanagi-Harada disease.
h. Musculoskeletal: Eaton-Lambert syndrome, myasthenia gravis (2.5%), myositis (1% to 3.3%), polymyalgia rheumatica, polymyositis, rhabdomyolysis
i. Neurologic: Confusion, demyelination of spinal cord, encephalitis, Guillain-Barre syndrome, meningitis, myelitis (0.5%), nerve palsy
j. Ophthalmic: Iritis, myasthenia gravis, ocular, optic neuritis, uveitis (up to 1.4%), visual impairment
k. Renal: Acute injury of kidney (13% to 21%), nephritis, renal failure
l. Respiratory: COVID-19 (10%), dyspnea (10% to 23%), pleural effusion (2% or more), pneumonia (2% or more), pneumonitis (2% to 11%), pulmonary embolism (2%), respiratory failure (2% or more)
m. Other: Fever (10% to 28%), Infusion reaction (0.2%), Infusion reaction (0.2% to 9%), Sepsis (Up to 10%).

G. Drug Interactions:

1. Concurrent use of pembrolizumab may result in an increased risk of infection with the use of live vaccines.
2. Pembrolizumab may enhance the adverse/toxic effect of thalidomide analogs. Mortality may be increased when this combination is used for treatment of refractory multiple myeloma. Avoid concomitant use with thalidomide analogs (thalidomide, pomalidomide, and lenalidomide).
3. Acetaminophen, antibiotics, and PPIs: may diminish the therapeutic effect of immune checkpoint inhibitors.
4. Axitinib: may enhance the hepatotoxic effect of pembrolizumab and diminish the therapeutic effect of immune checkpoint inhibitors.
5. Desmopressin: hyponatremia-associated agents may enhance the hyponatremic effect of desmopressin.
6. Efgartigimod Alfa: may diminish the therapeutic effect of Fc Receptor-Binding Agents.
7. Ketoconazole (Systemic): immune checkpoint inhibitors may enhance the hepatotoxic effect of Ketoconazole.
8. Drug-drug interactions may exist. Consult interaction database for patient specific assessment.

IV. ADMINISTRATIVE GUIDELINES

A. Administer through an intravenous line containing a sterile, non-pyrogenic, low-protein **binding 0.2 to 5 micron in-line or add-on filter**.

B. Do not co-administer with other medications in the same IV line.

C. If following NIOSH and USP <800> recommendations for handling and preparation, prepare the preparation under aseptic conditions in a containment primary engineering control.

D. Hazardous handling: It is the responsibility of the dispensing pharmacy to ensure medication handling follows organizational policies and procedures. This medication meets the definitions of a hazardous drug as outlined by the National Institute for Occupational Safety and Health (NIOSH).

V. NURSING PROCEDURE

A. Supplies may include but are not limited to:

1. Alcohol Swabs
2. Chemo gloves/prep pad/ gown
3. Chemo spill kit
4. Chemo waste bin
5. Peripheral IV access supplies for patients requiring peripheral IV access
    a. IV start kit
    b. Peripheral IV catheter (ex. 22 Gauge x1" and 24 Gauge x ¾")
    c. Extension set 8" with needless connector
6. Port access supplies for patients with a port
    a. Port needle (ex. 22 Gauge x ¾ to 1" safe step)
    b. Needless connector
    c. Central line dressing change kit
7. IV Pole
8. Tape
9. IV administration set (flow regulator or gravity tubing) with in-line or add-on 0.22-micron filter

B. Prescription items:

1. Pembrolizumab compounded sterile preparation
2. Standard flushes per protocol
3. Anaphylaxis kit per protocol

C. How Supplied:

1. Pembrolizumab injection (clear to slightly opalescent, colorless to slightly yellow solution): carton containing one 100 mg/4 mL (25 mg/mL), single-dose vial (NDC 0006-3026-02)
2. The pharmacy will provide pembrolizumab for home or clinic use as a compounded sterile product per manufacturer specifications. The final concentration of the diluted solution should be between 1 mg/mL to 10 mg/mL in 0.9% sodium chloride.

D. Storage and Handling:

1. Store vials under refrigeration at 2°C to 8°C (36°F to 46°F) in original carton to protect from light. Do not freeze. Do not shake.
2. Diluted sterile compounded pembrolizumab preparation stored at room temperature (temperatures at or below 25°C) is stable for no more than 6 hours from the time of dilution. This includes room temperature storage of the diluted solution, and the duration of infusion.
3. Diluted sterile compounded pembrolizumab preparation under refrigeration at 2°C to 8°C (36°F to 46°F) is stable for no more than 96 hours from the time of dilution. If refrigerated, allow the diluted solution to come to room temperature prior to administration.
4. Pembrolizumab does not contain preservative.

E. Compatibility: Compatible with Dextrose 5% and 0.9% sodium chloride.

F. Preparation of Product:

1. Visually inspect the solution for particulate matter and discoloration. The solution is clear to slightly opalescent, colorless to slightly yellow. Discard the vial if visible particles are observed.
2. Withdraw the required volume from the vial(s) of pembrolizumab and transfer into an intravenous (IV) bag containing 0.9% sodium chloride Injection or 5% Dextrose.
3. Mix diluted solution by gentle inversion. The final concentration of the diluted solution should be between 1 mg/mL to 10 mg/mL.
4. Discard any unused portion left in the vial.
5. Diluted sterile compounded preparations of pembrolizumab are stable for 6 hours at room temperature and 96 hours under refrigeration if mixed under aseptic conditions with a primary engineering control.

G. Procedures:

1. Explain the reasoning for visit and use of pembrolizumab.
2. Don chemo gloves and gown. Prepare chemotherapy prep mat.
3. Establish venous access prior to preparation of drug if applicable.
4. Counsel patient on warnings, precautions, and potential side effects including but not limited to: fatigue, musculoskeletal pain, rash, diarrhea, pyrexia, cough, decreased appetite, pruritis, dyspnea, constipation, abdominal pain, and nausea
5. Infuse pembrolizumab IV over 30 minutes using an in line 0.2 to 5 in micron filter.
6. Post infusion monitoring: The nurse should remain with the patient for 30 minutes following medication administration to monitor vital signs and response to therapy.

VI. CLINICAL MONITORING

A. Prior to therapy

1. Labs/Radiology: LFT's, CBC with differential, serum Cr, thyroid function test, blood glucose tests, cortisol levels
2. Additional suggested monitoring recommended by American Society of Clinical Oncology (ASCO) prior to initiating pembrolizumab:

    a. Serum chemistries
    b. Comprehensive clinical assessment including performance status, weight, BMI, heart rate, blood pressure, and oxygen saturation
    c. Consider chest x-ray, ECG, and CT scan
    d. Assess history of autoimmune conditions, organ-specific disease, endocrinopathies, neuropathy, and infectious disease; assess bowel habits, respiratory symptoms, skin (for rash), arthralgias, and neurologic symptoms

3. Pregnancy status for female patients of child-bearing age. Counsel patients on the risk of getting pregnant during pembrolizumab and for 4 months after the last dose.

B. During therapy:

1. Monitor necessary lab work including LFTs, CBC with differential, creatinine, thyroid function test, blood glucose tests, cortisol levels, and bone mineral density (with long-term therapy).

2. Monitor patients for signs and symptoms of infusion-related reactions including rigors, chills, wheezing, pruritus, flushing, rash, hypotension, hypoxemia, and fever.
3. Assessment of signs/symptoms of adverse effects:

    a. Adrenal insufficiency
    b. Diarrhea/colitis
    c. Dermatologic toxicity
    d. Nephrotoxicity
    e. Diabetes mellitus
    f. Hypophysitis
    g. Ocular disorders
    h. Thyroid disorders
    i. Pneumonitis
    j. Infections
    k. Other immune-mediated adverse reactions.

4. Monitor ocular toxicity through regularly scheduled eye exams including intraocular pressure 6 weeks after starting therapy.
5. If received/receiving hematopoietic stem cell transplant, monitor closely for early signs/symptoms of transplant-related complications.
6. Monitor PD-L1 expression, tumor specimen microsatellite instability-high (MSI-H) status, mismatch repair deficient (dMMR) status, mismatch repair proficient status, and/or tumor mutational burden-high (TMB-H) status (if applicable).
7. Additional suggested monitoring recommended by ASCO

    a. Assess blood pressure, weight, heart rate, and oxygen saturation
    b. Assess for infections
    c. Serum chemistries

Please refer to the package insert for the most up to date guidance on this medication.

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APPENDIX A: ANAPHYLAXIS KIT INTRUCTIONS FOR IV INFUSION
Emergency Medication after Your Infusion

Please call 1-800-755-4704 if you have any questions or concerns. We are available 24 hours a day, 7 days a week. In the event of an emergency, always call 911.

Your nurse will tell you when you need to use Emergency Medications.

Start with a clean work surface and clean hands.

Open the supply bag labeled Anaphylaxis Kit Contents.

You will need:

1. **Bag containing Pills** (2 Acetaminophen and 2 Diphenhydramine)
2. **Bag containing Alcohol Prep Pads**
3. **Bag labeled IM Epinephrine**

All other contents will not be needed.

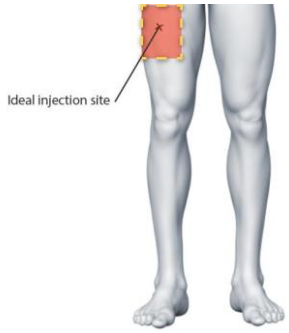
Open the IM Epinephrine Bag

1. **Remove 1 of each item**
    a. 1 -syringe
    b. 1 – brown labeled filter needle (BD Filter Needle)
    c. 1 – black labeled safety needle (Magellan Hypodermic Safety Needle 22G x 1”)
    d. 1 ampule of epinephrine

Prepare IM (intramuscular) injection of Epinephrine:

1. **Attach the brown filtered needle to syringe**
    a. Be careful to not touch the tip of the syringe or the needle.
2. Using an **alcohol swab, wipe the neck of the epinephrine ampule**
3. Holding the ampule upright, **swirl and flick the ampule until all fluid flows to the bottom chamber** (the top chamber should be empty).
4. Using a new alcohol wipe, grasp the neck of the ampule and with your other hand grasp the bottom chamber of the ampule. **Quickly snap the top of the ampule off, directing the snap way from you.**
5. **Place the tip of the brown filter needle inside the ampule**. Tilting the ampule, **withdrawal all the medication into the syringe** by gently pulling back on the plunger. Be careful to not pull the plunger out of the syringe.
6. Remove the needle from the ampule and h**old the syringe upright** with the needle pointing upward. **Gently tap the side of the syringe to bring any air to the top of the syringe.**
7. **Push the air out of the syringe by gently pushing on the plunger**.
8. Replace the cap on the brown filter needle.
9. **Remove the brown filter needle and place the black safety needle onto the syringe.**

Give your IM Epinephrine injection



1. **Grasp your leg muscle at the outer mid-thigh** and **cleanse the area** with a new alcohol wipe.
2. **Push the needle into your leg muscle straight** in at a 90-degree angle.
3. **Inject the medication** by depressing the plunger in a slow and steady motion.
4. **Remove the needle** and wipe the site with the alcohol wipe.

Take the pills by mouth.

a. 2 – Acetaminophen
b. 2 – Diphenhydramine

Place all trash in the bag the pills came in and take with you when you seek medical care. **Give the bag to the nurse or EMT**, so your doctor will know what medication you already took. They will properly dispose of the syringe and needles.

Call 911 or have someone drive you to the emergency department.