Pemetrexed: Drug information

(For additional information see "Pemetrexed: Patient drug information")

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

Brand Names: US

Alimta

Brand Names: Canada

Alimta

Pharmacologic Category

Antineoplastic Agent, Antimetabolite; Antineoplastic Agent, Antimetabolite (Antifolate)

Dosing: Adult

Note: Start vitamin supplements 1 week before initial pemetrexed dose: Folic acid 400 to 1000 mcg daily orally (begin 7 days prior to treatment initiation; continue daily during treatment and for 21 days after last pemetrexed dose) and vitamin B_{12} 1000 mcg IM 7 days prior to treatment initiation and then every 3 cycles. Give dexamethasone 4 mg orally twice daily for 3 days, beginning the day before treatment to minimize cutaneous reactions. New treatment cycles should not begin unless ANC ≥1500/mm^3, platelets ≥100,000/mm^3, and CrCl ≥45 mL/minute.

Malignant pleural mesothelioma: IV: 500 mg/m^2 on day 1 of each 21-day cycle (in combination with cisplatin) **or** (off-label) in combination with carboplatin (Castagneto 2008; Ceresoli 2006) **or** (off-label) as single-agent therapy (Taylor 2008)

Non-small cell lung cancer, nonsquamous: IV:

Initial treatment: 500 mg/m^2 on day 1 of each 21-day cycle (in combination with cisplatin)

Maintenance or second-line treatment: 500 mg/m^2 on day 1 of each 21-day cycle (as a single-agent)

Bladder cancer, metastatic (off-label use): IV: 500 mg/m^2 on day 1 of each 21-day cycle until disease progression or unacceptable toxicity (Sweeney 2006)

Cervical cancer, persistent or recurrent (off-label use): IV: 500 mg/m^2 on day 1 of each 21-day cycle until disease progression or unacceptable toxicity occurs (Lorusso 2010) **or** 900 mg/m^2 on day 1 of each 21-day cycle (Miller 2008)

Ovarian cancer, platinum-resistant (off-label use): IV: 500 mg/m^2 on day 1 of each 21-day cycle (Vergote 2009)

Thymic malignancies, metastatic (off-label use): IV: 500 mg/m^2 on day 1 of each 21-day cycle for 6 cycles or until disease progression or unacceptable toxicity occurs (Loehrer 2006)

Dosing: Geriatric

Refer to adult dosing.

Dosing: Renal Impairment

Renal function may be estimated using the Cockcroft-Gault formula (using actual body weight) or glomerular filtration rate (GFR) measured by Tc99m-DPTA serum clearance.

CrCl ≥45 mL/minute: No dosage adjustment necessary.

CrCl <45 mL/minute: Use is not recommended by the manufacturer (an insufficient number of patients have been studied for dosage recommendations).

According to a phase I study in advanced cancer patients with renal impairment, pemetrexed doses up to 500 mg/m^2 (with vitamin supplementation) were well tolerated in patients with glomerular filtration rate (GFR) 40 to 79 mL/minute; however, accrual was halted in patients with GFR <29 mL/minute (due to toxicity) and accrual did not occur in patients with GFR 30 to 39 mL/minute. Patients with GFR ≥80 mL/minute tolerated doses of 600 mg/m^2 (Mita 2006).

Concomitant NSAID use with renal dysfunction:

CrCl ≥80 mL/minute: No dosage adjustment necessary.

CrCl 45 to 79 mL/minute and NSAIDs with short half-lives (eg, ibuprofen, indomethacin, ketoprofen, ketorolac): Avoid NSAID for 2 days before, the day of, and for 2 days following a dose of pemetrexed.

Any creatinine clearance and NSAIDs with long half-lives (eg, nabumetone, naproxen, oxaprozin, piroxicam): Avoid NSAID for 5 days before, the day of, and 2 days following a dose of pemetrexed.

Dosing: Hepatic Impairment

Grade 3 (5.1 to 20 times ULN) **or** 4 (>20 times ULN) transaminase elevation during treatment: Reduce pemetrexed dose to 75% of previous dose (and cisplatin).

Dosing: Obesity

ASCO Guidelines for appropriate chemotherapy dosing in obese adults with cancer: Utilize patient's actual body weight (full weight) for calculation of body surface area- or weight-based dosing, particularly when the intent of therapy is curative; manage regimen-related toxicities in the same manner as for nonobese patients; if a dose reduction is utilized due to toxicity, consider resumption of full weight-based dosing with subsequent cycles, especially if cause of toxicity (eg, hepatic or renal impairment) is resolved (Griggs, 2012).

Dosing: Adjustment for Toxicity

Toxicity: Discontinue if patient develops grade 3 or 4 toxicity after two dose reductions or immediately if grade 3 or 4 neurotoxicity develops

Hematologic toxicity: Upon recovery, reinitiate therapy

Nadir ANC <500/mm^3 and nadir platelets ≥50,000/mm^3: Reduce dose to 75% of previous dose of pemetrexed (and cisplatin)

Nadir platelets <50,000/mm^3 **without bleeding** (regardless of nadir ANC): Reduce dose to 75% of previous dose of pemetrexed (and cisplatin)

Nadir platelets <50,000/mm^3 **with bleeding** (regardless of nadir ANC): Reduce dose to 50% of

previous dose of pemetrexed (and cisplatin)

Nonhematologic toxicity ≥grade 3 (excluding neurotoxicity): Withhold treatment until recovery to baseline; upon recovery, reinitiate therapy as follows:

Grade 3 or 4 toxicity (excluding mucositis): Reduce dose to 75% of previous dose of pemetrexed (and cisplatin)

Grade 3 or 4 diarrhea or any diarrhea requiring hospitalization: Reduce dose to 75% of previous dose of pemetrexed (and cisplatin)

Grade 3 or 4 mucositis: Reduce pemetrexed dose to 50% of previous dose (continue cisplatin at 100% of previous dose)

Neurotoxicity:

Grade 0 to 1: Continue pemetrexed at 100% of previous dose (and cisplatin)

Grade 2: Continue pemetrexed at 100% of previous dose; reduce cisplatin dose to 50% of previous dose

Dosage Forms

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

Solution Reconstituted, Intravenous:

Alimta: 100 mg (1 ea); 500 mg (1 ea)

Generic Equivalent Available (US)

No

Administration

IV: Infuse over 10 minutes.

Hazardous Drugs Handling Considerations

Hazardous agent (NIOSH 2016 [group 1]).

Use appropriate precautions for receiving, handling, administration, and disposal. Gloves (single) should be worn during receiving, unpacking, and placing in storage.

NIOSH recommends double gloving, a protective gown, ventilated engineering controls (a class II biological safety cabinet or a compounding aseptic containment isolator), and closed system transfer devices (CSTDs) for preparation. Double gloving, a gown, and (if dosage form allows) CSTDs are required during administration (NIOSH 2016).

Use

Mesothelioma: Treatment of unresectable malignant pleural mesothelioma (in combination with cisplatin)

Non-small cell lung cancer (NSCLC), nonsquamous: Treatment of locally advanced or metastatic **non**squamous NSCLC (as initial treatment in combination with cisplatin; as maintenance treatment after

4 cycles of initial platinum-based first-line therapy; as single-agent treatment after prior chemotherapy)

Limitation of use: Not indicated for the treatment of **squamous** cell NSCLC

Use: Off-Label

Bladder cancer, metastatic; Cervical cancer, persistent or recurrent; Malignant pleural mesothelioma (single agent and off-label combination); Ovarian cancer, platinum-resistant; Thymic malignancies, metastatic

Medication Safety Issues

Sound-alike/look-alike issues:

PEMEtrexed may be confused with methotrexate, PRALAtrexate

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

>10%:

Central nervous system: Fatigue (18% to 34%; dose-limiting)

Dermatologic: Desquamation (≤14%), skin rash (≤14%)

Gastrointestinal: Nausea (12% to 31%), anorexia (19% to 22%), vomiting (6% to 16%), stomatitis (5% to 15%), diarrhea (5% to 13%)

Hematologic & oncologic: Anemia (15% to 19%; grades 3/4: 3% to 5%), leukopenia (6% to 12%; grades 3/4: 2% to 4%), neutropenia (6% to 11%; grades 3/4: 3% to 5%; dose-limiting; nadir: 8 to 10 days; recovery: 4 to 8 days after nadir)

Respiratory: Pharyngitis (15%)

1% to 10%:

Cardiovascular: Edema (1% to 5%)

Central nervous system: Neuropathy (sensory: ≤9%; motor: ≤5%)

Dermatologic: Pruritus (1% to 7%), alopecia (1% to 6%), erythema multiforme (≤5%)

Endocrine & metabolic: Weight loss (1%)

Gastrointestinal: Constipation (1% to 6%), abdominal pain (≤5%)

Hematologic & oncologic: Thrombocytopenia (1% to 8%; grades 3/4: 2%; dose-limiting), febrile neutropenia (grades 3/4: 2%)

Hepatic: Increased serum ALT (8% to 10%; grades 3/4: ≤2%), increased serum AST (7% to 8%; grades 3/4: ≤1%)

Hypersensitivity: Hypersensitivity reaction (≤5%)

Infection: Infection (≤5%), sepsis (1%)

Ophthalmic: Conjunctivitis (≤5%), increased lacrimation (≤5%)

Renal: Decreased creatinine clearance (≤5%), increased serum creatinine (≤5%)

Miscellaneous: Fever (1% to 8%)

<1%, postmarketing, and/or case reports: Cardiac arrhythmia, chest pain, colitis, dehydration, depression, esophagitis, gastrointestinal obstruction, hemolytic anemia, hepatobiliary disease (failure), hypertension, increased gamma-glutamyl transferase, interstitial pneumonitis, pain, pancreatitis, pancytopenia, peripheral ischemia, pulmonary embolism, radiation recall phenomenon (median onset: 6 days; range: 1 to 35 days), renal failure, Stevens-Johnson syndrome, supraventricular cardiac arrhythmia, syncope, thromboembolism, toxic epidermal necrolysis, ventricular tachycardia

Contraindications

Severe hypersensitivity to pemetrexed or any component of the formulation

Canadian labeling: Additional contraindications; not in US labeling: Concomitant yellow fever vaccine

Warnings/Precautions

Concerns related to adverse effects:

• Bone marrow suppression: May cause anemia, neutropenia, thrombocytopenia and/or pancytopenia; frequent laboratory monitoring is necessary (myelosuppression is often dose-limiting). Dose reductions in subsequent cycles may be required. Prophylactic folic acid and vitamin B_{12} supplements are necessary to reduce hematologic toxicity, febrile neutropenia and infection; initiate supplementation 1 week before the first dose of pemetrexed.

• Cutaneous reactions: May occur; pretreatment with dexamethasone is necessary to reduce the incidence and severity of cutaneous reactions. Rarely, Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported.

• Gastrointestinal toxicity: May occur; prophylactic folic acid and vitamin B_{12} supplements are necessary to reduce gastrointestinal toxicity; initiate supplementation 1 week before the first dose of pemetrexed.

• Hepatotoxicity: Serious hepatotoxicity (including rare fatalities) has been observed with monotherapy and in association with other chemotherapy, although underlying risk factors were present in some cases. Use caution with hepatic impairment not due to metastases; may require dose adjustment.

• Hypersensitivity: Hypersensitivity (including anaphylaxis) has been reported with use.

• Respiratory: Interstitial pneumonitis with respiratory insufficiency has been observed with use; interrupt therapy and evaluate promptly with progressive dyspnea and cough.

Disease-related concerns:

• Renal impairment: Decreased renal function results in increased toxicity. The manufacturer does not recommend use if CrCl <45 mL/minute. Use caution in patients receiving concurrent nephrotoxins; may result in delayed pemetrexed clearance.

• Third space fluid: Although the effect of third space fluid is not fully defined, studies have determined pemetrexed concentrations in patients with mild-to-moderate ascites/pleural effusions were similar to concentrations in trials of patients without third space fluid accumulation. Drainage of fluid from ascites/effusions may be considered, but is not likely necessary.

Concurrent drug therapy issues:

• Drug-drug interactions: Potentially significant interactions may exist, requiring dose or frequency adjustment, additional monitoring, and/or selection of alternative therapy. Consult drug interactions database for more detailed information.

• NSAIDs: NSAIDs may reduce the clearance of pemetrexed. In patients with CrCl 45 to 79 mL/minute, interruption of NSAID therapy may be necessary prior to, during, and immediately after pemetrexed therapy.

Other warnings/precautions:

• NSCLC appropriate use: Not indicated for use in patients with squamous cell NSCLC.

Metabolism/Transport Effects

None known.

Drug Interactions

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

BCG (Intravesical): Immunosuppressants may diminish the therapeutic effect of BCG (Intravesical). *Risk X: Avoid combination*

BCG (Intravesical): Myelosuppressive Agents may diminish the therapeutic effect of BCG (Intravesical). *Risk X: Avoid combination*

CloZAPine: Myelosuppressive Agents may enhance the adverse/toxic effect of CloZAPine. Specifically, the risk for neutropenia may be increased. *Risk C: Monitor therapy*

Coccidioides immitis Skin Test: Immunosuppressants may diminish the diagnostic effect of Coccidioides immitis Skin Test. *Risk C: Monitor therapy*

Deferiprone: Myelosuppressive Agents may enhance the neutropenic effect of Deferiprone. *Risk X: Avoid combination*

Denosumab: May enhance the adverse/toxic effect of Immunosuppressants. Specifically, the risk for serious infections may be increased. *Risk C: Monitor therapy*

Dipyrone: May enhance the adverse/toxic effect of Myelosuppressive Agents. Specifically, the risk for agranulocytosis and pancytopenia may be increased *Risk X: Avoid combination*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy*

modification

Fingolimod: Immunosuppressants may enhance the immunosuppressive effect of Fingolimod. Management: Avoid the concomitant use of fingolimod and other immunosuppressants when possible. If combined, monitor patients closely for additive immunosuppressant effects (eg, infections). *Risk D: Consider therapy modification*

Leflunomide: Immunosuppressants may enhance the adverse/toxic effect of Leflunomide. Specifically, the risk for hematologic toxicity such as pancytopenia, agranulocytosis, and/or thrombocytopenia may be increased. Management: Consider not using a leflunomide loading dose in patients receiving other immunosuppressants. Patients receiving both leflunomide and another immunosuppressant should be monitored for bone marrow suppression at least monthly. *Risk D: Consider therapy modification*

Lenograstim: Antineoplastic Agents may diminish the therapeutic effect of Lenograstim. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Nivolumab: Immunosuppressants may diminish the therapeutic effect of Nivolumab. *Risk D: Consider therapy modification*

NSAID (Nonselective): May increase the serum concentration of PEMEtrexed. Management: Patients with mild-to-moderate renal insufficiency (estimated creatinine clearance 45-79 mL/min) should avoid NSAIDs for 2-5 days prior to, the day of, and 2 days after pemetrexed. *Risk D: Consider therapy modification*

Ocrelizumab: May enhance the immunosuppressive effect of Immunosuppressants. *Risk C: Monitor therapy*

Palifermin: May enhance the adverse/toxic effect of Antineoplastic Agents. Specifically, the duration and severity of oral mucositis may be increased. Management: Do not administer palifermin within 24 hours before, during infusion of, or within 24 hours after administration of myelotoxic chemotherapy. *Risk D: Consider therapy modification*

Pimecrolimus: May enhance the adverse/toxic effect of Immunosuppressants. *Risk X: Avoid combination*

Promazine: May enhance the myelosuppressive effect of Myelosuppressive Agents. *Risk C: Monitor therapy*

Roflumilast: May enhance the immunosuppressive effect of Immunosuppressants. *Risk D: Consider therapy modification*

Sipuleucel-T: Immunosuppressants may diminish the therapeutic effect of Sipuleucel-T. *Risk C: Monitor therapy*

Tacrolimus (Topical): May enhance the adverse/toxic effect of Immunosuppressants. *Risk X: Avoid combination*

Tertomotide: Immunosuppressants may diminish the therapeutic effect of Tertomotide. *Risk C: Monitor therapy*

Tofacitinib: Immunosuppressants may enhance the immunosuppressive effect of Tofacitinib. Management: Concurrent use with antirheumatic doses of methotrexate or nonbiologic disease

modifying antirheumatic drugs (DMARDs) is permitted, and this warning seems particularly focused on more potent immunosuppressants. *Risk X: Avoid combination*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). Management: Vaccine efficacy may be reduced. Complete all age-appropriate vaccinations at least 2 weeks prior to starting an immunosuppressant. If vaccinated during immunosuppressant therapy, revaccinate at least 3 months after immunosuppressant discontinuation. *Risk D: Consider therapy modification*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Immunosuppressants may diminish the therapeutic effect of Vaccines (Live). Management: Avoid use of live organism vaccines with immunosuppressants; live-attenuated vaccines should not be given for at least 3 months after immunosuppressants. *Risk X: Avoid combination*

Pregnancy Risk Factor

D (show table)

Pregnancy Implications

Adverse effects were observed in animal reproduction studies. Based on the mechanism of action, pemetrexed may cause fetal harm if administered to a pregnant woman. Women of childbearing potential should use effective contraceptive measures to avoid becoming pregnant during treatment. A negative serum pregnancy test prior to treatment is recommended in the Canadian labeling. The Canadian labeling also recommends that males receiving therapy use effective contraceptive measures and not father a child during, and for up to 6 months after, therapy. Additionally, the Canadian labeling recommends counseling on sperm storage prior to treatment, as irreversible infertility has been reported in males.

Breast-Feeding Considerations

According to the manufacturer, due to the potential for serious adverse reactions in the nursing infant, a decision should be made to discontinue pemetrexed or to discontinue breast-feeding during therapy, taking into account the benefits of treatment to the mother. The Canadian labeling recommends discontinuing nursing.

Dietary Considerations

Initiate folic acid supplementation 1 week before first dose of pemetrexed, continue for full course of therapy, and for 21 days after last dose. Institute vitamin B_{12} 1 week before the first dose; administer every 9 weeks thereafter.

Monitoring Parameters

CBC with differential and platelets (before each cycle and as needed; monitor for nadir and recovery); renal function tests (serum creatinine, creatinine clearance, BUN; prior to each cycle and as needed) total bilirubin, ALT, AST (periodic); signs/symptoms of mucositis and diarrhea

Mechanism of Action

Antifolate; disrupts folate-dependent metabolic processes essential for cell replication. Inhibits thymidylate synthase (TS), dihydrofolate reductase (DHFR), glycinamide ribonucleotide formyltransferase (GARFT), and aminoimidazole carboxamide ribonucleotide formyltransferase (AICARFT), the enzymes involved in folate metabolism and DNA synthesis, resulting in inhibition of purine and thymidine nucleotide and protein synthesis.

Pharmacodynamics/Kinetics

Distribution: V_{dss}: 16.1 L

Protein binding: ~81%

Metabolism: Minimal

Half-life elimination: Normal renal function: 3.5 hours

Excretion: Urine (70% to 90% as unchanged drug)

Pricing: US

Solution (reconstituted) (Alimta Intravenous)

100 mg (1): $768.74

500 mg (1): $3843.72

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

Alimta (AE, AR, AT, AU, BE, BG, BH, BR, CH, CL, CN, CO, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HK, HR, HU, ID, IE, IL, IS, IT, JO, JP, KR, KW, LB, LK, LT, LU, LV, MT, MX, MY, NL, NO, NZ, PE, PH, PL, PT, PY, QA, RO, RU, SA, SE, SG, SI, SK, TH, TR, TW, UA, VN); Emetex (TH); Empet (CR, DO, GT, HN, NI, PA, SV); Enzastar (VN); Jie Baili (CN); Pemecine (KR); Pemeker (EC); Pemetrex (BD); Pemex (LK); Virplazit (CR, DO, GT, HN, NI, PA, SV)

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