Drug Monograph

A - Drug Name

pemetrexed

COMMON TRADE NAME(S): Alimta®

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B - Mechanism of Action and Pharmacokinetics

Pemetrexed is a pyrrolopyrimidine antifolate that exerts its antineoplastic activity by inhibiting thymidylate synthase (TS), glycinamide ribonucleotide formyltransferase (GARFT) and dihydrofolate reductase (DHFR), which are involved in folate metabolism and DNA synthesis, resulting in inhibition of purine and thymidine nucleotide synthesis.

Distribution	Pemetrexed plasma concentration-time functions followed a two-compartment model. PK are dose proportional and no accumulation occurs over multiple cycles. Pemetrexed is primarily confined to the plasma and interstitial compartments. Accumulation in 3rd spaces may occur.	
	Cross blood brain barrier?	No information found
	PPB	81 %
Metabolism	Pemetrexed is not metabolized to an appreciable extent.	
	Active metabolites	Yes
	Inactive metabolites	No information found
Elimination	Urine	70 to 90% excreted as unchanged drug
	Half-life	3.5 hours

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C - Indications and Status

Health Canada Approvals:

- In combination with cisplatin for the first-line treatment of patients with malignant pleural mesothelioma whose disease is unresectable or who are otherwise not candidates for curative surgery
- In combination with cisplatin for initial treatment of good performance status patients with locally advanced or metastatic nonsquamous non-small cell lung cancer
- Monotherapy as a treatment option for patients with locally advanced or metastatic nonsquamous non-small cell lung cancer after prior chemotherapy*
- Monotherapy as maintenance treatment of locally advanced or metastatic nonsquamous non-small cell lung cancer, in good performance status patients without disease progression, immediately following 4 cycles of first-line platinum doublet chemotherapy

* Approval is based on similarity of the response rate, median survival rate and 1-year survival rate, for the overall study population, between pemetrexed and docetaxel.

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D - Adverse Effects

Emetogenic Potential: Low

Extravasation Potential: Minimal

The following table lists adverse effects that occurred in >1% of patients in phase III trials with pemetrexed monotherapy. Severe adverse events from other studies or post-marketing, may also be included.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Arrhythmia (<1%)	E
	Arterial thromboembolism (rare)	E D
	Venous thromboembolism (rare)	E D

Dermatological	Alopecia (6%)	E
	Radiation recall reaction (rare)	E
	Rash (14%) (may be severe)	E
Gastrointestinal	Abdominal pain (3%)	E
	Anorexia (22%)	I
	Constipation (6%)	I
	Diarrhea (13%) (may be severe)	I
	GI perforation (rare)	E
	GI ulcer (rare)	E
	Mucositis (15%) (including esophagitis, may be severe)	E
	Nausea, vomiting (31%)	I
General	Edema (8%)	E
	Fatigue (34%)	I E
Hematological	Hemolysis (rare)	E
	Myelosuppression ± infection, bleeding (15%) (3% severe)	E
Hepatobiliary	↑ LFTs (10%) (may be severe)	E
Hypersensitivity	Hypersensitivity (1%)	I
Nervous System	Neuropathy (9%)	D
Ophthalmic	Eye disorders (≤5%) (including conjunctivitis and increased lacrimation)	E
Renal	Creatinine increased (2%) (may be severe)	E D
Respiratory	Pneumonitis (rare)	E
Vascular	Peripheral ischemia (rare)	E

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

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

The most common side effects for pemetrexed include fatigue, nausea, vomiting, anorexia, mucositis, myelosuppression ± infection, bleeding, rash, diarrhea and ↑ LFTs.

Severe **myelosuppression** is often dose-limiting for pemetrexed. Sepsis, in some cases fatal, have occurred in approximately 1% of patients in clinical trials. Prophylactic folic acid and intramuscular vitamin B12 supplements are necessary to reduce hematologic or non-hematologic toxicities.

Pemetrexed may cause serious and in some cases fatal **dermatologic toxicities**. Rarely, Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported.

Severe (and potentially fatal) **renal toxicity** has been reported with pemetrexed. Renal toxicity may occur with single-agent pemetrexed or when used in combination with other chemotherapy agents.

Pneumonitis has been reported and may occur more frequently in association with radiation.

Radiation recall may occur in patients administered pemetrexed who received radiation previously (weeks to years).

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E - Dosing

Refer to protocol by which patient is being treated.

NSAIDs should be held for at least 2-5 days prior to, and at least 2 days after pemetrexed infusion (see Interactions section).

Premedications:

- Vitamin supplementation starting ≥ 1 week prior to first pemetrexed dose; continue until 3 weeks after last dose to reduce treatment-related toxicities:
  - Folic acid 0.4 mg - 1mg PO daily
  - Vitamin B_{12} 1000 mcg IM q9 weeks
- Dexamethasone (e.g. 4mg PO BID) beginning on the day before chemotherapy for a total of 3 days to reduce the incidence and severity of cutaneous reactions.

Patients should not begin a new treatment cycle unless:

- ANC ≥ 1.5 x 10^9/L
- Platelets ≥ 100 x 10^9/L
- Creatinine clearance is ≥ 45 mL/min

Adults:

Single agent or in combination with cisplatin:

500mg/m^2 IV on Day 1 q 3 weeks

Dosage with Toxicity:

Single-agent:

Hematologic:

Worst toxicity in previous cycle	Grade	Pemetrexed (% previous dose)*
Thrombocytopenic bleeding		50%
ANC	Grade 4	75%
Platelets	≥ Grade 3	
Recurrent myelosuppression after 2 dose reductions	≥ Grade 3	Discontinue

*Start next cycle only when ANC ≥ 1.5 x 10^9/L, platelets ≥ 100 x 10^9/L and related organ/non-hematologic toxicity ≤ grade 2 (or recovery to baseline).

Non-hematologic:

Worst toxicity in previous cycle	Grade	Pemetrexed (% previous dose)*
Neurotoxicity	Grade 2	100%
	≥ Grade 3	Discontinue
Mucositis	≥ Grade 3	50%
Diarrhea	≥ Grade 3 or requiring hospitalization	75%
Pneumonitis	Any	Hold and investigate; discontinue if confirmed
All other related organ / non-hematologic toxicity	Grade 3	75%
	Grade 4	Discontinue
Stevens-Johnson syndrome	Any	
Toxic epidermal necrolysis		
Recurrent non-hematologic toxicity after 2 dose reductions	≥ Grade 3	

*Start next cycle only when ANC ≥ 1.5 x 10^9/L, platelets ≥ 100 x 10^9/L and related organ/non-hematologic toxicity ≤ grade 2 (or recovery to baseline).

Combination: Refer to specific regimen monograph(s)

Dosage with Hepatic Impairment:

Pemetrexed is not extensively metabolized in the liver. No specific studies have been performed in patients with moderate or severe hepatic impairment. Pemetrexed should be used with caution in patients with hepatic impairment.

Dosage with Renal Impairment:

Use with caution as pemetrexed exposure is increased in renal impairment.

Creatinine clearance (mL/min)	Pemetrexed (% of previous dose)
≥ 45	100%*
< 45	Discontinue

* Exercise caution with co-administration of NSAIDs for patients with CrCl 45-79mL/min

Dosage in the elderly:

No dose adjustments are needed but patients should be monitored closely. Myelosuppression, infection, nausea and renal effects are more common in the elderly in combination with cisplatin for NSCLC. In maintenance therapy, more frequent myelosuppression, renal and severe GI adverse events were noted in patients ≥ 65 years of age. There was no observed effect of age on pemetrexed pharmacokinetics over the range of 26 to 80 years.

Children:

The safety and effectiveness of pemetrexed in children have not been established.

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F - Administration Guidelines

- Reconstitute as directed with Normal Saline (preservative free).
- Dilute drug to a total volume of 100mL with normal saline only and infuse intravenously over 10 minutes.

- Reconstituted solution maybe colourless to yellow or green-yellow.
- Incompatible with calcium-containing solutions.
- Do not co-administer with other drugs and diluents.
- Keep unopened vials at room temperature. Pemetrexed is not light sensitive.

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G - Special Precautions

Contraindications:

- Patients with a known hypersensitivity to the drug/excipients.
- Concomitant use of yellow fever vaccine.

Other Warnings/Precautions:

- Exercise caution in patients with pre-existing cardiovascular risk factors.
- Patients with moderate-severe renal dysfunction (CrCl < 45 mL/min).
- Avoid the use of live or live-attenuated vaccines.

Pregnancy and Lactation:

- Clastogenicity: Yes
- Mutagenicity: No
- Embryotoxicity: Yes
- Fetotoxicity: Yes
  Pemetrexed is not recommended for use in pregnancy. Adequate contraception should be used by both sexes during treatment, and for at least **6 months** after the last dose.
- Excretion into breast milk: Unknown
  Breastfeeding is not recommended.
- Fertility effects: Yes
  Pemetrexed may cause irreversible infertility. Sperm preservation should be considered prior to starting treatment in males.

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H - Interactions

In vitro results suggest that pemetrexed is unlikely to inhibit cytochrome P-450 isoenzymes (3A, 2D6, 2C9, 1A2). It is not expected to cause significant enzyme induction. Low to moderate ASA doses (e.g. 325 mg PO q6h) do not affect the pharmacokinetics of pemetrexed. Pemetrexed is a substrate of OAT3.

AGENT	EFFECT	MECHANISM	MANAGEMENT
Nephrotoxic drugs	↑ toxicity	↓ Clearance of pemetrexed	Caution
Tubular secreted drugs (e.g., probenecid)	↑ toxicity	Delayed clearance of pemetrexed	Caution
NSAIDs with short half-lives (i.e., ibuprofen) in patients with CrCl 45-79 ml/min	↑ toxicity	↓ Clearance of pemetrexed	Hold NSAIDs with short half-lives at least 2 days before to at least 2 days after pemetrexed
NSAIDs with long half-lives (i.e., piroxicam)	Potential ↑ in toxicity	Potentially ↓ clearance of pemetrexed	Hold NSAIDs with long half-lives at least 5 days before to at least 2 days after pemetrexed

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I - Recommended Clinical Monitoring

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
CBC	Baseline, before each cycle, on days 8 and 15 of each cycle (for nadir or recovery), and as clinically indicated.
Renal function tests	Baseline and at each visit
Liver function tests	Baseline and at each visit
Clinical toxicity assessment for fatigue, pneumonitis, thromboembolism, diarrhea, mucositis, neurotoxicity, infection, bleeding and rash	At each visit

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

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K - References

Baldwin CM, Perry CM. Pemetrexed: A review of its use in the management of advanced non-squamous non-small cell lung cancer. Drugs 2009:69(16);2279-302.

Hanauske AR, Chen V, Paoletti P, et al. Pemetrexed disodium: a novel antifolate clinically active against multiple solid tumors. Oncologist 2001;6(4):363-73.

Product Monograph: Alimta® (pemetrexed). Eli Lilly Canada Inc, May 10, 2013.

April 2023 removed NDFP forms

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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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