DRUG NAME: Pemetrexed

SYNONYM(S):

COMMON TRADE NAME(S): ALIMTA®

CLASSIFICATION: Antifolate antimetabolite[1,2]

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:

Like 5-fluorouracil and raltitrexed, pemetrexed primarily inhibits thymidylate synthase (TS) resulting in decreased thymidine available for DNA synthesis.[1-3] Pemetrexed also inhibits dihydrofolate reductase (DHFR) and glycinamide ribonucleotide formyltransferase (GARFT), which are key enzymes required for the *de novo* bio-synthesis of thymidine and purine nucleotides.[1-3] Once pemetrexed gains entry to the cell, through the reduced folate carrier, it is polyglutamated. Glutamation increases cellular retention and the intracellular half-life of pemetrexed, as well as making the polyglutamated metabolites greater than 60-fold more potent in their inhibition of TS.[1,3] Pemetrexed is a radiation-sensitizing agent.[4] Pemetrexed induces cell cycle arrest in the G1/S phase.[1]

PHARMACOKINETICS:

Interpatient variability	19% for clearance	
Distribution	plasma and interstitial compartments	
	cross blood brain barrier?	no information found
	volume of distribution	6.8 L/m^2
	plasma protein binding	81%
Metabolism	not metabolized to an appreciable extent	
	active metabolite(s)	no information found
	inactive metabolite(s)	no information found
Excretion	primarily eliminated in the urine	
	urine	70-90% eliminated unchanged in the urine
	feces	no information found
	terminal half life	2.2-7.2 h
	clearance	40 mL/min/m^2
Sex	no clinically significant difference	
Elderly	no clinically significant difference	
Children	no information found	
Ethnicity	no clinically significant difference between whites and blacks	

Adapted from standard references[1-3] unless specified otherwise.

USES:

Primary uses:
*Lung cancer, non-small cell
*Mesothelioma

Other uses:

*Health Canada approved indication

SPECIAL PRECAUTIONS:

Carcinogenicity: No information found.

Mutagenicity: Not mutagenic in Ames test or mammalian *in vitro* mutation test. Pemetrexed is clastogenic in mammalian *in vivo* chromosome test.[2]

Fertility: Animal studies have shown a reduction in male fertility at a dose of 0.1 mg/kg/day.[2]

Pregnancy: FDA Pregnancy Category D.[5] There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).

Breastfeeding is not recommended due to the potential secretion into breast milk.[2]

SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important.[6,7]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
allergy/immunology	allergic reaction/hypersensitivity (1%, severe 0%)
blood/bone marrow/ febrile neutropenia	***anemia*** (19%, severe 4%)
	febrile neutropenia (severe 2%)
	leucopenia (12%, severe 4%)
	neutropenia (11%, severe 5%)
	thrombocytopenia (8%, severe 2%)
cardiovascular (general)	***thrombosis/embolism*** (7%, severe 6%); only reported in patients receiving combination therapy
constitutional symptoms	***fatigue*** (34%, severe 5%)
	fever (8%, severe 0%)
dermatology/skin	*extravasation hazard: none*[8]
	alopecia (6%, severe <1%)
	erythema multiforme (1%)
	pruritis (7%, severe <1%)
	rash/desquamation (14%, severe 0%)
gastrointestinal	*emetogenic potential: low*[9]
	anorexia (22%, severe 2%)
	constipation (6%, severe 0%)
	diarrhea (13%, severe <1%)
	nausea (31%, severe 3%)

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	stomatitis/pharyngitis (15%, severe 1%)
	vomiting (16%, severe 2%)
infection	infection without neutropenia (2%, severe <1%)
metabolic/laboratory	ALT elevation (8%, severe 2%)
	AST elevation (7%, severe 1%)
	decreased creatinine clearance (2%, severe <1%)
	increased serum creatinine (2%, severe 0%)
neurology	motor neuropathy (3%, severe <1%)
	sensory neuropathy (5%, severe 0%)
pain	abdominal pain (3%, severe 0%)
	chest pain (40%, severe 9%); only reported in patients receiving combination therapy

Adapted from standard reference[11] unless specified otherwise.

Skin rash has been reported in patients not pre-treated with a corticosteroid. Standard therapy to reduce the incidence and severity of skin reactions includes dexamethasone 4 mg PO twice daily given the day before, the day of, and the day after pemetrexed administration.[2,12]

Treatment-related toxicity, including bone marrow suppression, diarrhea, and mucositis, are significantly reduced by supplementing with folic acid and vitamin B_{12}.[2,3,12] Patients should take 0.4 mg oral folic acid (0.35 – 1 mg) daily beginning 1 week prior to and continuing daily until 3 weeks after the last pemetrexed dose.[2] At least 5 daily doses must be taken during the 7 days prior to start of therapy. Patients should also receive vitamin B_{12} 1000 mcg IM injection 1 week before pemetrexed therapy. This should be repeated every 9 weeks until 3 weeks after the last pemetrexed dose.[2]

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
ibuprofen and NSAIDs with short half-lives (e.g., diclofenac, indomethacin, ketoprofen, ketorolac)	may increase pemetrexed levels	decrease pemetrexed clearance	avoid ibuprofen, and NSAIDs with short half-lives in patients with mild to moderate renal insufficiency, at least 2 days before, the day of, and at least 2 days after pemetrexed
nephrotoxic drugs (e.g., aminoglycosides, radiocontrast media, sulphonamides)	may increase pemetrexed levels	decrease pemetrexed clearance	avoid concurrent administration

AGENT	EFFECT	MECHANISM	MANAGEMENT
NSAIDs with long half-lives (e.g., meloxicam, nabumetone, piroxicam, tenoxicam)	theoretically may increase pemetrexed levels	decrease pemetrexed clearance	interrupt therapy for at least 5 days before, the day of, and at least 2 days following pemetrexed ; if NSAID therapy cannot be interrupted, monitor for myelosuppression, renal, and gastrointestinal toxicity
tubularly secreted substances (e.g., probenecid)	may increase pemetrexed levels	decrease pemetrexed clearance	avoid concurrent administration
ASA in low to moderate doses (325 mg q6h)	does not affect the pharmacokinetics of pemetrexed		

Adapted from standard reference[2] unless specified otherwise.

Pemetrexed is not expected to have clinically significant interactions with drugs metabolized by CYP3A, CYP2D6, CYP2C9, and CYP1A2.[2]

SUPPLY AND STORAGE:

Injection: Eli Lilly Canada Inc. supplies pemetrexed as 100 mg and 500 mg single-use vials of sterile lyophilized powder. Store at room temperature.[10]

For basic information on the current brand used at the BC Cancer Agency, see Chemotherapy Preparation and Stability Chart in Appendix.

SOLUTION PREPARATION AND COMPATIBILITY:

For basic information on the current brand used at the BC Cancer Agency, see Chemotherapy Preparation and Stability Chart in Appendix.

Additional information:

Compatibility: consult detailed reference

PARENTERAL ADMINISTRATION:

BCCA administration guideline noted in ***bold***, ***italics***

Subcutaneous	no information found
Intramuscular	no information found
Direct intravenous	no information found
Intermittent infusion	***over 10 min;*** timing of cisplatin administration and corresponding hydration with NS does not affect pemetrexed activity[13]
Continuous infusion	no information found

BCCA administration guideline noted in ***bold***, ***italics***

Intraperitoneal	no information found
Intrapleural	no information found
Intrathecal	no information found
Intra-arterial	no information found
Intravesical	no information found

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response and concomitant therapy. Guidelines for dosing also include consideration of absolute neutrophil count (ANC). Dosage may be reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or with other toxicities.

Adults:

To minimize treatment-related toxicity, patients should be premedicated with:
- folic acid 0.4 mg (0.35 – 1 mg) PO daily, beginning 1 week before,
- vitamin B_{12} 1000 mcg IM every 9 weeks, beginning 1 week before,
- dexamethasone 4 mg PO twice daily for 3 days beginning the day before

BCCA usual dose noted in ***bold, italics***

	Cycle Length:	
Intravenous:	***3 weeks:***[2,12]	***500 mg/m^2 IV for one dose on day 1 (total dose per cycle 500 mg/m^2)***

Concurrent radiation: no information found

Dosage in myelosuppression: modify according to protocol by which patient is being treated; if no guidelines available, refer to Appendix 6 "Dosage Modification for Myelosuppression"

Dosage in renal failure[2]*:*

Creatinine clearance (mL/min)	Dose
≥ 45	100%
< 45	delay

Dosage in hepatic failure: no information found

Dosage in dialysis: no information found

Dosage in elderly: no adjustment required[2]

Children: no information found

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