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

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SPECIAL PRECAUTIONS:

Caution:
- routine premedication with dexamethasone plus vitamin supplementation with folic acid and vitamin B_{12} have been shown to reduce the frequency and severity of treatment-related toxicities and should be started before commencing pemetrexed treatment[5]

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.[6] 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.[7,8]

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*[9]
	alopecia (6%, severe <1%)
	bullous epidermolysis[5] (<1%)
	erythema multiforme (1%)
	pruritus (7%, severe <1%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	rash/desquamation (14%, severe 0%); see paragraph following **Side Effects** table
	Stevens-Johnson syndrome[5] (<1%); fatalities have been reported
	Toxic epidermal necrolysis[5] (<1%); fatalities have been reported
gastrointestinal	*emetogenic potential: low*[10]
	anorexia (22%, severe 2%)
	constipation (6%, severe 0%)
	diarrhea (13%, severe <1%)
	nausea (31%, severe 3%)
	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 corticosteroids. Pretreatment with dexamethasone (or equivalent) has been shown to reduce both the incidence and severity of cutaneous reactions. In clinical trials, dexamethasone premedication was given orally as 4 mg twice daily the day before, the day of, and the day after pemetrexed administration.[5,12] Alternate premedication dosing regimens may sometimes be used when pemetrexed is given in combination with other systemic therapy where dexamethasone is also given as an antiemetic pre and post treatment.[13-16] Refer to protocol by which patient is being treated for dexamethasone premedication regimen.

Overall ***treatment-related toxicity*** is significantly reduced by ***folic acid and vitamin B_{12} supplementation***, including the frequency and severity of grade 3 and 4 hematologic and non-hematologic toxicities.[3,5,12] Low-dose oral folic acid is required daily during treatment with pemetrexed, beginning at least 5-7 days prior to the first dose of pemetrexed, and continuing through the full course of treatment, until 21 days after the last dose of pemetrexed. Suggested folic acid doses range from 350-1000 micrograms daily, with 400 micrograms daily being the most commonly used dose. Vitamin B_{12} supplementation is to be provided as a 1000 microgram intramuscular injection, with the first injection administered at least 7 days prior to the first dose of pemetrexed, and then repeated every 9 weeks (i.e., every 3 cycles) through the full course of treatment, until 21 days after the last dose of pemetrexed.[5] The oral formulation of vitamin B_{12} should not be substituted for the intramuscular injection.[5,17] Refer to protocol by which patient is being treated.

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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
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:
Accord Healthcare Inc. supplies pemetrexed as 100 mg and 500 mg single-use (preservative free) vials of lyophilized powder. Store at room temperature.[18]

Accord Healthcare Inc. supplies pemetrexed as 100 mg/4 mL, 500 mg/20 mL, 850 mg/34 mL, and 1000 mg/40 mL ready-to-use, single-use (preservative free) vials in a concentration of 25 mg/mL. Store at room temperature. Keep vial in original packaging to protect from light.[19]

Dr. Reddy's Laboratories Limited supplies pemetrexed as 100 mg and 500 mg single-use (preservative free) vials of lyophilized powder. Store at room temperature.[20]

Eli Lilly Canada Inc. supplies pemetrexed as 100 mg and 500 mg single-use (preservative free) vials of lyophilized powder. Store at room temperature.[21]

Taro Pharmaceuticals Inc. supplies pemetrexed as 100 mg, 500 mg, and 1000 mg single-use (preservative free) vials of lyophilized powder. Store at room temperature.[22]

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

SOLUTION PREPARATION AND COMPATIBILITY:

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

Additional information:

Compatibility: consult detailed reference

PARENTERAL ADMINISTRATION:

BC Cancer 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[23]
Continuous infusion	no information found
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:

BC Cancer usual dose noted in ***bold, italics***

Intravenous:	Cycle Length: ***3 weeks:***[2,12]	***500 mg/m² IV for one dose on day 1*** (total dose per cycle 500 mg/m²)
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 "Dosage Modification for Myelosuppression"	

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BC Cancer usual dose noted in ***bold, italics***

Dosage in renal failure[2]*:*

Cycle Length:

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

calculated creatinine clearance = N* x (140 - Age) x weight in kg / serum creatinine in micromol/L

* For males N=1.23; for females N=1.04

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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