

Rx Pemetrexed for Injection 500 mg

ReliTrexed™-500

Composition

Pemetrexed for injection, is supplied as a sterile lyophilized powder for intravenous infusion available in single-dose vials.

Each vial contains:

Pemetrexed Disodium equivalent to Pemetrexed 500 mg

For I.V. use after reconstitution

Description

Pemetrexed for injection, is an antifolate antineoplastic agent that exerts its action by disrupting folate-dependent metabolic processes essential for cell replication.

Pemetrexed disodium heptahydrate has the chemical name L-Glutamic acid, N-[4-[2-(2-amino-4,7-dihydro-4-oxo-1H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-, disodium salt, heptahydrate. It is a white to almost-white solid with a molecular formula of $C_{20}H_{19}N_5Na_2O_7 \cdot 7H_2O$ and a molecular weight of 597.49.

Pharmacology

Pemetrexed is a multitargeted antifolate. Both the reduced folate carrier and membrane folate-binding protein transport system transport it into cells. Intracellularly, it is polyglutamated allowing for prolonged intracellular retention. Polyglutamated pemetrexed is approximately 60-fold more potent in inhibiting its primary enzyme target than the parent compound.

Polyglutamated pemetrexed inhibits multiple folate-dependent enzymes involved in purine and pyrimidine synthesis. The primary target is thymidylate synthase (TS), an enzyme involved in thymidine biosynthesis that is necessary for DNA synthesis. In addition, it is a weaker inhibitor of glycylamide ribonucleotide formyltransferase (GARFT), an enzyme involved in purine synthesis, and a very weak inhibitor of dihydrofolate reductase (DHFR), the enzyme required to reduce dihydrofolate to tetrahydrofolate which is generated in the synthesis of thymidylate by TS.

Mechanisms of resistance include decreased expression of the enzyme required for polyglutamation, increased activity of folylpolyglutamate hydrolase, and increased efflux by the multidrug resistance protein.

Table 1: Pemetrexed pharmacokinetics

Parameters	Pemetrexed values
Excretion	Renal (70-90% recovered unchanged)
Metabolism	Not to an appreciable extent. Does NOT inhibit CYP3A, 2D6, 1A2 or 2C9
Half-life	3.5 hours with normal renal function
Plasma protein binding	81%

Pre-Clinical studies

Two repeat dose 28-day toxicity studies have been performed in rats and mice by administering ReliTrexed™-500 by IV route. The toxicologic findings observed are consistent with commonly encountered anti-proliferative activities of folate antimetabolites and/or other oncolytic agents. The anti-proliferative activities observed in rats were a hypocellularity of the lymph nodes and an enteropathy of the ileum. In addition, mice showed hypocellularity in thymus and spleen, and testicular degeneration. All these changes were minimal/mild or moderate at lower dose levels. No unexpected toxicity was noticed.

Indications

• Non-Small Cell Lung Cancer — Single-Agent

Pemetrexed is indicated as a single-agent for the treatment of patients with locally advanced or metastatic non-squamous non-small cell lung cancer after prior chemotherapy. Pemetrexed for injection, is not indicated for treatment of patients with squamous cell non-small cell lung cancer.

• Mesothelioma

Pemetrexed in combination with cisplatin is indicated for the treatment of patients with malignant pleural mesothelioma whose disease is unresectable or who are otherwise not candidates for curative surgery.

Dosage and administration

Reconstitution:

To reconstitute, add 20 mL of 0.9% w/v sodium chloride injection IP and shake gently to make a clear solution containing approximately 25 mg/mL of Pemetrexed. Reconstituted solution must be further diluted before use.

Pemetrexed for injection, is for Intravenous Infusion Only.

• Combination Use with Cisplatin

Non-Small Cell Lung Cancer and Malignant Pleural Mesothelioma

The recommended dose of Pemetrexed is 500 mg/m² administered as an intravenous infusion over 10 minutes on Day 1 of each 21-day cycle. The recommended dose of cisplatin is 75 mg/m² infused over 2 hours beginning approximately 30 minutes after the end of Pemetrexed for injection, administration. Patients should receive appropriate hydration prior to and/or after receiving cisplatin.

• Single-Agent Use

Non-Small Cell Lung Cancer

The recommended dose of Pemetrexed is 500 mg/m² administered as an intravenous infusion over 10 minutes on Day 1 of each 21-day cycle.

Pre-medication Regimen

Vitamin Supplementation

To reduce toxicity, patients treated with Pemetrexed must be instructed to take a low-dose oral folic acid preparation or multivitamin with folic acid on a daily basis. At least 5 daily doses of folic acid must be taken during the 7-day period preceding the first dose of Pemetrexed and dosing should continue during the full course of therapy and for 21 days after the last dose of Pemetrexed. Patients must also receive one intramuscular injection of vitamin B12 during the week preceding the first dose of Pemetrexed and every 3 cycles thereafter. Subsequent vitamin B12 injections may be given the same day as Pemetrexed. In clinical trials, the dose of folic acid studied ranged from 350 to 1000 mcg, and the dose of vitamin B12 was 1000 mcg. The most commonly used dose of oral folic acid in clinical trials was 400 mcg.

Corticosteroid

Skin rash has been reported more frequently in patients not pretreated with a corticosteroid. Pre-treatment with dexamethasone (or equivalent) reduces the incidence and severity of cutaneous reaction. In clinical trials, dexamethasone 4 mg was given by mouth twice daily the day before, the day of, and the day after Pemetrexed for injection administration.

Laboratory Monitoring and Dose Reduction/Discontinuation Recommendations

Monitoring

Complete blood cell counts, including platelet counts, should be performed on all patients receiving Pemetrexed injection. Patients should be monitored for nadir and recovery, before each dose and on days 8 and 15 of each cycle. Patients should not begin a new cycle of treatment unless the ANC is 1500 cells/mm³, the platelet count is 100,000 cells/mm³, and creatinine clearance is 45 mL/min. Periodic chemistry tests should be performed to evaluate renal and hepatic function.

Dose Modification Recommendations

Dose adjustments at the start of a subsequent cycle should be based on nadir haematologic counts or maximum non-haematologic toxicity from the preceding cycle of therapy. Treatment may be delayed to allow sufficient time for recovery. Upon recovery, patients should be re-treated using the guidelines in Tables 2-4, which are suitable for using Pemetrexed for injection, as a single-agent or in combination with cisplatin.

Table 2: Dose Modification for Pemetrexed injection, (single-agent or in combination) and Cisplatin - Haematologic Toxicities

Nadir ANC <500/mm ³ and nadir platelets 50,000/mm ³ .	75% of previous dose (both drugs).
Nadir platelets <50,000/mm ³ without bleeding regardless of nadir ANC.	75% of previous dose (both drugs).
Nadir platelets <50,000/mm ³ with bleeding ^a , regardless of nadir ANC.	50% of previous dose (both drugs).
a These criteria meet the CTC version 2.0 (NCI 1998) definition of CTC Grade 2 bleeding.	

If patients develop non-haematologic toxicities (excluding neurotoxicity) Grade 3, treatment should be withheld until resolution to less than or equal to the patient's pre-therapy value. Treatment should be resumed according to guidelines in Table 3.

Table 3: Dose Modification for Pemetrexed injection, (single-agent or in combination) and Cisplatin - Non-haematologic Toxicities^{a,b}

	Dose of Pemetrexed for injection (mg/m ²)	Dose of Cisplatin (mg/m ²)
Any Grade 3 or 4 toxicities except mucositis	75% of previous dose	75% of previous dose
Any diarrhoea requiring hospitalization (irrespective of Grade) or Grade 3 or 4 diarrhoea	75% of previous dose	75% of previous dose
Grade 3 or 4 mucositis	50% of previous dose	100% of previous dose
a NCI Common Toxicity Criteria (CTC). b Excluding neurotoxicity (see Table 4).		

In the event of neurotoxicity, the recommended dose adjustments for Pemetrexed for injection and cisplatin are described in Table 4. Patients should discontinue therapy if Grade 3 or 4 neurotoxicity is experienced.

Table 4: Dose Modification for Pemetrexed injection, (single-agent or in combination) and Cisplatin - Neurotoxicity

CTC Grade	Dose of Pemetrexed for injection, (mg/m ²)	Dose of Cisplatin (mg/m ²)
0-1	100% of previous dose	100% of previous dose
2	100% of previous dose	50% of previous dose

Discontinuation Recommendation

Pemetrexed injection, therapy should be discontinued if a patient experiences any haematologic or non-haematologic Grade 3 or 4 toxicity after 2 dose reductions (except Grade 3 transaminase elevations) or immediately if Grade 3 or 4 neurotoxicity is observed.

Renally Impaired Patients

In clinical studies, patients with creatinine clearance 45 mL/min required no

dose adjustments other than those recommended for all patients. Insufficient numbers of patients with creatinine clearance below 45 mL/min have been treated to make dosage recommendations for this group of patients. Therefore, Pemetrexed for injection, should not be administered to patients whose creatinine clearance is < 45 mL/min using the standard Cockcroft and Gault formula (below) or GFR measured by Tc99m-DPTA serum clearance method:

$$\text{Males: } \frac{[140 - \text{Age in years}] \times \text{Actual Body Weight (kg)}}{72 \times \text{Serum Creatinine (mg/dL)}} = \text{mL/min}$$

Females: Estimated creatinine clearance for males \times 0.85

Caution should be exercised when administering Pemetrexed injection, concurrently with NSAIDs to patients whose creatinine clearance is <80 mL/min.

Preparation and Administration Precautions

1. Use aseptic technique during the reconstitution and further dilution of Pemetrexed injection, for intravenous infusion administration.
2. Calculate the dose of Pemetrexed and determine the number of vials needed. Vial contains 500 mg of Pemetrexed for injection.
3. Reconstitute 500-mg vial with 20 mL of 0.9% sodium chloride injection (preservative free). Reconstitution of vial gives a solution containing 25 mg/mL Pemetrexed for injection. Gently swirl the vial until the powder is completely dissolved. The resulting solution is clear and ranges in colour from colourless to yellow or green-yellow without adversely affecting product quality. The pH of the reconstituted Pemetrexed injection, solution is between 6.6 and 7.8.
4. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If particulate matter is observed, do not administer.
5. An appropriate quantity of the reconstituted Pemetrexed solution must be further diluted into a solution of 0.9% Sodium Chloride Injection (preservative free), so that the total volume of solution is 100 ml. Pemetrexed injection, is administered as an intravenous infusion over 10 minutes.
6. Chemical and physical stability of reconstituted and infusion solutions of Pemetrexed were demonstrated for up to 24 hours following initial reconstitution, when stored at refrigerated or ambient room temperature and lighting. When prepared as directed, reconstitution and infusion solutions of Pemetrexed for injection, contain no antimicrobial preservatives. Discard any unused portion.

Reconstitution and further dilution prior to intravenous infusion is only recommended with 0.9% sodium chloride injection (preservative free).

Contraindications

Pemetrexed is contraindicated in patients who have a history of severe hypersensitivity reaction to pemetrexed or to any other ingredient used in the formulation.

Adverse effects

The most common adverse reactions (incidence 20%) with single-agent use are fatigue, nausea, and anorexia. Additional common adverse reactions when used in combination with cisplatin include vomiting, neutropenia, leukopenia, anaemia, stomatitis/pharyngitis, thrombocytopenia, and constipation.

Haematological: Very common: Anaemia, leukopenia, thrombocytopenia, neutropenia. Common: Febrile neutropenia and infection without neutropenia. Uncommon: Pancytopenia.

Gastro-intestinal: Very common: Nausea, vomiting, stomatitis/pharyngitis, anorexia, diarrhoea, constipation. Common: Dyspepsia, abdominal pain. Rare: Colitis.

General: Very common: Fatigue. Common: Fever, conjunctivitis.

Metabolism and nutrition: Common: Dehydration.

Nervous system: Very common: Neuropathy - sensory. Common: Neuropathy - motor, dysgeusia.

Renal and urinary: Very common: Creatinine elevation, creatinine clearance decreased. Common: Renal failure.

Hepatobiliary: Common: SGPT (ALT) elevation and SGOT (AST) elevation, increased GGT. Rare: Cases of hepatitis, potentially serious, have been reported during trials.

Skin and subcutaneous tissue: Very common: Rash/desquamation, alopecia. Common: Urticaria, allergic reaction/hypersensitivity, erythema multiforme, pruritus.

Cardiovascular and cerebrovascular: Uncommon: Myocardial infarction, angina pectoris, cerebrovascular accident, arrhythmias, transient ischaemic attack. (Usually when given in combination with other cytotoxic agents and with pre-existing cardiovascular risk.) Common: Chest pain.

Drug interactions

Concomitant administration of nephrotoxic drugs and substances that are also tubularly secreted could potentially result in delayed clearance of pemetrexed. If necessary, creatinine clearance should be closely monitored.

Patients must avoid taking non-steroidal anti-inflammatory drugs (NSAIDs) with long elimination half-lives for at least 5 days prior to, on the day, and at least 2 days following pemetrexed administration. In patients with normal renal function (creatinine clearance > or = 80 ml/min), high doses of NSAIDs (such as ibuprofen >1600 mg/day) and aspirin at higher dosage (> or = 1.3 g daily) may decrease pemetrexed elimination and increase the occurrence of adverse events. Patients with mild to moderate renal insufficiency (creatinine clearance from 49 to 79 ml/min) should avoid taking NSAIDs (e.g., ibuprofen) or aspirin at higher dosage, for 2 days before, on the day of, and 2 days following pemetrexed administration.

There is a possible interaction between oral anticoagulants and pemetrexed; therefore, increase the frequency of International Normalised Ratio monitoring (INR) if treating with oral anticoagulants.

Warnings and special precautions

Myelosuppression is usually the dose-limiting toxicity.

Patients must be instructed to take folic acid and vitamin B12 as a prophylactic measure.

Pre-treatment with dexamethasone (or equivalent) can reduce the incidence and severity of skin reactions.

Serious renal events, including acute renal failure, have been reported with pemetrexed alone or in combination with other chemotherapeutic agents. Many of the patients in whom these occurred had underlying risk factors including dehydration or pre-existing hypertension or diabetes. Do not administer when CrCl < 45 mL/min.

In patients with clinically significant third space fluid, consideration should be given to draining the effusion prior to administration.

Serious cardiovascular events, including myocardial infarction and cerebrovascular events, have been uncommonly reported when pemetrexed is given in combination with other cytotoxic agents; most of these patients had pre-existing cardiovascular risk.

Concomitant use of live attenuated vaccines is not recommended.

Do not begin next cycle unless ANC 1500 cells/mm³, platelets 100,000 cells/mm³, and CrCl 45 mL/min.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

No carcinogenicity studies have been conducted with pemetrexed. Pemetrexed was clastogenic in the in vivo micronucleus assay in mouse bone marrow but was not mutagenic in multiple in vitro tests (Ames assay, CHO cell assay).

Pemetrexed administered at i.v. doses of 0.1 mg/kg/day or greater to male mice (about 1/1666 the recommended human dose on a mg/m² basis) resulted in reduced fertility, hypospermia, and testicular atrophy.

Pregnancy

Teratogenic Effects — Pregnancy Category D

There are no adequate and well controlled studies of Pemetrexed in pregnant women. Pemetrexed was embryotoxic, foetotoxic and teratogenic in mice. If Pemetrexed is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the foetus. Women of childbearing potential should be advised to use effective contraceptive measures to prevent pregnancy during the treatment with Pemetrexed.

Nursing Mothers

It is not known whether Pemetrexed or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from Pemetrexed, a decision should be made to discontinue nursing or discontinue the drug, taking into account the importance of the drug for the mother.

Paediatric Use

The safety and effectiveness of Pemetrexed in paediatric patients have not been established.

Geriatric Use

Pemetrexed is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection. Renal function monitoring is recommended with administration of Pemetrexed. No dose reductions other than those recommended for all patients are necessary for patients 65 years of age or older.

Overdosage

There have been few cases of Pemetrexed overdose. Reported toxicities included neutropenia, anaemia, thrombocytopenia, mucositis, and rash. Anticipated complications of overdose include bone marrow suppression as manifested by neutropenia, thrombocytopenia, and anaemia. In addition, infection with or without fever, diarrhoea, and mucositis may be seen. If an overdose occurs, general supportive measures should be instituted as deemed necessary by the treating physician.

Storage

Pemetrexed injection, should be stored below 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Chemical and physical stability of reconstituted and infusion solutions of Pemetrexed were demonstrated for up to 24 hours following initial reconstitution, when stored refrigerated, 2-8°C (36-46°F), or at 25°C (77°F), excursions permitted to 15-30°C (59-86°F).

Shelf life

2 years from the date of manufacturing.

Presentation

Relitrexed[™]-500 lyophilized powder in sterile single use vial with pack insert in a carton.