



PEMETREX

Pemetrexed

Lyophilized Powder for IV Infusion

COMPOSITION

Pemetrex Injection: Each vial contains Pemetrexed Disodium Heptahydrate BP equivalent to Pemetrexed 100 mg (as lyophilized powder).

Pemetrex 500 Injection: Each vial contains Pemetrexed Disodium Heptahydrate BP equivalent to Pemetrexed 500 mg (as lyophilized powder).

CLINICAL PHARMACOLOGY

Mechanism of Action

Pemetrexed for injection, is a folate analog metabolic inhibitor that exerts its action by disrupting folate-dependent metabolic processes essential for cell replication. In vitro studies have shown that Pemetrexed inhibits thymidylate synthase (TS), dihydrofolate reductase (DHFR), and glycinamide ribonucleotide formyltransferase (GARFT), which are folate-dependent enzymes involved in the de novo biosynthesis of thymidine and purine nucleotides. Pemetrexed is taken into cells by membrane carriers such as the reduced folate carrier and membrane folate binding protein transport systems. Once in the cell, Pemetrexed is converted to polyglutamate forms by the enzyme folypolyglutamate synthetase. The polyglutamate forms are retained in cells and are inhibitors of TS and GARFT. Polyglutamation is a time- and concentration-dependent process that occurs in tumor cells and, is thought to occur to a lesser extent, in normal tissues. Polyglutamated metabolites are thought to have an increased intracellular half-life resulting in prolonged drug action in malignant cells.

Pharmacodynamics

Preclinical studies have shown that Pemetrexed inhibits the in vitro growth of mesothelioma cell lines (MSTO-211H, NCI-H2052). Studies with the MSTO-211H mesothelioma cell line showed synergistic effects when Pemetrexed was combined concurrently with Cisplatin. Time to ANC nadir with Pemetrexed systemic exposure (AUC), varied between 8 to 9.6 days over a range of exposures from 38.3 to 316.8 mcg•hr/mL. Return to baseline ANC occurred 4.2 to 7.5 days after the nadir over the same range of exposures.

Pharmacokinetics

Absorption

The pharmacokinetics of Pemetrexed administered as a single-agent in doses ranging from 0.2 to 838 mg/m² infused over a 10-minute period have been evaluated in 426 cancer patients with a variety of solid tumors. Pemetrexed total systemic exposure (AUC) and maximum plasma concentration (C_{max}) increase proportionally with dose. The pharmacokinetics of Pemetrexed do not change over multiple treatment cycles.

Distribution

Pemetrexed has a steady-state volume of distribution of 16.1 liters. In vitro studies indicate that Pemetrexed is approximately 81% bound to plasma proteins. Binding is not affected by degree of renal impairment.

Metabolism and Excretion

Pemetrexed is not metabolized to an appreciable extent and is primarily eliminated in the urine, with 70% to 90% of the dose recovered unchanged within the first 24 hours following administration. The clearance decreases, and exposure (AUC) increases, as renal function decreases. The total systemic clearance of Pemetrexed is 91.8 mL/min and the elimination half-life of Pemetrexed is 3.5 hours in patients with normal renal function (creatinine clearance of 90 mL/min).

INDICATIONS

Nonsquamous Non-Small Cell Lung Cancer - Combination with Cisplatin

Pemetrexed is indicated in combination with Cisplatin therapy for the initial treatment of patients with locally advanced or metastatic nonsquamous non-small cell lung cancer.

Nonsquamous Non-Small Cell Lung Cancer - Maintenance

Pemetrexed is indicated for the maintenance treatment of patients with locally advanced or metastatic nonsquamous non-small cell lung cancer whose disease has not progressed after four cycles of Platinum-based first-line chemotherapy.

Nonsquamous Non-Small Cell Lung Cancer - After Prior Chemotherapy

Pemetrexed is indicated as a single-agent for the treatment of patients with locally advanced or metastatic nonsquamous non-small cell lung cancer after prior chemotherapy.

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.

Limitations of Use

Pemetrexed is not indicated for the treatment of patients with squamous cell non-small cell lung cancer.

DOSAGE AND ADMINISTRATION

Combination Use with Cisplatin

Nonsquamous 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 administration. Patients should receive appropriate hydration prior to and/or after receiving Cisplatin.

Single-Agent Use

Nonsquamous 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.

Premedication 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 (1) 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. Pretreatment 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 administration.

Laboratory Monitoring and Dose Reduction/Discontinuation Recommendations

Monitoring

Complete blood cell counts, including platelet counts, should be performed on all patients receiving Pemetrexed. Patients should be monitored for nadir and recovery, which were tested in the clinical study 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 $\geq 100,000$ cells/mm³, and creatinine clearance is ≥ 45 mL/min. Periodic chemistry tests should be performed to evaluate renal and hepatic function

Dose Reduction Recommendations

Dose adjustments at the start of a subsequent cycle should be based on nadir hematologic counts or maximum nonhematologic toxicity from the preceding cycle of therapy. Treatment may be delayed to allow sufficient time for recovery. Upon recovery, patients should be retreated using the standard guidelines.

Discontinuation Recommendation

Pemetrexed therapy should be discontinued if a patient experiences any hematologic or nonhematologic Grade 3 or 4 toxicity after 2 dose reductions or immediately if Grade 3 or 4 neurotoxicity is observed.

Preparation and Administration Precautions

As with other potentially toxic anticancer agents, care should be exercised in the handling and preparation of infusion solutions of Pemetrexed. The use of gloves is recommended. If a solution of Pemetrexed contacts the skin, wash the skin immediately and thoroughly with soap and water. If Pemetrexed contacts the mucous membranes, flush thoroughly with water. Several published guidelines for handling and disposal of anticancer agents are available. Pemetrexed is not a vesicant. There is no specific antidote for extravasation of Pemetrexed. To date, there have been few reported cases of Pemetrexed extravasation, which were not assessed as serious by the investigator. Pemetrexed extravasation should be managed with local standard practice for extravasation as with other non-vesicants.

Preparation for Intravenous Infusion Administration

1. Use aseptic technique during the reconstitution and further dilution of Pemetrexed for intravenous infusion administration.
2. Calculate the dose of Pemetrexed and determine the number of vials needed. Vials contain either 100 mg or 500 mg of Pemetrexed. The vials contain an excess of Pemetrexed to facilitate delivery of label amount.
3. Reconstitute each 100-mg vial with 4.2 ml of 0.9% Sodium Chloride Injection (preservative free). Reconstitute each 500-mg vial with 20 ml of 0.9% Sodium Chloride Injection (preservative free). Reconstitution of either size vial gives a solution containing 25 mg/mL Pemetrexed. Gently swirl each vial until the powder is completely dissolved. The resulting solution is clear and ranges in color from colorless to yellow or green-yellow without adversely affecting product quality. The pH of the reconstituted Pemetrexed solution is between 6.6 and 7.8. Further Dilution is Required.
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 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. When prepared as directed, reconstitution and infusion solutions of Pemetrexed 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). Pemetrexed is physically incompatible with diluents containing calcium, including Lactated Ringer's Injection, USP and Ringer's Injection, USP and therefore these should not be used. Co-administration of Pemetrexed with other drugs and diluents has not been studied, and therefore is not recommended. Pemetrexed is compatible with standard Polyvinyl Chloride (PVC) administration sets and intravenous solution bags.

USE IN SPECIFIC POPULATIONS

Pregnancy: Category D

Nursing Mothers: It is not known whether Pemetrexed or its metabolites are excreted in human milk.

Pediatric Use: The safety and effectiveness of Pemetrexed in pediatric 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.

Patients with Hepatic Impairment: There was no effect of elevated AST, ALT, or total bilirubin on the pharmacokinetics of pemetrexed.

Patients with Renal Impairment: Pemetrexed is known to be primarily excreted by the kidneys. Decreased renal function will result in reduced clearance and greater exposure (AUC) to Pemetrexed compared with patients with normal renal function.

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.

WARNINGS AND PRECAUTION

Premedication Regimen

Need for Folate and Vitamin B₁₂ Supplementation

Patients treated with Pemetrexed must be instructed to take Folic Acid and vitamin B₁₂ as a prophylactic measure to reduce treatment-related hematologic and GI toxicity

Corticosteroid Supplementation

Pretreatment with Dexamethasone (or equivalent) reduces the incidence and severity of cutaneous reaction.

Bone Marrow Suppression

Myelosuppression is usually the dose-limiting toxicity. Dose reductions for subsequent cycles are based on nadir ANC, platelet count, and maximum nonhematologic toxicity seen in the previous cycle.

Decreased Renal Function

Pemetrexed is primarily eliminated unchanged by renal excretion. No dosage adjustment is needed in patients with creatinine clearance ≥ 45 mL/min. Pemetrexed should not be administered to patients whose creatinine clearance is < 45 mL/min.

Use with Non-Steroidal Anti-Inflammatory Drugs with Mild to Moderate Renal Insufficiency

Caution should be used when administering Ibuprofen concurrently with Pemetrexed to patients with mild to moderate renal insufficiency (creatinine clearance from 45 to 79 mL/min). Other NSAIDs should also be used with caution

OVERDOSE

There have been few cases of Pemetrexed overdose. Reported toxicities included neutropenia, anemia, thrombocytopenia, mucositis, and rash. Anticipated complications of overdose include bone marrow suppression as manifested by neutropenia, thrombocytopenia, and anemia. In addition, infection with or without fever, diarrhea, and mucositis may be seen. If an overdose occurs, general supportive measures should be instituted as deemed necessary by the treating physician. In clinical trials, leucovorin was permitted for CTC Grade 4 leukopenia lasting ≥ 3 days, CTC Grade 4 neutropenia lasting ≥ 3 days, and immediately for CTC Grade 4 thrombocytopenia, bleeding associated with Grade 3 thrombocytopenia, or Grade 3 or 4 mucositis. The following intravenous doses and schedules of leucovorin were recommended for intravenous use: 100 mg/m², intravenously once, followed by leucovorin, 50 mg/m², intravenously every 6 hours for 8 days.

ADVERSE EFFECTS

The most common adverse reactions (incidence $\geq 20\%$) during therapy with Pemetrexed as a single-agent were fatigue, nausea, and anorexia. Additional common adverse reactions (incidence $\geq 20\%$) during therapy with Pemetrexed when used in combination with Cisplatin included vomiting, neutropenia, leukopenia, anemia, stomatitis/pharyngitis, thrombocytopenia, and constipation.

Non-Small Cell Lung Cancer (NSCLC) - Combination with Cisplatin

Incidence 1% to 5%

Febrile neutropenia, infection, pyrexia, dehydration, increased AST, increased ALT, creatinine clearance decrease, renal failure, conjunctivitis

Incidence Less than 1%

Arrhythmia, chest pain, increased GGT, motor neuropathy

Non-Small Cell Lung Cancer (NSCLC) - Maintenance

Incidence 1% to 5%

Alopecia, pruritis/itching, constipation, edema, fever (in the absence of neutropenia), thrombocytopenia, decreased creatinine clearance, increased creatinine, decreased glomerular filtration rate, ocular surface disease (including conjunctivitis), increased lacrimation,

Incidence Less than 1%

Supraventricular arrhythmia, erythema multiforme, febrile neutropenia, allergic reaction/hypersensitivity, motor neuropathy, renal failure.

Non-Small Cell Lung Cancer (NSCLC) - After Prior Chemotherapy

Incidence 1% to 5%

Abdominal pain, allergic reaction/hypersensitivity, febrile neutropenia, infection, erythema multiforme, motor neuropathy, sensory neuropathy, increased creatinine.

Incidence Less than 1%

Supraventricular arrhythmias.

PHARMACEUTICAL INFORMATION

Storage Conditions

Store the vial in original carton below 30°C, away from light. Keep out of the reach of children.

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°C to 8°C).

Presentation & Packaging

Pemetrex Injection: Each commercial box contains 1 vial of Pemetrex Injection as lyophilized powder.
Pemetrex 500 Injection: Each commercial box contains 1 vial of Pemetrex 500 Injection as lyophilized powder.