Pemetor™ for IV Injection

Pemetrexed for injection USP

DESCRIPTION

Pemetor™ is a preparation of Pemetrexed. Pemetrexed for injection, is a folate analog metabolic inhibitor that exerts its action by disrupting folate-dependent metabolic processes essential for cell replication. 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, membrane folate binding protein transport systems. Once in the cell, Pemetrexed is converted to polyglutamate forms by the enzyme folylpolyglutamate 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.

PHARMACOKINETICS

The pharmacokinetics of Pemetrexed administered as a single-agent in doses ranging from 0.2 to 838 mg/m^2 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. 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. 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

- Non-Small Cell Lung Cancer — Combination with Cisplatin
- Non-Small Cell Lung Cancer — Single-Agent

DOSAGE AND ADMINISTRATION

- **Combination use in Non-Small Cell Lung Cancer and Mesothelioma:** Recommended dose of Pemetrexed is 500 mg/m^2 i.v. on Day 1 of each 21-day cycle in combination with cisplatin 75 mg/m^2 i.v. beginning 30 minutes after Pemetrexed administration.
- **Single-Agent use in Non-Small Cell Lung Cancer:** Recommended dose of Pemetrexed is 500 mg/m^2 i.v. on Day 1 of each 21-day cycle.
- **Dose Reductions:** Dose reductions or discontinuation may be needed based on toxicities from the preceding cycle of therapy.

CONTRAINDICATIONS

- Hypersensitivity

SIDE EFFECTS

- Single-agent use are fatigue, nausea, and anorexia
- In combination with cisplatin include vomiting, neutropenia, leukopenia, anemia, stomatitis/pharyngitis, thrombocytopenia, and constipation.

WARNING AND PRECAUTION

Premedication regimen: Instruct patients to take folic acid and vitamin B_{12}. Pretreatment with dexamethasone or equivalent reduces cutaneous reaction. Bone marrow suppression: Reduce doses for subsequent cycles based on hematologic and nonhematologic toxicities. Renal function: Do not administer when CrCl <45 mL/min. NSAIDs with renal insufficiency: Use caution in patients with mild to moderate renal insufficiency (CrCl 45-79 mL/min). Lab monitoring: Do not begin next cycle unless ANC u1500 cells/mm3, platelets u100,000 cells/mm^3, and CrCl u45 mL/min.

USE IN PREGNANCY AND LACTATION

Pregnancy Category D. 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.

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.

3. Reconstitute each 100 mg vial with 4.2 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 no 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. Coadministration 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.

PHARMACEUTICAL PRECAUTION

Do not store above 30 °C temperature. Keep away from light & wet place. Keep out of reach of children. Store reconstituted and infusion solution at refrigerator 2-8 °C (36-46 °F) or at 25 °C (77 °F), excursions permitted to 15-30 °C (59-86 °F). Administer infusion solution within 24 hours after initial reconstitution.

PACKAGING

Pemetor™ 100 for IV Injection : Each box contains 1 vial of Pemetrexed Disodium Heptahydrate USP equivalent to Pemetrexed 100 mg (as lyophilized powder).

Pemetor™ 500 for IV Injection : Each box contains 1 vial of Pemetrexed Disodium Heptahydrate USP equivalent to Pemetrexed 500 mg (as lyophilized powder).

SK+F ONCOLOGY

Manufactured by
ESKAYEF PHARMACEUTICALS LIMITED
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