For the use only of a Registered Medical Practioner, Hospital or a Laboratory

Pemetrexed for Injection 100mg / 500mg

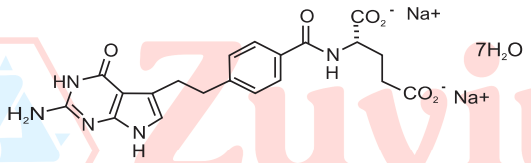
Antifol ™

COMPOSITION

Each 100 mg vial contains:	Each 100 mg vial contains:
Pemetrexed Disodium IP Equivalent to	Pemetrexed Disodium IP Equivalent to
Pemetrexed.....100 mg	Pemetrexed.....500 mg
Mannitol .....106 mg	Mannitol .....500 mg

DRUG Description

Pemetrexed disodium heptahydrate has the chemical name L-Glutamine acid, N-[4-[2-(2-amino-4,7-dihydro-4-oxo1H-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 $C_{20}H_{19}N_5Na_2O_6 7H_2O$ and a molecular weight of 597.49. The Structural formula is as follows:



CLINICAL PHARMACOLOGY

Mechanism of Action

Pemetrexed 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 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

a. 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 solids tumors. Pemetrexed total systemic exposure (AUC) and maximum plasma

concentration (Cmax) increase proportionally with dose. The pharmacokinetics of Pemetrexed do not change over multiple treatment cycles.

b. Distribution
Pemetrexed has a steady-state volume of distribution of 16.1 liters. Pemetrexed is approximately 81% bound to plasma proteins. Binding is not affected by degree of renal impairment.

c. 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.

INDICATIONS

A. 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.

B. 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.

C. Nonsquamous Non-Small Cell Lung Cancer – After Prior Chemotherapy

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

D. Mesothelioma

Pemetrexed in combination with cisplatin in 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

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

DOSAGE AND ADMINISTRATION

I. **Combination Use with Cisplatin for Nonsqamous Non-Small Cell Lung Cancer or Malignant Pleural Mesothelioma**

The recommended dose of Pemetrexed is 500 mg/m^2 infused over 2 hours beginning approximately 30 minutes after the end of cycle. The recommended dose of cisplatin is 75 mg/m^2

infused over 2 hours beginning approximately 30 minutes after the end of Pemetrexed administration.

Single-Agent Use as Maintenance Following First-Line Therapy, or as a Second-Line Therapy

The recommended dose of Pemetrexed is 500 mg/m^2 administered as an intravenous infusion over 10minutes on Day 1 of each 21-day cycle.

II. **Premedication Regimen and Concurrent Medications**

a. Vitamin Supplementation

Folic acid 400 mcg to 1000 mcg orally to be initiated once daily, beginning 7 days before the first

Dose of Pemetrexed. Continue folic acid during the full course of therapy and for 21 days the last dose of Pemetrexed.

Vitamin B12 1mg intramuscularly 1 week prior to the first dose of Pemetrexed and every 3 cycles thereafter to be administered. Subsequent vitamin B12 injections may be given the same day as treatment with Pemetrexed.

b. Corticosteroids

Administer dexamethasone 4mg by mouth twice daily the day before, the day of, and the day after Pemetrexed administration.

1. **LABORATORY MONITORING AND DOSE REDUCTION/DISCONTINUATION RECOMMENDATIONSI**

I. 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/mm^3, the platelet count is = 100,000 cells/mm^3 and creatinine clearance is = 45mL/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 recover, patients should be retreated using the guidelines in Tables 1-3, which are suitable for using Pemetrexed as a single-agent or in combination with cisplatin.

Table 1: Dose Reduction for Pemetrexed (single-agent or in combination) and Cisplatin- Hematologic Toxicities

Nadir ANC < 500/mm^3 and nadir platelets 50,000/ mm^3	75% of previous dose (Pemetrexed and cisplatin).
Nadir platelets < 50,000/ mm^3 without bleeding regardless of nadir ANC.	75% of previous dose (Pemetrexed and cisplatin).
Nadir platelets < 50,000/ mm^3 without bleeding regardless of nadir ANC.	50% of previous dose (Pemetrexed and cisplatin).

*These criteria meet the CTC version 2.0 (NCI 1998) definition of = CTC Grade 2 bleeding.

If patients develop nonhematologic 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 2.

Table 2: Dose Reduction for Pemetrexed (single-agent or in combination) and Cisplatin-Nonhematologic Toxicities a, b

	DOSE OF Pemetrexed (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 diarrhea requiring hospitalization (irrespective of Grade) or Grade 3 or 4 diarrhea	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 3).		

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

Table 3: Dose Reduction for Pemetrexed (single-agent or in combination) and Cisplatin - Neurotoxicity

CTCGRADE	**DOSE OF Pemetrexed (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

iii. 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.

Renal 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 should not be administered to patients whose creatinine clearance is < 45ml/min using the standard Cockcroft and Gault formula (below) or GFR measured by Tc99m-DTPA serum clearance method:

(weight in kg) x (140-age)

Males : (72) x serum creatinine (mg/100ml.)

Females estimated creatinine clearance for males x 0.85

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

USE IN SPECIFIC POPULATIONS

i. Pregnance-Tertogenic Effects-Pregnancy Category D

Embryotoxicity was characterized by increased embryo-fetal deaths and reduced litter sized. 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 feotus.

ii. 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.

iii. Pediatric Use

Efficacy of Pemetrexed in pediatric patients has not been demonstrated. The most common toxicities reported were hematological (Leukopenia, Neutropenia / Granulocytopenia, Anemia, thrombocytopenia, and Lymphopenia), liver function abnormalities (increased ALT/AST), fatigue, and nausea.

iv. Geriatric Use

Pemetrexed is known to be substantially excreted by the kidney, and the risk of adverse reactions to this durg may be greater in patients with impaired renal function. Renal fusion 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.

v. Patients with Hepatic Impairment

there was no effect of elevated AST, ALT, or total bilirubin on the pharmacokinetics of Pemetrexed.

WARNING AND PRECAUTIONS

i. Bone Marrow Suppression

Pemetrexed can suppress bone marrow function, as manifested by Neutropenia. Thrombocytopenia, and Anemia (or pancytopenia): myelosuppression is usually the dose-limiting toxicity. Dose reductions for subsequent cycles are based on nadir ANC, platelet count, and maximum non hematologic toxicity seen in the previous cycle.

ii. Decreased Renal Function

Pemetrexed is primarily eliminated unchanged by renal excretion. No dosage adjustment is needed in patients with creatinine = 45ml/min. Use with Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) with Mild to Moderate Renal Insufficiency caution should be used when administering NSAIDs concurrently with Pemetrexed to patients with mild to moderate renal insufficiency caution should be used when administering NSAIDs concurrently with Pemetrexed to patients with mild to moderate renal insufficiency (creatinine clearance from 45 to 79ml/min.

iii. Required Laboratory Monitoring

Obtain a complete blood count and renal function tests at the beginning of each cycle and as needed. Do not initiate a cycle of treatment unless the ANC is = 1500 cells/mm^3, and creatinine clearance is = 45 ml/min.

iv. Nonclinical Toxicology – Carcinogenesis, Mutagenesis, Impairment of Fertility

PREPARATION ADMINSTRATION PRECAUTIONS

Each 100mg vial to be reconstituted with 4.22 ml of 0.9% (w/v) Sodium Chloride Injection IP and gently mixed so that the powder is completely dissolved.

Each 500mg vial to be reconstituted with 20ml of 0.9% (w/v) Sodium Chloride IP and gently mixed so that the powder is complety dissolved. The resulting solution is clear and ranges in color from colorless to yellow or green-yellow 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). When prepared as directed, reconstituted and infusion solutions of Pemetrexed contain no antimicrobial preservatives. Unused portion is discarded. Pemetrexed is not light sensitive.

ADVERSE REACTIONS

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

Clinically relevant adverse reactions occurring in < 5% of patients that received Pemetrexed Treatment but >5% of patients that received Docetaxel include CTC Grade ¾ febrile neutropenia (1.9% Pemetrexed, 12.7% Docetaxel).

DRUG INTERACTIONS

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

No dose adjustment of Pemetrexed is needed with concomitant NSAIDs in patients with normal renal function. Caution should be used when administering NSAIDs concurrently with Pemetrexed to patients with mild to moderate renal insufficiency (creatinine clearance form 45 to 79 ml/min).

NSAIDs with short elimination half-lives (e.g. diclofenac, indomethacin) should be avoided for a period of 2 days before, the day of, and 2 days following administration of Pemetrexed. Nephrotoxic Drugs.

Pemetrexed is primarily eliminated unchanged renally as a result of glomerular filtration and tubular secretion. Concomitant administration of nephrotoxic drugs could result in delayed clearance of Pemetrexed. Concomitant administration of substances that are also tubularly secreted (e.g. probenecid) could potentially result in delayed clearance of Pemetrexed.

OVERDOSE

There have been few cases of Pemetrexed overdose. Reported toxicities included neutropenia, anemia, thrompocytopenia, 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.

CONTRAINDICATION

Pemetrexed is contraindicated in patients who have a history of severe hypersensitivity reaction to Pemetrexed.

STORAGE AND HANDLING

Pemetrexed injection, should be stored at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

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. Pemetrexed is not a vesicant. There is no specific antidote for extravasation of Pemetrexed. Pemetrexed extravasation should be managed with local standard practice for extravasation as with other non-vesicants.

PRESENTATION:

Antifol ™: Single vial of Pemetrexed injection 100mg and 500mg

Manufactured in India by:

ZUVIUS LIFESCIENCES PVT. LTD.
A WHO-GMP CERTIFIED COMPANY
B/111, 112, 113, Kanara Business Centre,
Link Road, Ghatkopar (East), Mumbai 400075.
www.zuviuslifesciences.in

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