- Unusual bleeding or bruising.
- Unusual tiredness or weakness.

Less serious effects

- Bad or unpleasant taste in mouth.
- Constipation, diarrhea, nausea, or vomiting, or upset stomach.
- Depression or mood changes.
- Hair loss.
- Loss of appetite.
- Mild sore throat or difficulty with swallowing.
- Muscle or joint pain.
- Numbness, tingling, burning, or painful feelings.
- Sores or white patches on lips, mouth, or throat.

DRUG INTERACTIONS

Ibuprofen: Although ibuprofen (400 mg four times daily) can be administered with pemetrexed in patients with normal renal function (creatinine clearance greater than or equal to 80 mL/min), caution should be used when administering ibuprofen concurrently with pemetrexed to patients with renal insufficiency (creatinine clearance 45 - 79 mL/min). It is recommended that patients with mild to moderate renal insufficiency should avoid taking NSAIDs with short elimination half-lives at least 2 days prior to, on the day of, and at least 2 days after 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.

Other NSAIDs: In the absence of data regarding potential interaction between pemetrexed and NSAIDs with longer half-lives, all patients taking these NSAIDs should interrupt dosing for at least 5 days before, on the day of, and at least 2 days after pemetrexed administration. If concomitant administration of NSAIDs is necessary, patients should be monitored closely for toxicity, especially myelosuppression and gastrointestinal toxicity.

Aspirin: Acetylsalicylic acid, administered in low to moderate doses (325 mg orally every 6 hours) does not affect the pharmacokinetics of pemetrexed.

Concomitant cytotoxic therapy: The pharmacokinetics of pemetrexed are not influenced by concurrently administered cisplatin or carboplatin. Similarly, the pharmacokinetics of total platinum are unaltered by pemetrexed. Oral folic acid and intramuscular vitamin B_{12} supplementation do not affect the pharmacokinetics of pemetrexed.

Cytochrome P450: Pemetrexed undergoes limited hepatic metabolism, pemetrexed would not be predicted to cause clinically significant inhibition of the metabolic clearance of drugs metabolised by CYP3A, CYP2D6, CYP2C9, and CYP1A2.

OVERDOSAGE

Symptoms of overdose include 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. In the event of suspected overdose, patients should be monitored with blood counts and should receive supportive therapy as necessary. The use of leucovorin in the management of Pemetrexed overdose should be considered. The ability of pemetrexed to be dialyzed is unknown.

DIRECTIONS

Store below 30°C. Protect from direct light. To be sold on prescription only. Keep out of the reach of children.

PRESENTATION

PEMEX 100 mg: (Pemetrexed for Injection USP) is available as a sterile lyophilized powder for intravenous infusion packed in single dose vial containing 100 mg pemetrexed along with package insert.

PEMEX 500 mg: (Pemetrexed for Injection USP) is available as a sterile lyophilized powder for intravenous infusion packed in single dose vial containing 500 mg pemetrexed along with package insert.

Marketed by:

Revive healthcare

503, 5th Floor, Eden Heights, 6 Main Gulberg, Jail Road, Lahore - Pakistan 54600.

Manufactured by:
United Biotech (P) Limited
Bagbania, Baddi-Nalagarh Road, Distt. Solan (HP) - 174 101 - India

پیمکس

پیمی ٹریکسیڈ ۵۰۰ ملی گرام

انجکشن

دوا کو ۳۰ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔
دوا کو روشنی اور نمی سے محفوظ رکھیں۔
ڈاکٹری ہدایات کے مطابق استعمال کریں۔
بچوں کی پہنچ سے دور رکھیں۔

EDa 10-01

^{Rx} Pemetrexed for Injection USP

PEMEX 100/500 mg (Lyophilized) for I.V. Infusion only

PHARMACEUTICALS WORLDWIDE
UNITED BIOTECH
The Emergence of a New Standard

COMPOSITION

PEMEX 100 mg

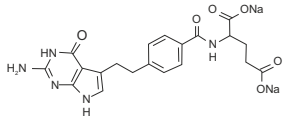
Each vial contains:	
Pemetrexed USP (as Pemetrexed Disodium)	100mg
Excipients (U.S.P. Specs.)	q.s.

PEMEX 500 mg

Each vial contains:	
Pemetrexed USP (as Pemetrexed Disodium)	500mg
Excipients (U.S.P. Specs.)	q.s.

DESCRIPTION

Pemetrexed for Injection is a multitarget anticancer, antifolate agent. Pemetrexed disodium heptahydrate has the chemical name N-[4-[2-(2-amino-4,7-dihydro-4-oxo-1H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-L-glutamic acid, disodium salt, its structural formula is;



Molecular formula $C_{20}H_{19}N_5Na_2O_6.7H_2O$,

CLINICAL PHARMACOLOGY

Mechanism of action

Pemetrexed for Injection exerts its action by disrupting crucial folate-dependent metabolic processes essential for cell replication.

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 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 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).

The clearance decreases, and exposure (AUC) increases, as renal function decreases. 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.

INDICATIONS

Pemetrexed is indicated for the treatment of patients with malignant pleural mesothelioma in combination with cisplatin.

Pemetrexed is indicated for treatment of patients with locally advanced or metastatic non-squamous non-small cell lung cancer, after prior chemotherapy, in combination with cisplatin in initial as well as maintenance treatment.

DOSAGE & ADMINISTRATION

Pemetrexed should only be administered under the supervision of a physician qualified in the use of anticancer chemotherapy.

In Malignant Pleural Mesothelioma (combination use with cisplatin): The recommended dose of Pemetrexed is 500 mg/m^2 administered as an intravenous infusion over 10 minutes on the first day of each 21-day cycle. The recommended dose of cisplatin is 75 mg/m^2 infused over two hours approximately 30 minutes after completion of the pemetrexed infusion on the first day of each 21-day cycle. Patients should receive hydration consistent with local practice prior to and/or after receiving cisplatin. (See cisplatin package insert for specific dosing advice).

In non-squamous Non-Small Cell Lung Cancer (NSCLC): The recommended dose of Pemetrexed is 500 mg/m^2 administered as an intravenous infusion over 10 minutes on the first day of each 21 day cycle, when used as a single agent or in combination with Cisplatin.

Premedication Regimen

- To reduce the incidence and severity of skin reactions, a corticosteroid should be given the day prior to, on the day of, and the day after Pemetrexed administration. The corticosteroid should be equivalent to 4 mg of dexamethasone administered orally twice a day.
- To reduce toxicity, patients treated with pemetrexed should also receive vitamin supplementation. Patients must take oral folic acid or a multivitamin containing folic acid (350 to 1000 micrograms) on a daily basis. At least five doses of folic acid must be taken during the seven days 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 an intramuscular injection of vitamin B_{12} (1000 micrograms) in the week preceding the first dose of pemetrexed and every three cycles thereafter. Subsequent vitamin B_{12} injections may be given on the same day as Pemetrexed.

Laboratory Monitoring

Patients taking pemetrexed should be monitored before each dose with a complete blood count, including a differential and platelet count. Periodic blood chemistry tests should be collected to evaluate renal and hepatic function. Absolute Neutrophil Count (ANC) should be greater than or equal to 1500 cells/mm^3 and platelets should be greater than or equal to 100,000 cells/mm^3 prior to the start of each cycle.

Dose Adjustments

Dose adjustments at the start of a subsequent cycle should be based on nadir haematologic counts or maximum nonhaematologic 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 guidelines in Tables 1, 2 and 3, which are applicable for pemetrexed used as a single agent or in combination with cisplatin.

TABLE 1
Dose Modification Table for PEMEX (as Single Agent or in Combination) and Cisplatin - Haematologic Toxicities

Nadir ANC < 500 /mm^3 and nadir platelets greater than or equal to 50,000 /mm^3	75 % of previous dose (both drugs)
Nadir platelets less than or equal to 50,000 /mm^3 regardless of nadir ANC	50 % of previous dose (both drugs)

If patients develop nonhaematologic toxicities (excluding neurotoxicity) greater than or equal to Grade 3 (with the exception of Grade 3 transaminase elevations), pemetrexed should be withheld until resolution to less than or equal to the patient's pretherapy value. Treatment should be resumed according to the guidelines in Table 2.

TABLE 2
Dose Modification Table for PEMEX (as Single Agent or in Combination) and Cisplatin- Nonhaematologic Toxicities[a,b]

	Dose of PEMEX (mg/m^2)	Dose of Cisplatin (mg/m^2)
Any Grade 3[c] or 4 toxicities except mucositis	75 % of previous dose	75 % of previous dose
Any diarrhoea requiring hospitalisation (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 National Cancer Institute Common Toxicity Criteria (CTC).
b Excluding neurotoxicity.
c Except Grade 3 transaminase elevation.

In the event of neurotoxicity, the recommended dose adjustment for pemetrexed and cisplatin is documented in Table 3. Patients should discontinue therapy if Grade 3 or 4 neurotoxicity is observed.

TABLE 3
Dose Modification Table for PEMEX (as Single Agent or in Combination) and Cisplatin - Neurotoxicity

CTC* Grade	Dose of PEMEX (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

* Common Toxicity Criteria (CTC).

Treatment with pemetrexed should be discontinued if a patient experiences any haematologic or nonhaematologic Grade 3 or 4 toxicity after 2 dose reductions (except Grade 3 transaminase elevations) or immediately if Grade 3 or 4 neurotoxicity is observed.

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 so dosage should be adjusted accordingly.

CONTRAINDICATIONS

Pemetrexed is contraindicated in patients with known hypersensitivity to pemetrexed or to any of the excipients.

WARNINGS & PRECAUTIONS

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: 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

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 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. Therefore, 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.

Required Laboratory Monitoring: 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

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. 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.

PREGNANCY AND LACTATION

Pregnancy: Based on its mechanism of action, Pemetrexed can cause fetal harm when administered to a pregnant woman. There are no adequate and well controlled studies of pemetrexed in pregnant women. 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 fetus. 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.

ADVERSE EFFECTS

Serious effects

- Allergic reaction: Itching or hives, swelling in face or hands, swelling or tingling in mouth or throat, chest tightness, trouble breathing.
- Chest pain, shortness of breath, or coughing up blood.
- Decrease in urination
- Dry mouth or skin, increased thirst, lightheadedness, dizziness, or fainting.
- Fever, chills, cough, sore throat, and body aches.
- Lower back or side pain.
- Numbness or weakness in arm or leg, or on one side of body.
- Pain in lower leg (calf).
- Pain or redness of the skin in the area of earlier radiation treatment.
- Rapid weight gain.
- Red or dark brown urine.
- Skin rash.
- Sudden or severe headache, problems with vision, speech, or walking.
- Swelling in hands, ankles, or feet.