Pemeta Injection

DRUG INTERNATIONAL LTD.

Composition : **Pemeta :** Each vial contains Pemetrexed 100mg as Pemetrexed Disodium Heptahydrate USP lyophilized powder for IV infusion.

Pemeta-500 : Each vial contains Pemetrexed 500mg as Pemetrexed Disodium Heptahydrate USP lyophilized powder for IV infusion.

Pharmacology : Pemetrexed is a folate analog metabolic inhibitor that disrupts folate-dependent metabolic processes essential for cell replication. In vitro studies show that Pemetrexed inhibits thymidylate synthase (TS), dihydrofolate reductase, 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 of TS and GARFT.

Pharmacodynamics : Pemetrexed inhibited the in vitro growth of mesothelioma cell lines (MSTO-211H, NCI-H2052) and showed synergistic effects when combined with Cisplatin. Based on population pharmacodynamic analyses, the depth of the absolute neutrophil counts (ANC) nadir correlates with the systemic exposure to pemetrexed and supplementation with folic acid and vitamin B12. There is no cumulative effect of Pemetrexed exposure on ANC nadir over multiple treatment cycles.

Pharmacokinetics :

Absorption : The pharmacokinetics of Pemetrexed when Pemeta was 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 (Cmax) increased proportionally with increase of dose. The pharmacokinetics of Pemetrexed did not change over multiple treatment cycles. **Distribution :** Pemetrexed has a steady-state volume of distribution of 16.1 liters. In vitro studies indicated that Pemetrexed is 81% bound to plasma proteins. **Metabolism and Excretion :** Pemetrexed is not metabolized to an appreciable extent. It 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 is 91.8 mL/min and the elimination half-life is 3.5 hours in patients with normal renal function (creatinine clearance of 90 mL/min). As renal function decreases, the clearance of Pemetrexed decreases and exposure (AUC) of Pemetrexed increases. Elimination half-life of Pemetrexed is 3.5 hours with normal renal function.

Indications : Non-Squamous Non-Small Cell Lung Cancer (NSCLC): Pemetrexed is indicated: • in combination with Pembrolizumab and platinum chemotherapy, for the initial treatment of patients with metastatic non-squamous NSCLC, with no EGFR or ALK genomic tumor aberrations. • in combination with Cisplatin for the initial treatment of patients with locally advanced or metastatic, nonsquamous, non-small cell lung cancer (NSCLC). • as a single agent for the maintenance treatment of patients with locally advanced or metastatic, nonsquamous NSCLC whose disease has not progressed after four cycles of platinum-based first-line chemotherapy. • as a single agent for the treatment of patients with recurrent, metastatic non-squamous, NSCLC after prior chemotherapy.Limitations of Use: Pemetrexed is not indicated for the treatment of patients with squamous cell, non-small cell lung cancer. Mesothelioma: Pemetrexed is indicated, in combination with Cisplatin, for the initial treatment of patients with malignant pleural mesothelioma whose disease is unresectable or who are otherwise not candidates for curative surgery.

Dosage & Administration : **Recommended Dosage for Non-Squamous NSCLC:** • The recommended dose of Pemetrexed when administered with Pembrolizumab and platinum chemotherapy for the initial treatment of metastatic non-squamous NSCLC in patients with a creatinine clearance (calculated by Cockcroft-Gault equation) of 45 mL/min or greater is 500 mg/m2 as an intravenous infusion over 10 minutes administered after Pembrolizumab and prior to Carboplatin or Cisplatin on Day 1 of each 21-day cycle for 4 cycles. Following completion of platinum-based therapy, treatment with Pemetrexed with or without Pembrolizumab is administered until disease progression or unacceptable toxicity. Please refer to the full prescribing information for Pembrolizumab and for Carboplatin or Cisplatin. • The recommended dose of Pemetrexed when administered with Cisplatin for initial treatment of locally advanced or metastatic non-squamous NSCLC in patients with a creatinine clearance (calculated by Cockcroft-Gault equation) of 45 mL/min or greater is 500 mg/m2 as an intravenous infusion over 10 minutes administered prior to Cisplatin on Day 1 of each 21-day cycle for up to six cycles in the absence of disease progression or unacceptable toxicity.

• The recommended dose of Pemeta for maintenance treatment of non-squamous NSCLC in patients with a creatinine clearance (calculated by Cockcroft-Gault equation) of 45 mL/min or greater is 500 mg/m2 as an intravenous infusion over 10 minutes on Day 1 of each 21-day cycle until disease progression or unacceptable toxicity after four cycles of platinum-based first-line chemotherapy. • The recommended dose of Pemetrexed for treatment of recurrent non-squamous NSCLC in patients with a creatinine clearance (calculated by Cockcroft-Gault equation) of 45 mL/min or greater is 500 mg/m2 as an intravenous infusion over 10 minutes on Day 1 of each 21-day cycle until disease progression or unacceptable toxicity. **Recommended Dosage for Mesothelioma:** • The recommended dose of Pemetrexed when administered with Cisplatin in patients with a creatinine clearance (calculated by Cockcroft-Gault equation) of 45 mL/min or greater is 500 mg/m2 as an intravenous infusion over 10 minutes on Day 1 of each 21-day cycle until disease progression or unacceptable toxicity. **Renal Impairment:** • Pemetrexed dosing recommendations are provided for patients with a creatinine clearance (calculated by Cockcroft-Gault equation) of 45 mL/min or greater. There is no recommended dose for patients whose creatinine clearance is less than 45 mL/min. **Premedication and Concomitant Medications to Mitigate Toxicity**

Vitamin Supplementation • Initiate Folic acid 400mcg to 1000mcg orally once daily, beginning 7 days before the first dose of Pemetrexed and continuing until 21 days after the last dose of Pemetrexed.

• Administer vitamin B, 1mg intramuscularly, 1 week prior to the first dose of Pemetrexed and every 3 cycles thereafter. Subsequent vitamin B injections may be given the same day as treatment with Pemetrexed. Do not substitute oral vitamin B12 for intramuscular vitamin B12. **Corticosteroids** • Administer Dexamethasone 4mg orally twice daily for three consecutive days, beginning the day before each Pemetrexed administration.

Recommended Dosage Modifications for Adverse Reactions:

Toxicity in Most Recent Treatment Cycle	Pemeta Dose Modification for Next Cycle
Myelosuppressive toxicity	
ANC less than 500/mm^3 **and** platelets greater than or equal to 50,000/mm^3 **OR** Platelet count less than 50,000/mm^3 without bleeding.	75% of previous dose
Platelet count less than 50,000/mm^3 with bleeding	50% of previous dose
Recurrent Grade 3 or 4 myelosuppression after 2 dose reductions	Discontinue
Non-hematologic toxicity	
Any Grade 3 or 4 toxicities EXCEPT mucositis or neurologic toxicity **OR** Diarrhea requiring hospitalization	75% of previous dose
Grade 3 or 4 mucositis	50% of previous dose
Renal toxicity	Withhold until creatinine clearance is 45 mL/min or greater
Grade 3 or 4 neurologic toxicity	Permanently discontinue
Recurrent Grade 3 or 4 non-hematologic toxicity after 2 dose reductions	Permanently discontinue
Severe and life-threatening Skin Toxicity	Permanently discontinue
Interstitial Pneumonitis	Permanently discontinue

Or, as directed by the registered physician.

Preparation for Administration : • Pemetrexed is a cytotoxic drug. Follow applicable special handling and disposal procedures. • Calculate the dose of Pemetrexed and determine the number of vials needed.

• Reconstitute Pemetrexed to achieve a concentration of 25mg/m2L as follows:

> Reconstitute each 100-mg vial with 4.2mL of 0.9% Sodium Chloride Injection, USP (preservative-free)

> Reconstitute each 500-mg vial with 20mL of 0.9% Sodium Chloride Injection, USP (preservative-free)

> Do not use Calcium-containing solutions for reconstitution.

• Gently swirl each vial until the powder is completely dissolved. The resulting solution is clear and ranges in color from. • Store reconstituted, preservative-free product under refrigerated conditions (2°-8°C) for no longer than 24 hours from the time of reconstitution. Discard vial after 24 hours.

• Inspect reconstituted product visually for particulate matter and discoloration prior to further dilution. If particulate matter is observed, discard vial. • Withdraw the calculated dose of Pemetrexed from the vial(s) and discard vial with any unused portion. • Further dilute Pemetrexed with 0.9% Sodium Chloride Injection (preservative-free) to achieve a total volume of 100mL for intravenous infusion. • Store diluted, reconstituted product under refrigerated conditions (2°-8°C) for no more than 24 hours from the time of reconstitution. Discard after 24 hours.

Contraindication : Pemetrexed is contraindicated in patients with a history of severe hypersensitivity reaction to Pemetrexed.

Precaution : **Myelosuppression and Increased Risk of Myelosuppression without Vitamin Supplementation :** Pemetrexed can cause severe myelosuppression resulting in a requirement for transfusions and which may lead to neutropenic infection. The risk of myelosuppression is increased in patients who do not receive vitamin supplementation. Supplementation with oral folic acid and intramuscular vitamin B12 should be initiated prior to the first dose of Pemetrexed; vitamin supplementation should be continued during treatment and for 21 days after the last dose of Pemetrexed to reduce the severity of hematologic and gastrointestinal toxicity of Pemetrexed.

Renal Failure : Pemetrexed can cause severe, and sometimes fatal, renal toxicity. The incidence of renal failure in clinical studies in which patients received Pemetrexed as a single agent ranged from 0.4% to 0.6%. Creatinine clearance should be determined before each dose and periodically monitored renal function during treatment with Pemetrexed. It should be withheld in patients with a creatinine clearance of less than 45mL/minute.

Bullous and Exfoliative Skin Toxicity : Serious and sometimes fatal, bullous, blistering and exfoliative skin toxicity, including cases suggestive of Stevens-Johnson Syndrome/Toxic epidermal necrolysis can occur with Pemetrexed. It should be permanently discontinued for severe and life-threatening bullous, blistering or exfoliating skin toxicity.

Interstitial Pneumonitis : Serious interstitial pneumonitis, including fatal cases, can occur with Pemetrexed treatment. Pemetrexed should be withheld for acute onset of new or progressive unexplained pulmonary symptoms such as dyspnea, cough, or fever pending diagnostic evaluation. If pneumonitis is confirmed, Pemeta should be permanently discontinued.

Radiation Recall : Radiation recall can occur with Pemetrexed in patients who have received radiation weeks to years previously. Patients should be monitored for inflammation or blistering in areas of previous radiation treatment. Pemetrexed should be permanently discontinued for signs of radiation recall.

Increased Risk of Toxicity with Ibuprofen in Patients with Renal Impairment : Exposure to Pemetrexed is increased in patients with mild to moderate renal impairment who take concomitant Ibuprofen, increasing the risks of adverse reactions of Pemetrexed. In patients with Creatinine clearances between 45mL/min and 79mL/min, Ibuprofen administration should be avoided for 2 days before, the day of, and 2 days following administration of Pemetrexed. If concomitant Ibuprofen use cannot be avoided, patients should be monitored more frequently for Pemetrexed adverse reactions, including myelosuppression, renal, and gastrointestinal toxicity.

Side Effects : • Myelosuppression • Renal failure • Bullous and exfoliative skin toxicity • Interstitial pneumonitis • Radiation recall

Use in pregnancy and lactation : can cause fetal harm when administered to a pregnant woman. There are no available data on Pemetrexed use in pregnant women. Pregnant women should be advised of the potential risk to a fetus. **Lactation :** There is no information regarding the presence of Pemetrexed or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production. Because of the potential for serious adverse reactions in breastfed infants from Pemetrexed, advise women not to breastfeed during treatment with Pemetrexed and for one week after last dose.

Females and Males of Reproductive Potential :

Contraception: Females : Pemetrexed can cause fetal harm when administered to a pregnant woman. Because of the potential for genotoxicity, advise females of reproductive potential to use effective contraception during treatment with Pemetrexed for at least 6 months after the final dose of Pemeta.

Males : Because of the potential for genotoxicity, advise males with female partners of reproductive potential to use effective contraception during treatment with Pemetrexed and for 3 months after the final dose.

Infertility : Males : Pemetrexed may impair fertility in males of reproductive potential. It is not known whether these effects on fertility are reversible.

Pediatric Use : The safety and effectiveness of Pemetrexed in pediatric patients have not been established.

Drug interactions : **Effects of Ibuprofen on Pemetrexed :** Ibuprofen increases exposure (AUC) of Pemetrexed. In patients with creatinine clearance between 45mL/min and 79mL/min: • Avoid administration of Ibuprofen for 2 days before, the day of, and 2 days following administration of Pemetrexed. • Monitor patients more frequently for myelosuppression, renal, and gastrointestinal toxicity, if concomitant administration of Ibuprofen cannot be avoided.

Overdose : No drugs are approved for the treatment of Pemetrexed overdose. Based on animal studies, administration of Leucovorin may mitigate the toxicities of Pemetrexed overdosage. It is not known whether Pemetrexed is dialyzable.

Storage : Store below 30°C in a cool and dry place, away from sunlight. Keep out of the reach of children.

Packing :

Pemeta : Each box contains one vial of 100mg Pemetrexed USP lyophilized powder for IV infusion.

Pemeta-500 : Each box contains one vial of 500mg Pemetrexed USP lyophilized powder for IV infusion.