Common: Urticaria, allergic reaction/hypersensitivity, erythema multiforme, pruritus.
Cardiovascular and cerebrovascular: Uncommon: Myocardial infarction, angina pectoris, cerebrovascular accident, arrhythmias, transient ischaemic attack. (Usually when given in combination with other cytotoxic agents and with preexisting cardiovascular risk.) Common: Chest pain.

WARNING AND PRECAUTIONS

Requirement for Premedication and Concomitant Medication to Reduce Toxicity

Vitamin Supplementation

Prior to treatment with PEMETRA™, initiate supplementation with oral folic acid and intramuscular vitamin B12 to reduce the severity of hematologic and gastrointestinal toxicity of PEMETRA™. Do not substitute oral vitamin B_{12} for intramuscular vitamin B_{12}. In clinical studies, the incidence of the following Grade 3-4 toxicities were higher in patients with mesothelioma who were never supplemented as compared to patients who were fully supplemented with folic acid and vitamin B12 prior to and throughout PEMETRA™ treatment: neutropenia [38% versus 23%], thrombocytopenia [9% versus 5%], febrile neutropenia [9% versus 0.6%], and infection with neutropenia [6% versus. 0].*Corticosteroids* Administer dexamethasone the day before, the day of, and the day after PEMETRA™ administration.

Bone Marrow Suppression

PEMETRA™ 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

PEMETRA™ is primarily eliminated unchanged by renal excretion. No dosage adjustment is needed in patients with creatinine clearance = 45 mL/min. Insufficient numbers of patients have been studied with creatinine clearance <45 mL/min to give a dose recommendation. Therefore, PEMETRA™ should not be administered to patients whose creatinine clearance is <45 mL/min. One patient with severe renal impairment (creatinine clearance 19 mL/min) who did not receive folic acid and vitamin B12 died of drug-related toxicity following administration of PEMETRA™ alone.

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

Caution should be used when administering NSAIDs concurrently with PEMETRA™ to patients with mild to moderate renal insufficiency (creatinine clearance from 45 to 79 mL/min).

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/mm3, the platelet count is = 100,000 cells/mm3, and creatinine clearance is
45 mL/min.

Pregnancy Category D

Based on its mechanism of action, PEMETRA™ can cause fetal harm when administered to a pregnant woman. Pemetrexed administered intraperitoneally to mice during organogenesis was embryotoxic, fetotoxic and teratogenic in mice at greater than 1/833rd the recommended human dose. If PEMETRA™ 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 avoid becoming pregnant. Women should be advised to use effective contraceptive measures to prevent pregnancy during treatment with PEMETRA™.

DRUG INTERACTION

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

Although ibuprofen (400 mg four times a day) can decrease the clearance of pemetrexed, it can be administered with PEMETRA™ in patients with normal renal function (creatinine clearance = 80 mL/min). No dose adjustment of PEMETRA™ is needed with concomitant NSAIDs in patients with normal renal function.

Caution should be used when administering NSAIDs concurrently with PEMETRA™ to patients with mild to moderate renal insufficiency (creatinine clearance from 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 PEMETRA™. In the absence of data regarding potential interaction between PEMETRA™ and NSAIDs with longer half-lives (e.g., meloxicam, nabumetone), patients taking these NSAIDs should interrupt dosing for at least 5 days before, the day of, and 2 days following PEMETRA™ administration. If concomitant administration of NSAIDs is necessary, patients should be monitored closely for toxicity, especially myelosuppression, renal, and gastrointestinal toxicity.
Nephrotoxic Drugs

PEMETRA™ 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 PEMETRA™. Concomitant administration of substances that are also tubularly secreted (e.g., probenecid) could potentially
result in delayed clearance of PEMETRA™.

USE IN SPECIAL POPULATION

Pregnancy

Teratogenic Effects – Pregnancy Category D

Based on its mechanism of action, PEMETRA™ can cause fetal harm when administered to a pregnant woman. There are no adequate and well controlled studies of PEMETRA™ in pregnant women. Pemetrexed was embryotoxic, fetotoxic, and teratogenic in mice. In mice, repeated intraperitoneal doses of pemetrexed when given during organogenesis caused fetal malformations (incomplete ossification of talus and skull bone; about 1/833rd the recommended intravenous human dose on a mg/m2 basis), and cleft palate (1/33rd the recommended intravenous human dose on a mg/m2 basis). Embryotoxicity was characterized by increased embryo-fetal deaths and reduced litter sizes. If PEMETRA™ 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 PEMETRA™.

Nursing Mothers

It is not known whether PEMETRA™ 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 PEMETRA™, a decision should be made to discontinue nursing or discontinue the drug, taking into account the importance of the drug for the mother.

Pediatric Use

Efficacy of PEMETRA™ in pediatric patients has not been demonstrated. PEMETRA™ was administered as an intravenous infusion over 10 minutes on Day 1 of a 21 day cycle to pediatric patients with recurrent solid tumors in a Phase 1 study (32 patients) and a Phase 2 study (72 patients). All patients received pretreatment with vitamin B12 and folic acid supplementation and dexamethasone. The dose escalation in the Phase 1 study determined the maximum tolerated dose was 1910 mg/m2 and this dose (or 60 mg/kg for patients <12 months old) was evaluated in the Phase 2 study of patients with relapsed or refractory osteosarcoma, Ewing sarcoma/peripheral PNET, rhabdomyosarcoma, neuroblastoma, ependymoma, medulloblastoma/supratentorial PNET, or non-brainstem high grade glioma. No responses were observed among the 72 patients in this Phase 2 trial. The most common toxicities reported were hematological (leukopenia, neutropenia/granulocytopenia, anemia, thrombocytopenia, and lymphopenia), liver function abnormalities (increased ALT/AST), fatigue, and nausea.

The single dose pharmacokinetics of PEMETRA™ administered in doses ranging from 400 to 2480 mg/m2 were evaluated in the Phase 1 trial in 22 patients (13 males and 9 females) aged 4 to 18 years (average age 12 years). Pemetrexed exposure (AUC and Cmax) appeared to increase proportionally with dose. The average pemetrexed clearance (2.30 L/h/m2) and half-life (2.3 hours) in pediatric patients were comparable to values reported in adults.

Geriatric Use

PEMETRA™ 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. Renal function monitoring is recommended with administration of PEMETRA™. No dose reductions other than those recommended for all patients are necessary for patients 65 years of age or older.

Patients with Hepatic Impairment

There was no effect of elevated AST, ALT, or total bilirubin on the pharmacokinetics of pemetrexed. However, no formal studies have been conducted to examine the pharmacokinetics of pemetrexed in patients with hepatic impairment.

Patients with Renal Impairment

PEMETRA™ is known to be primarily excreted by the kidneys. Decreased renal function will result in reduced clearance and greater exposure (AUC) to PEMETRA™ compared with patients with normal renal function. Cisplatin coadministration with PEMETRA™ has not been studied in patients with moderate renal impairment.

OVERDOSE

There have been few cases of PEMETRA™ 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.

The ability of PEMETRA™ to be dialyzed is unknown.

STORAGE

Store powder at 25°C (77°F); excursions permitted to 15-30°C.
Store reconstituted and infusion solution at refrigerated, 2-8°C (38-46°F).

PRESENTATION

Pemetrexed for Injection 100mg & 500mg is presented as a single dose vial for IV Use only.

HANDLING AND DISPOSAL

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published. There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

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Getwell Oncology Pvt. Ltd.
(A unit of Getwell)
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0700PPDM0615-00

GETWELL

For the use of Registered Medical Practitioner or Hospital or a Laboratory only.

Pemetrexed for Injection

PEMETRA™

FOR INTRAVENOUS USE ONLY

Rx only

WARNING

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.

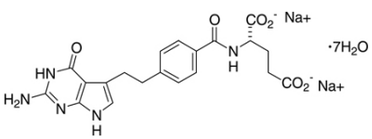
NSAIDs with renal insufficiency: Use caution in patients with mild to moderate renal insufficiency (CrCl 45-79 mL/min).

Lab monitoring: Do not begin next cycle unless ANC ≥1500 cells/mm3, platelets ≥100,000 cells/mm3, and CrCl ≥45 mL/min. (5.5)

Pregnancy: Fetal harm can occur when administered to a pregnant woman. Women should be advised to use effective contraception measures to prevent pregnancy during treatment with PEMETRA™.

DESCRIPTION

Pemetrexed disodium heptahydrate has the chemical name L-Glutamic acid, *N*-[4-[2-(2-amino-4,7-dihydro-4-oxo-1*H*-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 $C_{20}H_{19}N_5Na_2O_6{\cdot}7H_2O$ and a molecular weight of 597.49. The structural formula is as follows:



COMPOSITION

PEMETRA™ is presented in 2 strengths, 100mg/vial and 500mg/vial supplied in sterile, single use vial, boxed individually

Each vial of PEMETRA™ 100mg/vial contains		
Pemetrexed Disodium IP		
Eq. to Pemetrexed	-	100mg
Mannitol IP	-	106mg
Hydrochloric Acid IP/Sodium Hydroxide IP to Adjust pH		

Each vial of PEMETRA™ 500mg/vial contains		
Pemetrexed Disodium IP		
Eq. to Pemetrexed	-	500mg
Mannitol IP	-	500mg
Hydrochloric Acid IP/Sodium Hydroxide IP to Adjust pH		

CLINICAL PHARMACOLOGY & MECHANISM OF ACTION

PEMETRA™ (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 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.

PHARMCOKINETICS & PHARMACODYNAMICS

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. Absolute neutrophil counts (ANC) following single-agent administration of PEMETRA™ to patients not receiving folic acid and vitamin B12 supplementation were characterized using population pharmacodynamic analyses. Severity of hematologic toxicity, as measured by the depth of the ANC nadir, correlates with the systemic exposure, or area under the curve (AUC) of pemetrexed. It was also observed that lower ANC nadirs occurred in patients with elevated baseline cystathionine or homocysteine concentrations. The levels of these substances can be reduced by folic acid and vitamin B12 supplementation. There is no cumulative effect of pemetrexed exposure on ANC nadir over multiple treatment cycles.

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 mcghr/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 PEMETRA™ 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) 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).

The pharmacokinetics of pemetrexed in special populations were examined in about 400 patients in controlled and single arm studies.

In vitro studies indicate that pemetrexed is a substrate of OAT3 (organic anion transporter 3), a transporter that may play a role in active secretion of pemetrexed.

Effect of Age, Gender or Race

No effect of age on the pharmacokinetics of pemetrexed was observed over a range of 26 to 80 years.

The pharmacokinetics of pemetrexed were not different in male and female patients.

The pharmacokinetics of pemetrexed were similar in Caucasians and patients of African descent. Insufficient data are available to compare pharmacokinetics for other ethnic groups.

Effect of Hepatic Insufficiency

There was no effect of elevated AST, ALT, or total bilirubin on the pharmacokinetics of pemetrexed. However, studies of hepatically impaired patients have not been conducted.

Effect of Renal Insufficiency

Pharmacokinetic analyses of pemetrexed included 127 patients with reduced renal function. Plasma clearance of pemetrexed decreases as renal function decreases, with a resultant increase in systemic exposure. Patients with creatinine clearances of 45, 50, and 80 mL/min had 65%, 54%, and 13% increases, respectively in pemetrexed total systemic exposure (AUC) compared to patients with creatinine clearance of 100 mL/min.

Effect of Third Space Fluid

The effect of third space fluid, such as pleural effusion and ascites, on PEMETRA™ is not fully defined. A study of PEMETRA™ 500 mg/m2 was performed in 31 solid tumor patients with stable third space fluid (All but 2 of the 31 patients included in study had mild or moderate amounts of third space fluid). Moderate pleural effusion was defined in the study as less than 1/3 the way up on one side with obscuring of the entire hemidiaphragm. Moderate ascites was defined as that detectable on physical exam. The pemetrexed plasma concentrations in these patients were comparable to those observed in previous clinical trials in patients without third space fluid collections. Thus, drainage of mild or moderate third space fluid collection prior to PEMETRA™ treatment should be considered, but is probably not necessary. The effect of severe third space fluid on pharmacokinetics is not known.

Effect of Ibuprofen

Ibuprofen doses of 400 mg four times a day reduce pemetrexed's clearance by about 20% (and increase AUC by 20%) in patients with normal renal function. The effect of greater doses of ibuprofen on pemetrexed pharmacokinetics is unknown.

Effect of Aspirin

Aspirin, administered in low to moderate doses (325 mg every 6 hours), does not affect the pharmacokinetics of pemetrexed. The effect of greater doses of aspirin on pemetrexed pharmacokinetics is unknown.

Effect of Cisplatin

Cisplatin does not affect the pharmacokinetics of pemetrexed and the pharmacokinetics of total platinum are unaltered by pemetrexed.

Effect of Vitamins

Coadministration of oral folic acid or intramuscular vitamin B12 does not affect the pharmacokinetics of pemetrexed.

Drugs Metabolized by Cytochrome P450 Enzymes

Results from in vitro studies with human liver microsomes predict that pemetrexed would not cause clinically significant inhibition of metabolic clearance of drugs metabolized by CYP_3A, CYP_2D_6, CYP_2C_9, and CYP_1A_2.

NON CLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity studies have been conducted with pemetrexed. Pemetrexed was clastogenic in the in vivo micronucleus assay in mouse bone marrow but was not mutagenic in multiple in vitro tests (Ames assay, CHO cell assay). Pemetrexed administered at i.v. doses of 0.1 mg/kg/day or greater to male mice (about 1/1666 the recommended human dose on a mg/m2 basis) resulted in reduced fertility, hypospermia, and testicular atrophy.

INDICATION

Nonsquamous Non-Small Cell Lung Cancer – Combination with Cisplatin

PEMETRA™ 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

PEMETRA™ 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

PEMETRA™ 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

PEMETRA™ 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

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

DOSAGE AND ADMINISTRATION

Combination Use with Cisplatin for Nonsquamous Non-Small Cell Lung Cancer or Malignant Pleural Mesothelioma

The recommended dose of PEMETRA™ is 500 mg/m^2 administered as an intravenous infusion over 10 minutes on Day 1 of each 21-day cycle. The recommended dose of cisplatin is 75 mg/m^2 infused over 2 hours beginning approximately 30 minutes after the end of PEMETRA™ administration. See cisplatin package insert for more information.

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

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

Premedication Regimen and Concurrent Medications

Vitamin Supplementation

Instruct patients to initiate folic acid 400 mcg to 1000 mcg orally once daily beginning 7 days before the first dose of PEMETRA™. Continue folic acid during the full course of therapy and for 21 days after the last dose of PEMETRA™.

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

Corticosteroids

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

Laboratory Monitoring and Dose Reduction/Discontinuation Recommendations

Monitoring

Complete blood cell counts, including platelet counts, should be performed on all patients receiving PEMETRA™. 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 = 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 guidelines in Tables 1-3, which are suitable for using PEMETRA™ as a single-agent or in combination with cisplatin.

Table 1: Dose Reduction for PEMETRA™(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 with bleeding a, regardless of nadir ANC.	50% of previous dose (pemetrexed and cisplatin).

a 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 PEMETRA™(single-agent or in combination) and Cisplatin – Nonhematologic Toxicities[a,b]

	Dose of PEMETRA™(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 PEMETRA™and cisplatin are described in Table 3. Patients should discontinue therapy if Grade 3 or 4 neurotoxicity is experienced.

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

CTC Grade	Dose of PEMETRA™ (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

Discontinuation Recommendation

PEMETRA™ 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.

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

Males:	$\frac{[140 - \text{Age in years}] \times \text{Actual Body Weight (kg)}}{72 \times \text{Serum Creatinine (mg/dL)}}$ = mL/min
Females:	Estimated creatinine clearance for males × 0.85

Caution should be exercised when administering PEMETRA™ concurrently with NSAIDs to patients whose creatinine clearance is <80 mL/min.

Preparation and Administration Precautions

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

Preparation for Intravenous Infusion Administration

· Use aseptic technique during the reconstitution and further dilution of PEMETRA™ for intravenous infusion administration.

· Calculate the dose of PEMETRA™. and determine the number of vials needed. Vials contain either 100 mg or 500 mg of PEMETRA™. The vials contain an excess of PEMETRA™. to facilitate delivery of label amount.

· 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 PEMETRA™. 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. FURTHER DILUTION IS REQUIRED.

· 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.

· An appropriate quantity of the reconstituted PEMETRA™. 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. PEMETRA™. is administered as an intravenous infusion over 10 minutes.

· Chemical and physical stability of reconstituted and infusion solutions of PEMETRA™. were demonstrated for up to 24 hours following initial reconstitution, when stored refrigerated. When prepared as directed, reconstitution and infusion solutions of PEMETRA™. 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). PEMETRA™. 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 PEMETRA™ with other drugs and diluents has not been studied, and therefore is not recommended. PEMETRA™ is compatible with standard polyvinyl chloride (PVC) administration sets and intravenous solution bags.

CONTRAINDICATIONS

PEMETRA™ is contraindicated in patients who have a history of severe hypersensitivity reaction to pemetrexed.

ADVERSE EVENTS

The most common adverse reactions (incidence =20%) with single-agent use are fatigue, nausea, and anorexia. Additional common adverse reactions when used in combination with cisplatin include vomiting, neutropenia, leukopenia, anaemia, stomatitis/pharyngitis, thrombocytopenia, and constipation.

Haematological: Very common: Anaemia, leukopenia, thrombocytopenia, neutropenia. Common: Febrile neutropenia and infection without neutropenia. Uncommon: Pancytopenia. Gastro-intestinal: Very common: Nausea, vomiting, stomatitis/pharyngitis, anorexia, diarrhoea, constipation. Common: Dyspepsia, abdominal pain. Rare: Colitis.

General: Very common: Fatigue. Common: Fever, conjunctivitis. Metabolism and nutrition: Common: Dehydration.

Nervous system: Very common: Neuropathy - sensory. Common: Neuropathy - motor, dysgeusia.

Renal and urinary: Very common: Creatinine elevation, creatinine clearance decreased. Common: Renal failure.

Hepatobiliary: Common: SGPT (ALT) elevation and SGOT (AST) elevation, increased GGT. Rare: Cases of hepatitis, potentially serious, have been reported during trials.

Skin and subcutaneous tissue: Very common: Rash/desquamation, alopecia.