

Pemetrexed Disodium for Injection

Lyophilised

SYMXYX[®] 100/500

ExttqYxf 100/500

COMPOSITION

SYMXYX[®] 100
Each Vial contains
Pemetrexed Disodium
Equivalent to Pemetrexed 100mg

SYMXYX[®] 500
Each Vial contains
Pemetrexed Disodium
Equivalent to Pemetrexed 500mg

DESCRIPTION

Pemetrexed disodium heptahydrate has the chemical name L-Glutamic acid, N-[4-[(2-(2-amino-4, 7-dihydro-4-oxo-1H pyrrolo [2, 3-d]pyrimidin-5-ylthio)benzoyl]-, disodium salt, heptahydrate. It is a white to almost-white solid with a molecular formula of $C_{12}H_{14}N_4Na_2O_7 \cdot 7H_2O$ and a molecular weight of 597.49. Pemetrexed is supplied as a sterile lyophilized powder for intravenous infusion available in single-dose vials.

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 folypolyglutamate 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

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 solid tumors. Total systemic exposure (AUC) and maximum plasma concentration (C_{max}) of Pemetrexed increases proportionally with dose. The pharmacokinetics of Pemetrexed does 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).

INDICATIONS AND USAGE

Nonsquamous Non-Small Cell Lung Cancer (Combination with Cisplatin) - SYMXYX[®] 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) - SYMXYX[®] 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) - SYMXYX[®] 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 - SYMXYX[®] 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.

Clinical Studies

Non-Small Cell Lung Cancer (NSCLC) - Combination with Cisplatin. A multi-center, randomized, open-label study in 1725 chemo-naïve patients with Stage IIb/IV NSCLC was conducted to compare the overall survival following treatment with Pemetrexed in combination with Cisplatin (AC) versus Gemcitabine in combination with Cisplatin (GC). Pemetrexed was administered intravenously over 10 minutes at a dose of 500 mg/m² with Cisplatin administered intravenously at a dose of 75 mg/m² after Pemetrexed administration, on Day 1 of each 21-day cycle. Gemcitabine was administered at a dose of 1250 mg/m² on Day 1 and Day 8, and Cisplatin was administered intravenously at a dose of 75 mg/m² after administration of Gemcitabine, on Day 1 of each 21-day cycle. Treatment was administered up to a total of 6 cycles, and patients in both treatment arms received folic acid, vitamin B₁₂, and Dexamethasone. The primary endpoint in this study was overall survival. The median survival time was 10.3 months in the Pemetrexed plus Cisplatin treatment arm and 10.3 months in the gemcitabine plus Cisplatin arm, with an adjusted hazard ratio of 0.94. **Table 1: First-Line Therapy: Efficacy in NSCLC - ITT Population**

	Pemetrexed plus Cisplatin (N=862)	Gemcitabine plus Cisplatin (N=863)
Median overall survival (95% CI)	10.3 mos (9.8-11.2)	10.3 mos (9.6-10.9)
Adjusted hazard ratio (HR) ^{a,b} (95% CI)	0.94 (0.84-1.05)	
Median progression-free survival (95% CI)	4.8 mos (4.6-5.3)	5.1 mos (4.6-5.5)
Adjusted hazard ratio (HR) ^{a,b} (95% CI)	1.04 (0.94-1.15)	
Overall response rate (95% CI)	27.1% (24.2-30.1)	24.7% (21.8-27.6)

^a Adjusted for gender, stage, basis of diagnosis, and performance status.
^b A HR that is less than 1.0 indicates that survival is better in the AC arm than in the GC arm. Alternatively, a HR that is greater than 1.0 indicates survival is better in the GC arm than in the AC arm.

Non-Small Cell Lung Cancer - Maintenance

A multi-center, randomized, double-blind, placebo-controlled study was conducted in 663 patients with Stage IIb/IV NSCLC who did not progress after four cycles of platinum-based chemotherapy. Patients who did not progress were randomized 2:1 to receive Pemetrexed or placebo immediately following platinum-based chemotherapy. Pemetrexed was administered intravenously over 10 minutes at a dose of 500 mg/m² on Day 1 of each 21-day cycle, until disease progression. Patients in both study arms received folic acid, vitamin B₁₂, and dexamethasone.

Patients received a median of 5 cycles of Pemetrexed and 3.5 cycles of placebo. In the overall study population, Pemetrexed was statistically superior to placebo in terms of overall survival (OS) (median 13.4 months versus 10.6 months, HR=0.79 (95% CI: 0.65-0.95), p-value=0.012) and PFS (median 4.0 months versus 2.0 months, HR=0.60 (95% CI: 0.49-0.73), p-value < 0.00001). A difference in treatment outcomes was observed according to histologic classification. For the population of patients with nonsquamous NSCLC, Pemetrexed was superior to placebo for OS (median 15.5 months versus 10.3 months, HR=0.70 (95% CI: 0.56-0.88)) and PFS (median 4.4 months versus 1.8 months, HR=0.47 (95% CI: 0.37-0.60)). For the population of patients with squamous NSCLC, Pemetrexed did not improve OS compared to placebo (median 9.9 months versus 10.8 months, HR=1.07 (95% CI: 0.77-1.50)) or PFS (median 2.4 months versus 2.5

Efficacy Parameter^{a,b}	Pemetrexed (N=441)	Placebo (N=222)
Median overall survival (95% CI)	13.4 mos (11.9-15.9)	10.6 mos (8.7-12.0)
Hazard ratio (HR) ^c (95% CI)	0.79 (0.65-0.95)	
p-value	p=0.012	
Median progression-free survival (95% CI)	4.0 mos (3.1-4.4)	2.0 mos (1.5-2.8)
Hazard ratio (HR) ^c (95% CI)	0.60 (0.49-0.73)	
p-value	p < 0.0	0001

^a PFS and OS were calculated from time of randomization, after completion of 4 cycles of induction platinum-based chemotherapy.
^b Values for PFS given based on independent review (Pemetrexed N=387, Placebo N=194).
^c Unadjusted hazard ratios are provided. A HR < 1.0 indicates that the result is better in the Pemetrexed arm than in the placebo arm.

months, HR=1.03 (95% CI: 0.71-1.49)). This difference in treatment effect for Pemetrexed based on histology demonstrating lack of benefit in squamous cell histology was also observed in the first-line and second line studies.

Efficacy results for the overall patient population are presented in Table 2.

Table 2: Maintenance Therapy: Efficacy of Pemetrexed versus Placebo in NSCLC - ITT Population

CONTRAINDICATIONS

SYMXYX[®] is contraindicated in patients who have a history of severe hypersensitivity reaction to Pemetrexed or to any other ingredient used in the formulation.

WARNINGS AND PRECAUTIONS

- Premedication Regimen**
Need for Folate and Vitamin B₁₂ Supplementation - Patients treated with Pemetrexed must 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 in clinical trials. 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 non-hematologic 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. Insufficient numbers of patients have been studied with creatinine clearance < 45 mL/min to give a dose recommendation. 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 and other NSAIDs concurrently with Pemetrexed to patients with mild to moderate renal insufficiency (creatinine clearance from 45 to 79 mL/min).
- Required Laboratory Monitoring** - Patients should not begin a new cycle of treatment unless the ANC is ≥ 1500 cells/mm³, the platelet count is $\geq 100,000$ cells/mm³, and creatinine clearance is ≥ 45 mL/min.
- Pregnancy Category D** - Based on its mechanism of action, Pemetrexed can cause fetal harm when administered to a pregnant woman. 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 avoid becoming pregnant. Women should use effective contraceptive measures to prevent pregnancy during 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.
- Third Space Fluid** - The effect of third space fluid, such as pleural effusion and ascites, on Pemetrexed is unknown. In patients with clinically significant third space fluid, consideration should be given to draining the effusion prior to Pemetrexed administration.
- Nonclinical 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, hypospemia, and testicular atrophy.

SIDE EFFECTS

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reactions rates cannot be directly compared to rates in other clinical trials and may not reflect the rates observed in clinical practice.

Non-Small Cell Lung Cancer (NSCLC) - Combination with Cisplatin

Table 3 provides the frequency and severity of adverse reactions that have been reported in > 5% of 839 patients with NSCLC who were randomized to study and received Pemetrexed plus Cisplatin and 830 patients with NSCLC who were randomized to study and received gemcitabine plus Cisplatin. Patients in both treatment groups were fully supplemented with folic acid and vitamin B₁₂.

Table 3: Adverse Reactions in Fully Supplemented Patients Receiving Pemetrexed plus Cisplatin in NSCLC^a

Reaction^b	Pemetrexed/Cisplatin (N=839)		Gemcitabine/Cisplatin (N=830)	
	All Grades Toxicity (%)	Grade 3-4 Toxicity (%)	All Grades Toxicity (%)	Grade 3-4 Toxicity (%)
All Adverse Reactions	90	37	91	53
LABORATORY HEMATOLOGIC				
Anemia	33	6	46	10
Neutropenia	29	15	38	27
Leukopenia	18	5	21	8
Thrombocytopenia	10	4	27	13
RENAL				
Creatinine elevation	10	1	7	1
CLINICAL CONSTITUTIONAL SYMPTOMS				
Fatigue	43	7	45	5
GASTROINTESTINAL				
Nausea	56	7	53	4
Vomiting	40	6	36	6
Anorexia	27	2	24	1
Constipation	21	1	20	0
Stomatitis/Pharyngitis	14	1	12	0
Diarrhea	12	1	13	2
Dyspepsia/Heartburn	5	0	6	0
NEUROLOGY				
Neuropathy-sensory	9	0	12	1
Taste disturbance	8	0 ^c	9	0 ^c
DERMATOLOGY/SKIN				
Alopecia	12	0 ^c	21	1 ^c
Rash/Desquamation	7	0	8	1

^a For the purpose of this table a cut off of 5% was used for inclusion of all events where the reporter considered a possible relationship to Pemetrexed.
^b Refer to NCI CTC Criteria version 2.0 for each Grade of toxicity.
^c According to NCI CTC Criteria version 2.0, this adverse event term should only be reported as Grade 1 or 2.

No clinically relevant differences in adverse reactions were seen in patients based on histology.

The following additional adverse reactions were observed in patients with non-small cell lung cancer randomly assigned to receive Pemetrexed plus Cisplatin. Incidence 1% to 5%
Body as a Whole - febrile neutropenia, infection, pyrexia
General Disorders - dehydration
Metabolism and Nutrition - increased AST, increased ALT
Renal - creatinine clearance decrease, renal failure
Special Senses - conjunctivitis

Incidence Less than 1%

Cardiovascular - arrhythmia
General Disorders - chest pain
Metabolism and Nutrition - increased GGT
Neurology - motor neuropathy

Effects of Vitamin Supplementations

Table 4 compares the incidence (percentage of patients) of CTC Grade 3/4 toxicities in patients who received vitamin supplementation with daily folic acid and vitamin B₁₂ from the time of enrollment in the study (fully supplemented) with the incidence in patients who never received vitamin supplementation (never supplemented) during the study in the Pemetrexed plus Cisplatin arm.

Table 4: Selected Grade 3/4 Adverse Events Comparing Fully Supplemented versus Never Supplemented Patients in the Pemetrexed plus Cisplatin arm (% incidence)

Adverse Event^a (%)	Fully Supplemented Patients (N=168)	Never Supplemented Patients (N=32)
Neutropenia/granulocytopenia	23	38
Thrombocytopenia	5	9
Vomiting	11	31
Febrile neutropenia	1	9
Infection with Grade 3/4 neutropenia	0	6
Diarrhea	4	9

^a Refer to NCI CTC criteria for lab and non-laboratory values for each grade of toxicity (Version 2.0).

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ExlffqYxt 100/500

The following adverse events were greater in the fully supplemented group compared to the never supplemented group: hypertension (11%, 3%), chest pain (8%, 6%), and thrombosis/embolism (6%, 3%).

These reactions have occurred with Pemetrexed when used as a single-agent and in combination therapies.

Gastrointestinal - colitis
General Disorders and Administration Site Conditions - edema
Injury, poisoning, and procedural complications - Radiation recall has been reported in patients who have previously received radiotherapy.
Respiratory - interstitial pneumonitis

DRUG INTERACTIONS

Ibuprofen and other Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) : Patients with mild to moderate renal insufficiency should avoid taking Ibuprofen and other NSAIDs with short elimination half-lives for a period of 2-5 days before, the day of, and 2 days following administration of Pemetrexed.

If concomitant administration of an NSAID is necessary, patients should be monitored closely for toxicity, especially myelosuppression, renal, and gastrointestinal toxicity.

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.

DOSAGE AND ADMINISTRATION

Combination Use with Cisplatin

Nonsquamous Non-Small Cell Lung Cancer and Malignant Pleural Mesothelioma - The recommended dose of SYMXYX[®] is 500 mg/m² administered as an intravenous infusion over 10 minutes on Day 1 of each 21-day cycle. The recommended dose of Cisplatin is 75 mg/m² infused over 2 hours beginning approximately 30 minutes after the end of SYMXYX[®] administration. Patients should receive appropriate hydration prior to and/or after receiving Cisplatin. (See Cisplatin package insert for more information).

Single-Agent Use

Nonsquamous Non-Small Cell Lung Cancer - The recommended dose of SYMXYX[®] is 500 mg/m² administered as an intravenous infusion over 10 minutes on Day 1 of each 21-day cycle.

Laboratory Monitoring and Dose Reduction/Discontinuation Recommendations
Monitoring Complete blood cell counts, including platelet counts, should be performed on all patients receiving SYMXYX[®]. 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 $\geq 100,000$ 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 non-hematologic 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 5-7, which are suitable for using SYMXYX[®] as a single-agent or in combination with Cisplatin.

Table 5: Dose Reduction for Pemetrexed (single-agent or in combination) and Cisplatin - Hematologic Toxicities

Nadir ANC < 500/mm ³ and nadir platelets $\geq 50,000$ /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 \geq CTC Grade 2 bleeding.	

If patients develop non-hematologic 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 6.

Table 6: 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 8).		

In the event of neurotoxicity, the recommended dose adjustments for Pemetrexed and Cisplatin are described in Table 7. Patients should discontinue therapy if Grade 3 or 4 neurotoxicity is experienced.

Table 7: Dose Reduction for Pemetrexed (single-agent or in combination) and Cisplatin - Neurotoxicity

CTC Grade	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

Discontinuation Recommendation

SYMXYX[®] 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, Pemetrexed 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 ¹²⁵I-iothalamate (DTPA) serum clearance method:

$$\text{Males: } [140 - \text{Age in years}] \times \text{Actual Body Weight (kg)} / 72 \times \text{Serum Creatinine (mg/dL)} = \text{mL/min}$$

Females:

Estimated creatinine clearance for males $\times 0.85$

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

Preparation for Intravenous Infusion Administration
Use aseptic technique during the reconstitution and further dilution of SYMXYX[®] for intravenous infusion administration.

Calculate the dose of SYMXYX[®] and determine the number of vials needed. Vials contain either 100 mg or 500 mg of SYMXYX[®]. The vials contain an excess of SYMXYX[®] to facilitate delivery of label amount.

Reconstitute each 100-mg vial with 4.0 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 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.

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 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. SYMXYX[®] is administered as an intravenous infusion over 10 minutes.

Chemical and physical stability of reconstituted and infusion solutions were demonstrated for up to 24 hours following initial reconstitution, when stored at refrigerated (2-8°C) or ambient room temperature (25°C, excursions permitted to 15-30°C) and lighting.

Reconstitution and further dilution prior to intravenous infusion is only recommended with 0.9% Sodium Chloride Injection (preservative free). SYMXYX[®] 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. Co-administration of SYMXYX[®] with other drugs and diluents has not been studied, and therefore is not recommended. SYMXYX[®] is compatible with standard polyvinyl chloride (PVC) administration sets and intravenous solution bags.

OVERDOSAGE

There have been few cases of Pemetrexed 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 Pemetrexed to be dialyzed is unknown.

PRESENTATION AND STORAGE CONDITIONS

SYMXYX[®] is available in sterile single dose vials containing 100 mg / 500 mg of Pemetrexed.

Storage: Store below 25°C. Protect from light.

INFORMATION FOR PATIENTS

Need for Folic Acid and Vitamin B₁₂ - Patients treated with Pemetrexed must be instructed to take folic acid and vitamin B₁₂ as a prophylactic measure to reduce treatment-related hematologic and gastrointestinal toxicity.

Low Blood Cell Counts - Patients should be adequately informed of the risk of low blood cell counts and instructed to immediately contact their physician should any sign of infection develop including fever. Patients should also contact their physician if bleeding or symptoms of anemia occur.

Gastrointestinal Effects - Patients should be instructed to contact their physician if persistent vomiting, diarrhea, or signs of dehydration appear.

Concomitant Medications - Patients should be instructed to inform the physician if they are taking any concomitant prescription or over-the-counter medications including those for pain or inflammation such as non-steroidal anti-inflammatory drugs.

References

- Preventing Occupational Exposures to Antineoplastic and Other Hazardous Drugs in Health Care Settings. NIOSH Alert 2004-165.
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- American Society of Health-System Pharmacists. ASHP guidelines on handling hazardous drugs. Am J Health-Syst Pharm. 2006; 63:1172-1193.
- Polovich, M., White, J. M., & Kelleher, L. O. (eds.) 2005. Chemotherapy and biotherapy guidelines and recommendations for practice (2nd. ed.) Pittsburgh, PA: Oncology Nursing Society.

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