PRODUCT MONOGRAPH

Pemetrexed for Injection

Solution: 25 mg / mL pemetrexed (as pemetrexed disodium hemipentahydrate)

House Std.

Antineoplastic Agent

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Pr Pemetrexed for Injection
25 mg/mL, (4 mL, 20 mL, 34 mL and 40 mL)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Nonmedicinal Ingredients
Intravenous infusion	Solution, 100 mg/4 mL (25 mg / mL), 500 mg/20 mL (25 mg / mL), 850 mg/34 mL (25 mg / mL), 1000 mg/40 mL (25 mg / mL)	Citric Acid, L-Methionine, Monothioglycerol, Sodium Hydroxide, Hydrochloric Acid and Water for Injection.

INDICATIONS AND CLINICAL USE

Malignant Pleural Mesothelioma
Pemetrexed for Injection (pemetrexed disodium hemipentahydrate) in combination with cisplatin is indicated for the first-line treatment of patients with malignant pleural mesothelioma whose disease is unresectable or who are otherwise not candidates for curative surgery.

First Line – Nonsquamous Non-Small Cell Lung Cancer – Combination with Cisplatin
Pemetrexed for Injection in combination with cisplatin therapy is indicated for the initial treatment of good performance status patients with locally advanced or metastatic nonsquamous non-small cell lung cancer. See Part II: CLINICAL TRIALS.

Maintenance Therapy – Nonsquamous Non-Small Cell Lung Cancer - Monotherapy
Pemetrexed for Injection monotherapy is indicated for the maintenance treatment of locally advanced or metastatic nonsquamous non-small cell lung cancer, in good performance status patients without disease progression immediately following four cycles of first-line platinum doublet chemotherapy. See Part II: CLINICAL TRIALS.

Second Line – Nonsquamous Non-Small Cell Lung Cancer - Monotherapy
Pemetrexed for Injection monotherapy is indicated as a treatment option for patients with locally advanced or metastatic nonsquamous non-small cell lung cancer after prior chemotherapy. Approval is based on similarity of the response rate, median survival rate and 1-year survival rate, for the overall study population, between pemetrexed and docetaxel. See Part II: CLINICAL TRIALS.

Geriatrics (> 65 years of age):
The safety and effectiveness of Pemetrexed for Injection in geriatric patients has been established (see ACTION AND CLINICAL PHARMACOLOGY and Part II: CLINICAL TRIALS Sections).
Pediatrics (< 18 years of age):

The safety and effectiveness of Pemetrexed for Injection in pediatric patients have not been established.

CONTRAINDICATIONS

- Hypersensitivity to pemetrexed or to any other ingredient used in the formulation. For a complete listing, see DOSAGE FORMS, COMPOSITION AND PACKAGING Section.
- Concomitant yellow fever vaccine (see DRUG INTERACTIONS).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- Pemetrexed for Injection should only be administered by, or under the supervision of, a physician who is experienced in cancer chemotherapy and in the management of related toxicities.

- Hepatotoxicity: See WARNINGS AND PRECAUTIONS - Hepatic/Biliary.

Carcinogenesis and Mutagenesis

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/m^2 basis) resulted in reduced fertility, hypospermia, and testicular atrophy. Because pemetrexed may cause irreversible infertility, men are advised to seek counselling on sperm storage before starting treatment. See Part II: TOXICOLOGY Section.

Cardiovascular

No thorough clinical QT/QTc study was performed to rule out the effect of Pemetrexed for Injection on QT prolongation. Routine ECG assessments during clinical trials did not identify any concerns regarding QT prolongation. Serious cardiovascular and cerebrovascular events, including myocardial infarction, angina pectoris, cerebrovascular accident and transient ischemic attack have been uncommonly reported in clinical trials with pemetrexed, usually when given in combination with another cytotoxic agent. Most of the patients in whom these events have been observed had preexisting cardiovascular risk factors.

Gastrointestinal

Stomatitis, nausea, vomiting, and diarrhea are common in patients receiving pemetrexed with or without cisplatin. In rare cases gastrointestinal toxicity may lead to severe dehydration. Gastrointestinal toxicity should be vigorously managed (see ADVERSE REACTIONS – Clinical Trial Adverse Drug Reactions and DOSAGE AND ADMINISTRATION – Nonhematologic Toxicities).

Hepatic/Biliary

Serious hepatobiliary toxicity and rare cases of fatal hepatic failure, have been reported with pemetrexed alone or in association with other chemotherapeutic agents in clinical trials. Underlying risk factors for the development of hepatic toxicity including hepatic metastases

and/or underlying hepatic disease have been present in some cases. A causal relationship between pemetrexed and these events has not been established.

Hematologic

Pemetrexed can suppress bone marrow function, as manifested by neutropenia, thrombocytopenia, and anemia (or pancytopenia) (see ADVERSE REACTIONS Section); myelosuppression is usually the dose-limiting toxicity (see Laboratory Monitoring and Dose Reduction Recommendations under DOSAGE AND ADMINISTRATION Section). In clinical trials, sepsis which in some cases was fatal occurred in approximately 1% of patients. Dose reductions for subsequent cycles are based on nadir Absolute Neutrophil Count (ANC), platelet count, and maximum nonhematologic toxicity seen in the previous cycle (see Dose Reduction Recommendations under DOSAGE AND ADMINISTRATION Section).

In the Phase 3 mesothelioma clinical trial, less overall toxicity and reductions in Grade 3/4 hematologic and nonhematologic toxicities such as neutropenia, febrile neutropenia and infection with Grade 3/4 neutropenia were reported when pre-treatment with folic acid and vitamin B_{12} was administered. Prior to treatment with pemetrexed patients must receive supplementation with folic acid and intramuscular vitamin B_{12} as a prophylactic measure to reduce treatment-related toxicity (see DOSAGE AND ADMINISTRATION Section). The intramuscular vitamin B_{12} should not be substituted with an oral formulation.

Immune

Cases of hypersensitivity, including anaphylaxis, have been reported in patients treated with pemetrexed.

Renal

Serious renal events, including acute renal failure, have been reported with pemetrexed alone or in association with other chemotherapeutic agents. Most, but not all, of the patients in whom these serious renal events occurred had underlying risk factors for the development of renal events including dehydration or pre-existing hypertension or diabetes. A causal relationship between pemetrexed and these events has not been established.

Respiratory

Interstitial pneumonitis with respiratory insufficiency, sometimes fatal, has been reported in clinical trials. In patients with progressive dyspnea and cough, pemetrexed should be interrupted and prompt investigation initiated.

Cases of radiation pneumonitis have been reported in patients with radiation either prior to, during, or subsequent to their pemetrexed therapy.

Skin

Rare cases of bullous epidermolysis have been reported including Stevens-Johnson syndrome and Toxic epidermal necrolysis which in some cases were fatal.

Treatment-related adverse events of pemetrexed seen in clinical trials have been reversible. Skin rash has been reported in patients not pretreated with a corticosteroid in clinical trials.

Pretreatment with dexamethasone (or equivalent) reduces the incidence and severity of cutaneous reaction (see DOSAGE AND ADMINISTRATION Section).
Radiation recall dermatitis has been reported in patients on pemetrexed who have previously received radiotherapy. Severity of symptoms can vary from mild dermatitis to necrosis (see REFERENCES Barlesi et al, Hureaux et al).

Third Space Fluid
The effect of third space fluid, such as pleural effusion or ascites, on pemetrexed is not fully defined. A phase 2 study of pemetrexed in 31 solid tumor patients with stable third space fluid suggested no difference in pemetrexed dose-normalized plasma concentrations or clearance compared to patients without third space fluid collections. Modest levels of pemetrexed were detectable in the third space fluid after multiple cycles. Drainage of third space fluid collection prior to pemetrexed treatment should be considered, but may not be necessary.

Special Populations
Pregnant Women:
Pemetrexed may cause fetal harm when administered to a pregnant woman. See Part II: TOXICOLOGY Section. Pemetrexed clinical studies excluded pregnant women. Women of child bearing potential should have a negative serum pregnancy test prior to treatment with pemetrexed and should be advised to avoid becoming pregnant while on treatment with pemetrexed. Women should be advised to use effective contraceptive measures to prevent pregnancy during treatment with pemetrexed. If pemetrexed is used during pregnancy, or if the patient becomes pregnant while taking pemetrexed, the patient should be informed of the potential hazard to the fetus.

Nursing Women:
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, it is recommended that nursing be discontinued if the mother is treated with pemetrexed.

Men:
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/m^2 basis) resulted in reduced fertility, hypospermia, and testicular atrophy. Because pemetrexed may cause irreversible infertility, men are advised to seek counselling on sperm storage before starting treatment. See Part II: TOXICOLOGY Section.

Pemetrexed is clastogenic in the in vivo micronucleus assay in mouse bone marrow and can have genetically damaging effects. Men are advised to use effective contraceptive measures and thus not to father a child during treatment with pemetrexed and up to 6 months thereafter.

Pediatrics (< 18 years of age):
The safety and effectiveness of pemetrexed in pediatric patients have not been established.

Geriatrics (> 65 years of age):
Dose adjustments based on age other than those recommended for all patients have not been necessary. However, because renal function declines with age, and decreased renal function will result in reduced clearance of pemetrexed, older patients should be followed closely for toxicity.

Patients with Hepatic Impairment:
Pemetrexed is not extensively metabolized by the liver. However, patients with hepatic impairment such as bilirubin > 1.5 times the upper limit of normal (ULN) or aminotransferase > 3 times the ULN (hepatic metastases absent) or > 5 time the ULN (hepatic metastases present) have not been specifically studied.

For dose adjustments based on hepatic impairment, refer to Laboratory Monitoring and Dose Reduction Recommendations under DOSAGE AND ADMINISTRATION Section.

Patients with Renal Impairment:
Pemetrexed is known to be primarily excreted by the kidney. There is limited clinical experience in patients with calculated creatinine clearance below 45 mL/min. Therefore, patients whose creatinine clearance is < 45 mL/min should not receive pemetrexed. Decreased renal function will result in reduced clearance of pemetrexed compared with patients with normal renal function.

For dose adjustments based on renal impairment, refer to Laboratory Monitoring and Dose Reduction Recommendations under DOSAGE AND ADMINISTRATION Section.

Use of Non-Steroidal Anti-Inflammatory Drugs in 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 (see DRUG INTERACTIONS).

Monitoring and Laboratory Tests
All patients receiving pemetrexed should have frequent complete blood counts, including differential and platelets as well as periodic blood chemistry tests performed, including creatinine. Patients should not begin a new treatment cycle unless the absolute neutrophil count (ANC) is ≥ 1500 cells/mm^3, the platelet count is ≥ 100,000 cells/mm^3, and the creatinine clearance is ≥ 45 mL/min (see DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

Adverse Drug Reaction Overview
In clinical trials, the most common adverse reactions (incidence ≥ 10%) during therapy with pemetrexed as a single agent were fatigue, nausea, anorexia, anemia, vomiting, stomatitis/ pharyngitis, rash/desquamation, diarrhea, leukopenia, and neutropenia. Additional common adverse reactions (incidence ≥ 10%) during therapy with pemetrexed when used in combination with cisplatin included thrombocytopenia, decreased creatinine clearance, constipation, alopecia, creatinine elevation, and sensory neuropathy.

In clinical trials, sepsis which in some cases was fatal occurred in approximately 1% of patients.

In clinical trials, cases of gastrointestinal haemorrhage, ulceration, perforation and necrosis, sometimes fatal, have been reported uncommonly in patients treated with pemetrexed. Esophagitis/radiation esophagitis has also been uncommonly reported in clinical trials. Supplementation with folic acid and vitamin B_{12} during treatment with pemetrexed reduces the frequency and severity of hematologic and nonhematologic toxicities.

Clinical Trial Adverse Drug Reactions

Malignant Pleural Mesothelioma

Combination Use with Cisplatin

The following tables list adverse events, considered to be related to Pemetrexed disodium, reported in clinical trial patients with MPM treated with 500 mg/m^2 of pemetrexed and 75 mg/m^2 of cisplatin.

Overall, serious adverse events (SAEs) occurred significantly more frequently in patients on the pemetrexed plus cisplatin arm regardless of drug causality. This was expected because this regimen adds one drug (pemetrexed) to the control regimen (cisplatin). Among the fully supplemented (FS) subgroup, no single SAE, regardless of drug causality, occurred in > 5% of patients in either arm. Most SAEs were hematologic or gastrointestinal and were expected effects of cytotoxic chemotherapy.

Table 1 displays the incidence (percentage of patients) of CTC Grade 3/4 toxicities in patients who received vitamin supplementation with daily folic acid and vitamin B_{12} from the time of enrolment in the study (fully supplemented) versus patients who never received vitamin supplementation (never supplemented) during the study in the pemetrexed plus cisplatin arm. Patients who received supplementation from the start of therapy experienced markedly less laboratory and nonlaboratory toxicity compared with patients who never received supplementation.

Table 1: Selected Grade 3/4 Adverse Events Comparing Fully Supplemented versus Never Supplemented Patients in the Pemetrexed plus Cisplatin Arm (% incidence)

Adverse Event Regardless of Causality*(%)	Fully Supplemented Patients (N=168)	Never Supplemented Patients (N=32)
Neutropenia	24	38
Thrombocytopenia	5	9
Nausea	12	31
Vomiting	11	34
Anorexia	2	9
Diarrhea without colostomy	4	9
Dehydration	4	9
Fever	0	6
Febrile neutropenia	1	9
Infection with Grade 3/4 neutropenia	1	6
Fatigue	17	25

* Refer to National Cancer Institute (NCI) Common Toxicity Criteria (CTC) criteria for laboratory values for each Grade of toxicity (Version 2.0).

Table 2 provides the frequency and severity of adverse events that have been reported in > 5% of 168 patients with MPM who were randomly assigned to receive cisplatin and pemetrexed and 163 patients with mesothelioma randomly assigned to receive single agent cisplatin. In both treatment arms, these chemonaive patients were fully supplemented with folic acid and vitamin B_{12}.

Table 2: Adverse Events* in Fully Supplemented Patients Receiving Pemetrexed plus Cisplatin in MPM
CTC Grades (% incidence)

	All Reported Adverse Events Regardless of Causality					
	Pemetrexed/Cisplatin (N=168)			Cisplatin (N=163)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Laboratory						
Hematologic						
Neutropenia	58	19	5	16	3	1
Leukopenia	55	14	2	20	1	0
Anemia	33	5	1	14	0	0
Thrombocytopenia	27	4	1	10	0	0
Renal						
Creatinine elevation	16	1	0	12	1	0
Renal failure	2	0	1	1	0	0
Clinical						
Constitutional Symptoms						
Fatigue	80	17	0	74	12	1
Fever	17	0	0	9	0	0
Other constitutional symptoms	11	2	1	8	1	1
Cardiovascular General						
Thrombosis/embolism	7	4	2	4	3	1
Gastrointestinal						
Nausea	84	11	1	79	6	0
Vomiting	58	10	1	52	4	1
Constipation	44	2	1	39	1	0
Anorexia	35	2	0	25	1	0
Stomatitis/pharyngitis	28	2	1	9	0	0
Diarrhea without colostomy	26	4	0	16	1	0
Dehydration	7	3	1	1	1	0
Dysphagia/esophagitis/ odynophagia	6	1	0	6	0	0
Pulmonary						
Dyspnea	66	10	1	62	5	2
Pain						
Chest pain	40	8	1	30	5	1
Neurology						
Neuropathy/sensory	17	0	0	15	1	0

	All Reported Adverse Events Regardless of Causality					
	Pemetrexed/Cisplatin (N=168)			Cisplatin (N=163)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Mood alteration/depression	14	1	0	9	1	0
Infection/Febrile Neutropenia						
Infection without neutropenia	11	1	1	4	0	0
Infection with Grade 3 or Grade 4 neutropenia	6	1	0	4	0	0
Infection/febrile neutropenia-other	3	1	0	2	0	0
Febrile neutropenia	1	1	0	1	0	0
Immune						
Allergic reaction/ hypersensitivity	2	0	0	1	0	0
Dermatology/Skin						
Rash/desquamation	22	1	0	9	0	0

* Refer to National Cancer Institute (NCI) Common Toxicity Criteria (CTC) (Version 2.0).

Drug related clinically relevant toxicity that was reported in ≥ 1% and ≤ 5% (common) of the patients that were randomly assigned to receive cisplatin and pemetrexed included: increased AST, ALT, and GGT, infection, febrile neutropenia, renal failure, chest pain, pyrexia and urticaria.

Drug related clinically relevant toxicity that was reported in <1% (uncommon) of the patients that were randomly assigned to receive cisplatin and pemetrexed included: arrhythmia and motor neuropathy.

Non-Small Cell Lung Cancer (NSCLC)

Combination Use with Cisplatin

Table 3 provides the frequency and severity of adverse reactions that have been reported in > 5% of 839 NSCLC patients who were randomized to study and received pemetrexed plus cisplatin and 830 NSCLC patients who were randomized to study and received gemcitabine plus cisplatin. All patients received study therapy as initial treatment for locally advanced or metastatic NSCLC and patients in both treatment groups were fully supplemented with folic acid and vitamin B_{12}.

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[c,d]	33	6	46	10
Neutropenia[c,d]	29	15	38	27
Leukopenia[c]	18	5	21	8
Thrombocytopenia[c,d]	10	4	27	13
Renal				
Creatinine elevation[d]	10	1	7	1
Clinical				
Constitutional Symptoms				
Fatigue	43	7	45	5
Gastrointestinal				
Nausea[c]	56	7	53	4
Vomiting	40	6	36	6
Anorexia[c]	27	2	24	1
Constipation	21	1	20	0
Stomatitis/Pharyngitis	14	1	12	0
Diarrhea	12	1	13	2
Dyspesia/Heartburn	5	0	6	0
Neurology				
Neuropathy-sensory[c,d]	9	0	12	1
Taste disturbance	8	0[e]	9	0[e]
Dermatology/Skin				
Alopecia[d]	12	0[e]	21	1[e]
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/cisplatin.
b Refer to NCI CTC Criteria version 2.0 for each Grade of toxicity.
c $p < 0.05$ for Grades 3/4 toxicity
d $p < 0.05$ for any grade toxicity
e According to NCI CTC Criteria version 2.0, this adverse event term should only be reported as Grade 1 or 2

Drug related clinically relevant toxicity that was reported in ≥ 1% and ≤ 5% (common) of the patients that were randomly assigned to receive cisplatin and pemetrexed include: AST increase, ALT increase, infection, febrile neutropenia, renal failure, pyrexia, dehydration, conjunctivitis, and creatinine clearance decrease.

The incidence of febrile neutropenia was 1.7% on the pemetrexed /cisplatin arm compared to 4.1% on the gemcitabine/cisplatin arm. There were 4 patient deaths on the pemetrexed /cisplatin arm compared to 1 patient death on the gemcitabine/cisplatin arm due to sepsis.

Drug related clinically relevant toxicity that was reported in < 1% (uncommon) of the patients that were randomly assigned to receive cisplatin and pemetrexed include: GGT increase, chest pain, arrhythmia, and motor neuropathy.

No clinically relevant differences in adverse reactions were seen in subpopulations based on

gender, ethnicity, or histology. Patients aged ≥ 65 years generally experienced more toxicity (eg. neutropenia, febrile neutropenia, thrombocytopenia, nausea, renal failure) than patients aged < 65 years, regardless of treatment arm.

Maintenance Following Non- Pemetrexed Containing, Platinum-Based Induction Therapy
Table 4 provides the frequency and severity of adverse reactions that have been reported in > 5% of 441 patients with NSCLC who were randomized to receive pemetrexed and 222 patients with NSCLC who were randomized to receive placebo. All patients without progressive disease received study therapy immediately following 4 cycles of platinum-based treatment for locally advanced or metastatic NSCLC. Patients in both study arms were fully supplemented with folic acid and vitamin B_{12}.

Table 4: Adverse Reactions in Patients Randomized to pemetrexed versus Placebo in NSCLC Following Non-Pemetrexed-containing, Platinum –Based Induction Therapy[a]

Reaction[b]	Pemetrexed (N=441)		Placebo (N=222)	
	All Grades Toxicity (%)	Grade 3-4 Toxicity (%)	All Grades Toxicity (%)	Grade 3-4 Toxicity (%)
All Adverse Reactions	66	16	37	4
Laboratory				
Hematologic				
Anemia	15	3	5	1
Neutropenia	6	3	0	0
Leukopenia	6	2	1	1
Hepatic				
Increased ALT	10	0	4	0
Increased AST	8	0	4	0
Clinical				
Constitutional Symptoms				
Fatigue	25	5	10	1
Gastrointestinal				
Nausea	19	1	5	1
Anorexia	19	2	5	0
Vomiting	9	0	1	0
Mucositis/stomatitis	7	1	2	0
Diarrhea	5	1	3	0
Infection	5	2	2	0
Neurology				
Neuropathy-sensory	9	1	4	0
Dermatology/Skin				
Rash/Desquamation	10	0	3	0

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 CTCAE Criteria version 3.0 for each Grade of toxicity.

All-grade renal events were more frequent in patients ≥ 65 years of age than in patients < 65 years of age (12.2% vs 6.8%). All-grade myelosuppression events were more frequent in patients ≥ 65 years of age than in patients < 65 years of age (24.5% vs 16.7%).

No clinically relevant differences in Grade 3/4 adverse reactions were seen in patients based on age, gender, ethnic origin, or histology except a higher incidence of Grade 3/4 gastrointestinal

events for patients ≥ 65 years of age compared to patients < 65 years of age (7.5% vs 2.4%) and fatigue for Caucasian patients compared to non-Caucasian patients (6.5% versus 0.6%).

Safety was assessed by exposure for patients who were randomized and received at least one dose of pemetrexed (N = 434). The incidence of adverse reactions was evaluated for patients who received ≤ 6 cycles of pemetrexed, and compared to patients who received > 6 cycles of pemetrexed. Increases in adverse reactions (all grades) were observed with longer exposure; however no clinically relevant differences in Grade 3/4 adverse reactions were seen.

Consistent with the higher incidence of anemia (all grades) on the pemetrexed arm, use of transfusions (mainly RBC) and erythropoiesis stimulating agents (ESAs; erythropoietin and darbepoetin) were significantly higher in the pemetrexed arm compared to the placebo arm (transfusions 9.5% versus 3.2%, p = 0.003; ESAs 5.9% versus 1.8%, p = 0.017).

Drug related clinically relevant toxicity that was reported in ≥ 1% and ≤ 5% (common) of the patients that were randomly assigned to receive pemetrexed include: edema, fever (in the absence of neutropenia), constipation, thrombocytopenia, decreased creatinine clearance, increased creatinine, decreased glomerular filtration rate, alopecia, pruritis/itching, ocular surface disease (including conjunctivitis), and increased lacrimation.

Drug related clinically relevant toxicity that was reported in < 1% (uncommon) of the patients that were randomly assigned to receive pemetrexed include: febrile neutropenia, allergic reaction/hypersensitivity, motor neuropathy, renal failure, supraventricular arrhythmia, and erythema multiforme.

Continuation of pemetrexed as Maintenance Following Pemetrexed plus Platinum Induction Therapy

Table 5 provides the frequency and severity of adverse reactions that have been reported in > 5% of 359 patients with NSCLC who were randomized to receive pemetrexed and 180 patients with NSCLC who were randomized to receive placebo. All patients without progressive disease received study therapy immediately following 4 cycles of platinum-based treatment for locally advanced or metastatic NSCLC. Patients in both study arms were fully supplemented with folic acid and vitamin B_{12}.

Table 5: Adverse Reactions in Patients Randomized to pemetrexed versus Placebo in Nonsquamous NSCLC Following pemetrexed plus Cisplatin Induction Therapy[a]

Reaction[b]	Pemetrexed (N=359)		Placebo (N=180)	
	All Grades Toxicity (%)	Grades 3-4 Toxicity (%)	All Grades Toxicity (%)	Grades 3-4 Toxicity (%)
All Adverse Reactions	62	22	35	6
Laboratory				
Hematologic				
Anemia	21	7	5	1
Neutropenia	12	6	1	0
Leukopenia	5	2	0	0
Clinical				
Constitutional Symptoms				
Fatigue	24	5	12	1
Gastrointestinal				
Nausea	15	1	2	0
Vomiting	8	0	1	0
Anorexia	6	0	1	0
Mucositis/Stomatitis	7	1	2	0
Neurology				
Neuropathy Sensory	6	1	7	1
Pain				
Pain, any event	6	1	2	0
Lymphatics				
Edema	8	0	3	0

[a] For the purpose of this table, a cut off of 5% was used for inclusion of all events that were considered to have a possible relationship to pemetrexed.
[b] Refer to NCI CTCAE Criteria version 3.0 (NCI 2006) for each grade of toxicity.
[c] There were no incidences of Grade 5 CTCAE toxicities for the specific toxicities listed in this table.

The incidence of adverse reactions was evaluated for patients who received ≤ 6 cycles of pemetrexed maintenance, and compared to patients who received > 6 cycles of pemetrexed maintenance. Increases in adverse reactions (any grades) were observed with longer exposure (laboratory CTCAE toxicities: > 6 cycles = 45.1% compared with ≤ 6 cycles = 27.9%; non-laboratory CTCAE toxicities: > 6 cycles = 61.7% compared with ≤ 6 cycles = 43.4%). The Grade 3/4/5 adverse reactions observed with longer exposure were as follows: laboratory CTCAE toxicities: > 6 cycles = 16.5% compared with ≤ 6 cycles = 11.1%; non-laboratory CTCAE toxicities: > 6 cycles = 11.3% compared with ≤ 6 cycles = 12.4%. The incidence of Grade 3/4/5 neutropenia observed with longer exposure was as follows: > 6 cycles = 9.8% compared with ≤ 6 cycles = 4.0%. This increase in neutropenia did not result in an increase in Grade 3/4/5 infections.

Consistent with the higher incidence of anemia (all grades) on the pemetrexed arm, use of transfusions (mainly RBC) and erythropoiesis stimulating agents (ESAs; erythropoietin and darbepoetin) were higher in the pemetrexed arm compared to the placebo arm (transfusions 18.4% versus 6.1%, ESAs 12.3% versus 7.2%, anti-infectives 33.7% versus 21.1% and colony stimulating factor 7.0% versus 0.6%).

The following clinically relevant toxicities (any CTCAE grade) were reported in ≥ 1% to ≤ 5% of patients in the maintenance pemetrexed arm: infection, platelets, diarrhea, alanine

aminotransferase, increased lacrimation, constipation, fever (in the absence of neutropenia), aspartate aminotransferase, febrile neutropenia, glomerular filtration rate, rash/desquamation, creatinine, dizziness, motor neuropathy, and ocular surface disease (including conjunctivitis).

The following clinically relevant toxicities (any CTCAE grade) were reported in < 1% (uncommon) of patients in the maintenance pemetrexed arm: alopecia, pulmonary embolism, allergic reaction/hypersensitivity, pruritus/itching, renal/genitourinary-other, renal failure and supraventricular arrhythmia.

In the maintenance pemetrexed arm, 11.4% of patients experienced study drug-related SAEs, compared with 3.3% of patients in the placebo arm. In the pemetrexed arm, deaths due to AEs (on-study and within 30 days of last maintenance treatment, regardless of causality) were reported in 6 patients (1.7%), compared with 3 patients (1.7%) in the placebo arm. The grade 5 AEs that were possibly related to pemetrexed, per investigator's assessment are one case of pneumonia and one case of endocarditis.

Scheduling conflict was the most commonly reported reason for dose delays in both study arms (83.7% patients in the pemetrexed arm and 76.8% patients in the placebo arm). In the maintenance pemetrexed arm, 40.5% of patients experienced a dose delay due to an AE compared with 32.3% in the placebo arm. All dose reductions in both study arms were a result of AEs. In the maintenance pemetrexed arm, 6.1% of patients experienced a dose reduction due to an AE compared with 0.6% in the placebo arm.

In the pemetrexed arm, 12% of patients discontinued due to possibly study drug-related AEs, compared with 4.4% in the placebo arm. The following are the discontinuations due to possibly study drug-related AEs reported in >1% in the maintenance pemetrexed arm: renal failure, asthenia, blood creatinine increased and fatigue.

<u>After Prior Chemotherapy</u>
Pemetrexed has been evaluated for safety in 265 patients randomly assigned to receive single-agent pemetrexed with folic acid and vitamin B_{12} supplementation and 276 patients randomly assigned to receive single-agent docetaxel. All patients were diagnosed with locally advanced or metastatic NSCLC and had received prior chemotherapy. Drug-related adverse events that were reported in > 1% of patients are listed in Table 6.

Table 6: Selected Adverse Events (> 1%) in Patients Receiving Pemetrexed versus Docetaxel in NSCLC

Adverse Event	CTC Grades (% incidence)					
	Pemetrexed (N=265)			Docetaxel (N=276)		
	All Grades (%)	Grade 3 (%)	Grade 4 (%)	All Grades (%)	Grade 3 (%)	Grade 4 (%)
Laboratory*						
Hematologic						
Hemoglobin	19.2	2.6	1.5	22.1	4.3	0
Leukocytes[a]	12.1	3.8	0.4	34.1	16.7	10.5
Neutrophils[a]	10.9	3.4	1.9	45.3	8.7	31.5
Platelets	8.3	1.9	0	1.1	0.4	0
Hepatic/Renal						
ALT Elevation[b]	7.9	1.5	0.4	1.4	0	0
AST Elevation	6.8	0.8	0.4	0.7	0	0
Decreased creatinine clearance	2	< 1	0	< 1	0	0
Creatinine elevation	2.3	0	0	0	0	0
Clinical*						
Constitutional Symptoms						
Fatigue	34.0	5.3	0	35.9	5.1	0.4
Fever	8.3	0	0	7.6	0	0
Alopecia**	6.4	0.4	0	37.7	1.4	0.7
Gastrointestinal						
Nausea	30.9	2.6	0	16.7	1.8	0
Anorexia	21.9	1.5	0.4	23.9	2.2	0.4
Vomiting	16.2	1.5	0	12.0	1.1	0
Stomatitis/pharyngitis	14.7	1.1	0	17.4	1.1	0
Diarrhea	12.8	0.4	0	24.3	2.5	0
Constipation	5.7	0	0	4.0	0	0
Pain						
Abdominal Pain	2.6	0	0	3.3	1.1	0
Neurology						
Sensory - neuropathy	4.9	0	0	15.9	1.1	0
Neuropathy - motor	2.6	0.4	0	4.7	1.1	0
Infection/Febrile Neutropenia						
Infection without neutropenia	1.9	0.4	0	3.3	0	0.4
Febrile neutropenia[a]	1.9	1.1	0.8	13.8	10.1	2.5
Immune						
Allergic reaction/ hypersensitivity	1.1	0	0	2.2	1.1	0
Dermatology/Skin						
Rash/desquamation	14.0	0	0	6.2	0	0
Pruritus	6.8	0.4	0	1.8	0	0
Erythema multiforme	1.1	0	0	2.5	0	0

* Refer to National Cancer Institute (NCI) Common Toxicity Criteria (CTC) for lab values for each Grade of toxicity (Version 2.0).
** According to NCI CTC Criteria (version 2.0), alopecia should only be reported as Grade 1 or 2.
a $p<0.001$ for Grades 3/4 toxicity
b $p=0.028$ for Grades 3/4 toxicity

There was a statistically significant difference between the pemetrexed treatment arm and docetaxel arm with respect to the incidence of any CTC Grade 3 or 4 laboratory toxicity (12.8% vs. 46.4%; $p < 0.001$), largely due to the significantly higher rate of neutropenia in the docetaxel arm. The percentage of patients hospitalized for any adverse event was significantly lower in the pemetrexed arm than in the docetaxel arm (31.7% vs. 40.6%, $p = 0.032$), particularly for drug-related febrile neutropenia (1.5% vs. 13.4%, $p < 0.001$). However, the total number of days of hospitalization for any reason (i.e. drug administration, adverse events, protocol tests, social reasons) was higher in the pemetrexed arm than in the docetaxel arm (1722 vs. 1410 days).

Drug related clinically relevant CTC toxicity that was reported in < 1% (uncommon) of the patients that were randomly assigned to pemetrexed include supraventricular arrhythmias.

The drug related clinically relevant Grade 3 and Grade 4 laboratory toxicities were similar between integrated Phase 2 results from three single agent pemetrexed studies (n=164, patients received vitamin supplementation) and the Phase 3 single agent pemetrexed study described above, with the exception of neutropenia (12.8% versus 5.3%, respectively) and alanine aminotransferase elevation (15.2% versus 1.9%, respectively). These differences were likely due to differences in the patient population, since the Phase 2 studies included chemonaive and heavily pretreated breast cancer patients with pre-existing liver metastases and/or abnormal baseline liver function tests.

There were no clinically relevant differences observed for the safety profile of pemetrexed within the histological subgroups.

Post-Market Adverse Drug Reactions

Gastrointestinal – Rare cases of colitis have been reported in patients treated with pemetrexed.

General disorders and administration site conditions - Rare cases of edema have been reported in patients treated with pemetrexed.

Hepatobiliary –Cases of hepatobiliary failure, sometimes fatal, have been reported very rarely.

Immune – Rare cases of haemolytic anemia have been reported in patients treated with pemetrexed.

Injury, poisoning and procedural complications – Rare cases of radiation recall have been reported in patients who have previously received radiotherapy.

Peripheral ischaemia leading to extremity necrosis has been reported.

Renal – Serious cases of acute renal failure have been reported rarely.

Respiratory – Rare cases of interstitial pneumonitis have been reported in patients treated with pemetrexed.

Skin – Rare cases of bullous conditions have been reported including Stevens-Johnson syndrome and Toxic epidermal necrolysis which in some cases were fatal.

DRUG INTERACTIONS

Drug-Drug Interactions

Pemetrexed is primarily eliminated unchanged renally as a result of glomerular filtration and tubular secretion. *In vitro* studies indicate that pemetrexed is actively secreted by OAT3 (organic anion transporter 3). 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.

NSAIDs

Use in patients with normal renal function: Although ibuprofen (400 mg qid) can decrease the clearance of pemetrexed, it, as well as other NSAIDs, can be administered with pemetrexed in patients with normal renal function (creatinine clearance ≥80 mL/min).

Use in 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 79 mL/min). Clinical trials have shown a decrease in pemetrexed clearance following co-administration of ibuprofen. 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. In the absence of data regarding potential interaction between pemetrexed and NSAIDs with longer half-lives, patients taking these NSAIDs should interrupt dosing for at least 5 days before, the day of, and at least 2 days following pemetrexed administration. If concomitant administration of NSAIDs is necessary, patients should be monitored closely for toxicity, especially myelosuppression, renal, 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.

Chemotherapeutic Agents:

The pharmacokinetics of pemetrexed are not influenced by concurrently administered cisplatin or carboplatin. Similarly, the pharmacokinetics of total platinum are unaltered by pemetrexed.

Vitamins:

Oral folic acid and intramuscular vitamin B_{12} supplementation do not affect the pharmacokinetics of pemetrexed.

Drugs Metabolized by Cytochrome P450 Enzymes:

Pemetrexed undergoes limited hepatic metabolism. Results from *in vitro* studies with human liver microsomes predict that pemetrexed would not cause clinically significant inhibition of the metabolic clearance of drugs metabolized by CYP3A, CYP2D6, CYP2C9, and CYP1A2. No studies were conducted to determine the cytochrome P450 isozyme induction potential of

pemetrexed, because pemetrexed used as recommended (once every 21 days) would not be expected to cause any significant enzyme induction.

Vaccines
Concomitant administration of yellow fever vaccine is contraindicated due to the risk of fatal generalised vaccinale disease (see CONTRAINDICATIONS).

Concomitant administration of live attenuated vaccines (except yellow fever, for which concomitant use is contraindicated) is not recommended due to the risk of systemic, possibly fatal, disease. The risk is increased in subjects who are already immunosuppressed by their underlying disease. Use an inactivated vaccine where it exists (e.g., poliomyelitis).

Drug-Food Interactions
Interactions with food have not been established.

Drug-Herb Interactions
Interactions with herbal products have not been established.

Drug-Laboratory Interactions
Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations
Pemetrexed for Injection is for intravenous infusion only. It should be administered under the supervision of a qualified physician experienced in the use of antineoplastic agents.

Recommended Dose and Dosage Adjustment
Malignant Pleural Mesothelioma (MPM)
Combination Use with Cisplatin: The recommended dose of Pemetrexed for Injection 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 Pemetrexed for Injection administration. Patients should receive appropriate hydration prior to and/or after receiving cisplatin. In clinical trials the median number of cycles was 6 (range = 1 to 12 cycles). Please see Part II: CLINICAL TRIALS Section for further information.

Non-Small Cell Lung Cancer (NSCLC)
Combination Use with Cisplatin: The recommended dose of Pemetrexed for Injection 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 completion of the Pemetrexed for Injection administration. Patients should receive appropriate hydration prior to and/or after receiving cisplatin. In the clinical trial, treatment was administered up to a total of 6 cycles of therapy, and the median number of cycles was 5 (range 1-7). Please see Part II: CLINICAL TRIALS Section for further information.

Single-Agent Use: The recommended dose of Pemetrexed for Injection is 500 mg/m^2 administered as an intravenous infusion over 10 minutes on Day 1 of each 21-day cycle for both

maintenance therapy and second line therapy. For both indications, patients were administered Pemetrexed for Injection until progression. The median number of cycles was 5 (range 1-55) when used as maintenance therapy and 4 (range 1-20) when used as second line treatment.

Premedication Regimen for All Indications:
Corticosteroid - Skin rash has been reported in patients not pretreated with a corticosteroid. Pretreatment with dexamethasone (or equivalent) reduces the incidence and severity of cutaneous reaction. In clinical trials, dexamethasone 4 mg was given by mouth twice daily the day before, the day of, and the day after Pemetrexed for Injection administration.

Vitamin Supplementation - To reduce potential toxicity, patients treated with Pemetrexed for Injection must be instructed to take a low-dose oral folic acid preparation or multivitamin with folic acid on a daily basis (see Table 7). At least 5 daily doses of folic acid (400 mcg/day) must be taken during the 7-day period preceding the first dose of Pemetrexed for Injection; and dosing should continue during the full course of therapy and for 21 days after the last dose of Pemetrexed for Injection. Patients must also receive one (1) intramuscular injection of vitamin B_{12} (1000 mcg) during the week preceding the first dose of Pemetrexed for Injection and every 3 cycles thereafter. Subsequent vitamin B_{12} injections may be given the same day as Pemetrexed for Injection. In clinical trials, the dose of folic acid studied ranged from 350 to 1000 mcg, and the dose of vitamin B_{12} was 1000 mcg. The most commonly used dose of oral folic acid in clinical trials was 400 mcg (see WARNINGS AND PRECAUTIONS Section).

Table 7: Vitamin Supplementation

Drug	Dose and Route	Timing
Folic acid	350 to 600 micrograms by mouth (may give 1000 micrograms but usual dose has been 400 micrograms).	Daily beginning 1 week prior to chemotherapy with Pemetrexed for Injection (at least 5 of the 7 days prior to commencement of Pemetrexed for Injection chemotherapy) and continuing daily until 3 weeks after the last dose of Pemetrexed for Injection
Vitamin B_{12}	1000 micrograms intramuscular injection	Beginning at least 1 week prior to the first dose of Pemetrexed for Injection and continuing every 9 weeks from the previous dose until 3 weeks after the last dose of Pemetrexed for Injection.

Laboratory Monitoring and Dose Reduction Recommendations:
Monitoring: Complete blood cell counts, including platelets, and blood chemistries should be performed on all patients receiving Pemetrexed for Injection. Patients should be monitored for nadir and recovery on days 8 and 15 of each cycle. Patients should not begin a new cycle of treatment unless the ANC is $\geq$ 1500 cell/mm^3, platelet count $\geq$ 100,000 cells/mm^3 and creatinine clearance $\geq$ 45 mL/min. Periodic chemistry tests should be collected to evaluate renal and hepatic function.
General 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 guidelines in Table 8-10, which are suitable for using Pemetrexed for Injection as a single agent or in combination with cisplatin. Pemetrexed

for Injection therapy should be discontinued if a patient experiences any Grade 3 or 4 toxicity after 2 dose reductions.

Hematologic Toxicities: In the event of hematologic toxicities, the recommended dose adjustments for pemetrexed and cisplatin are described in Table 8.

Table 8: Dose Reduction for pemetrexed **as Single-Agent or In Combination with Cisplatin - Hematologic Toxicities**

Nadir ANC < 500/mm^3 and nadir platelets ≥ 50,000/mm^3.	75% of previous dose of Pemetrexed and Cisplatin
Nadir platelets <5 0,000/mm^3 regardless of nadir ANC.	75% of previous dose of Pemetrexed and Cisplatin
Nadir platelets < 50,000/mm^3 with bleeding[a], regardless of nadir ANC.	50% of previous dose of Pemetrexed and Cisplatin

[a] These criteria meet the CTC version 2.0 (NCI 1998) definition of ≥ CTC Grade 2 bleeding.

Nonhematologic Toxicities: If patients develop nonhematologic toxicities (excluding neurotoxicity) ≥ Grade 3, Pemetrexed for Injection 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 9.

Table 9: Dose Reduction for pemetrexed as Single-Agent or In Combination with Cisplatin - Nonhematologic Toxicities[a,b]

	Dose of Pemetrexed (mg/m^2)	**Dose of Cisplatin (mg/m^2)**
Grade 3 or 4 mucositis	50% of previous dose	100% of previous dose
Any diarrhea requiring hospitalization (irrespective of Grade) or Grade 3 or 4 diarrhea	75% of previous dose	75% of previous dose
Any Grade 3 or 4 toxicities except mucositis	75% of previous dose	75% of previous dose

[a] NCI Common Toxicity Criteria (CTC).

[b] Guidelines for neurotoxicity are provided in Table 10, below.

Neurotoxicity: In the event of neurotoxicity, the recommended dose adjustments for Pemetrexed for Injection and cisplatin are described in Table 10. Patients should immediately discontinue therapy if Grade 3 or 4 neurotoxicity is experienced.

Table 10: Dose Reduction for pemetrexed as Single-Agent or In Combination with 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

Special Populations and Conditions:

Elderly Patients: In clinical trials, no dose reductions other than those recommended for all patients were specifically recommended for elderly patients. However, in the study comparing first-line pemetrexed/cisplatin with gemcitabine/cisplatin in NSCLC patients, those patients aged ≥ 65 years generally experienced more toxicity (e.g. neutropenia, febrile neutropenia, thrombocytopenia, nausea, renal failure) than patients aged < 65 years, regardless of treatment arm. In the maintenance non-small cell lung cancer trial, patients ≥ 65 years of age experienced more myelosuppression and renal adverse events. Because renal function declines with age and

decreased renal function results in reduced clearance of pemetrexed, older patients should be followed closely for toxicity.

Children: Pemetrexed for Injection is not recommended for use in children as safety and efficacy have not yet been established in this group of patients.

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 for Injection 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-DPTA serum clearance method:

Male:	$\frac{[140 - \text{Age in years}] \times \text{Actual Body Weight (kg)}}{50 \times \text{Serum Creatinine (mcmol/L)}}$	= mL/sec[a]
Females:	Estimated creatinine clearance for males x 0.85	

[a] To convert from SI (mL/sec) to (mL/min), multiply the mL/sec value by 60.

Caution should be exercised when administering Pemetrexed for Injection concurrently with NSAIDs to patients whose creatinine clearance is < 80 mL/min (see DRUG INTERACTIONS Section).

Hepatically Impaired Patients: Pemetrexed is not extensively metabolized by the liver. Dose adjustments based on hepatic impairment experienced during treatment with pemetrexed are provided in Table 9 (see WARNINGS AND PRECAUTIONS, Hepatic/Biliary and Special Populations, Patients with Hepatic Impairment subsections).

Missed Dose

If chemotherapy treatment is missed, physicians should advise patients to contact them in order to provide further instruction on the administration of folic acid and intramuscular vitamin B_{12} (see DOSAGE AND ADMINISTRATION Section).

Administration

Pemetrexed for Injection is for intravenous infusion only.

PREPARATION AND ADMINISTRATION PRECAUTIONS:

As with other potentially toxic anticancer agents, care should be exercised in the handling and preparation of infusion solutions of Pemetrexed. The use of gloves is recommended. If a solution of Pemetrexed for Injection contacts the skin, wash the skin immediately and thoroughly with soap and water. If Pemetrexed contacts the mucous membranes, flush thoroughly with water. Several published guidelines for handling and disposal of anticancer agents are available (see Part II: REFERENCES). There is no general agreement that all of the procedures recommended in the guideline are necessary or appropriate.

Pemetrexed is not a vesicant. There is not a specific antidote for extravasation of pemetrexed. To date, there have been few reported cases of pemetrexed extravasation, which were not assessed

as serious by the investigator. Pemetrexed extravasation should be managed with local standard practice for extravasation as with other non-vesicants.

The appropriate volume/dose of Pemetrexed for Injection solution should be diluted to a total volume of 100 mL with 0.9% Sodium Chloride Injection (preservative free) and administered as an intravenous infusion over 10 minutes.

PREPARATION FOR INTRAVENOUS INFUSION ADMINISTRATION:

1. Use aseptic technique during dilution of Pemetrexed for Injection for intravenous infusion administration.
2. Calculate the dose and the number of Pemetrexed for Injection vials needed. Vials are available with four different fill volumes i.e. 100 mg/4 mL (25 mg/mL), 500 mg/20 mL (25 mg/mL), 850 mg/34 mL (25 mg/mL) and 1000 mg/40 mL (25 mg/mL) of pemetrexed. Each vial contains sufficient amount of pemetrexed to facilitate delivery of label amount.
3. As with all parenteral drug products vials and diluted admixtures should be inspected visually for clarity, particulate matter, precipitate, discolouration and leakage prior to administration. Solutions showing haziness, particulate matter, precipitate, discolouration or leakage should not be used. Discard unused portion.
4. The appropriate required dose/volume of Pemetrexed for Injection solution should be diluted to a total volume of 100 mL with 0.9% Sodium Chloride Injection (preservative free) and administered as an intravenous infusion over 10 minutes.
5. Because Pemetrexed for Injection and the recommended diluents contain no antimicrobial preservatives, infusion solutions should be used immediately. Diluted solution of Pemetrexed for Injection is chemically and physically stable up to 24 hours when stored at refrigerated, 2-8°C. Discard any unused portion.

Dilution of Pemetrexed for Injection prior to intravenous infusion is only recommended with 0.9% Sodium Chloride Injection (preservative free), USP. Pemetrexed for Injection is physically incompatible with diluents containing calcium, including Lactated Ringer's Injection, USP and Ringer's Injection, USP, and therefore those should not be used. Co-administration of Pemetrexed for Injection with other drugs and diluents has not been studied, and therefore is not recommended.

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. There is no known antidote for pemetrexed overdose. If an overdose occurs, general supportive measures should be instituted as deemed necessary by the treating physician.

The ability of pemetrexed to be dialyzed is unknown. In clinical trials, leucovorin was permitted for CTC Grade 4 leukopenia lasting $\geq$ 3 days, CTC Grade 4 neutropenia lasting $\geq$ 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/m^2, intravenously once, followed by leucovorin, 50 mg/m^2, intravenously every 6 hours for 8 days.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Pemetrexed is an antifolate antineoplastic agent that exerts its action by disrupting crucial folate-dependent metabolic processes essential for cell replication.

Pharmacodynamics

Pemetrexed is an antifolate containing the structurally novel pyrrolopyrimidine-based nucleus that exerts its antineoplastic activity by disrupting crucial folate-dependent metabolic processes that are essential for cell replication. *In vitro* studies have shown that pemetrexed behaves as a multi-targeted antifolate by inhibiting thymidylate synthase (TS), dihydrofolate reductase (DHFR), and glycinamide ribonucleotide formyltransferase (GARFT), which are key folate-dependent enzymes for the *de novo* bio-synthesis of thymidine and purine nucleotides. Pemetrexed is transported into cells by both the reduced folate carrier and membrane folate binding protein transport systems. Once in the cell, pemetrexed is rapidly and efficiently converted to polyglutamate forms by the enzyme folylpolyglutamate synthetase. The polyglutamate forms are retained in cells and are even more potent inhibitors of TS and GARFT. Polyglutamation is a time- and concentration-dependent process that occurs in tumor cells and, to a lesser extent, in normal tissues. Polyglutamated metabolites have an increased intracellular half-life resulting in prolonged drug action in malignant cells. Data indicate that overexpression of thymidylate synthase (TS) correlates with reduced sensitivity to pemetrexed in antifolate-resistant cell lines. Results in a recent study with specimens from chemonaive patients with NSCLC demonstrated lower levels of TS expression in adenocarcinoma as compared to squamous cell carcinoma tumors. Although these data suggest that pemetrexed may offer greater efficacy for patients with adenocarcinoma as compared to squamous carcinoma histology, this hypothesis requires further validation in studies that assess the predictive and prognostic value of TS expression in patients with NSCLC.

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.

Absorption:
Pemetrexed total systemic exposure (AUC) and maximum plasma concentration (C_{max}) increase proportionally with dose. The pharmacokinetics of pemetrexed are consistent 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 renal impairment.

Metabolism:
Pemetrexed is not metabolized to an appreciable extent.

Excretion:
Pemetrexed is primarily eliminated in the urine with 70% to 90% of the dose recovered unchanged within the first 24 hours following administration. Pemetrexed total systemic clearance is 91.8 mL/min and the elimination half-life from plasma is 3.5 hours in patients with normal renal function (creatinine clearance of 90 mL/min [calculated using the standard Cockcroft and Gault formula or measured glomerular filtration rate using the Tc99m-DPTA serum clearance method]). Between patient variability in clearance is moderate at 19.3%.

Absolute neutrophil counts (ANC) following single-agent administration of pemetrexed to patients not receiving folic acid and vitamin B_{12} supplementation were characterized using population pharmacodynamic analyses. Severity of hematologic toxicity, as measured by the depth of the ANC nadir, is inversely proportional to the systemic exposure 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 B_{12} 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 mcg.hr/mL. Return to baseline ANC occurred 4.2 to 7.5 days after the nadir over the same range of exposures.

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

Pediatrics:
The safety and effectiveness of pemetrexed has not been established in pediatric patients.

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

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

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

Hepatic Insufficiency:
There was no effect of elevated AST (SGOT), ALT (SGPT), or total bilirubin on the pharmacokinetics of pemetrexed. However, studies of hepatically impaired patients have not been conducted (see WARNINGS AND PRECAUTIONS section).

Renal Insufficiency:
Pharmacokinetic analyses of pemetrexed included 127 patients with reduced renal function. Plasma clearance of pemetrexed in the presence of cisplatin decreases as renal function decreases, with 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 WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION sections).

STORAGE AND STABILITY
PEMETREXED FOR INJECTION should be stored at 20 - 25°C, excursions permitted between 15°C and 30°C.

Upon dilution of the original vial of Pemetrexed for Injection, diluted solutions for infusion is chemically and physically stable up to 24 hours when stored at refrigerated, 2-8°C. When prepared as directed, infusion solutions of Pemetrexed for Injection contain no antimicrobial preservatives and should be used immediately. Discard unused portion.

Pemetrexed for Injection is light sensitive. Keep vial in the carton until use and protect from light.

SPECIAL HANDLING INSTRUCTIONS
Please see ADMINISTRATION Section.

DOSAGE FORMS, COMPOSITION AND PACKAGING
Availability of Dosage Forms:
Pemetrexed for Injection is available as a sterile solution in single-dose vials in below mentioned strengths and fill volume. The drug product is a clear, colourless to pale yellow solution in a clear glass vial.

PRODUCT	STRENGTH / FILL VOLUME	PACK STYLE
Pemetrexed for Injection	100 mg/4 mL (25 mg/mL)	1 single dose vial in a carton
	500 mg/20 mL (25 mg/mL)	1 single dose vial in a carton
	850 mg/34 mL (25 mg/mL)	1 single dose vial in a carton
	1000 mg/40 mL (25 mg/mL)	1 single dose vial in a carton

Composition:
Pemetrexed for Injection, is a single-dose, sterile, colourless to pale yellow solution in a clear glass vials. Each mL of drug product vials contains pemetrexed disodium equivalent to 25 mg of pemetrexed, 15 mg of citric acid, 0.5 mg of L-methionine, 4.4 mg of Monothioglycerol and Water for injection (quantity sufficient to 1 mL). Hydrochloric acid and/or sodium hydroxide, may have been added to adjust pH.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

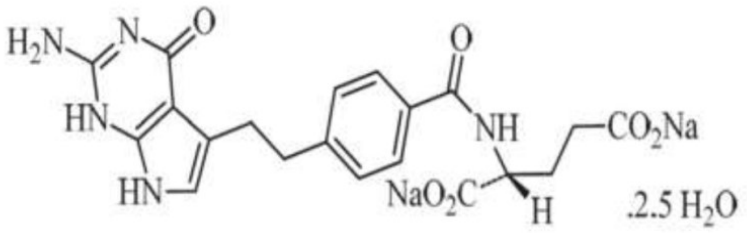
Drug Substance

Common name: Pemetrexed disodium hemipentahydrate

Chemical name: Disodium N-[4-[2-(2-Amino-4,7-dihydro-4- oxo-1H-pyrrolo[2,3-d]pyrimidin-5 - yl) ethyl]benzoyl]-L-glutamic acid, Hemipentahydrate.

Molecular formula and molecular mass: $C_{20}H_{19}N_5Na_2O_6$. 2.5 H_2O
516.41 g/mol

Structural formula:



Physicochemical properties:
Description: White to off-white crystalline powder

Solubility of pemetrexed disodium hemipentahydrate:

Solvent	Solubility
Water	Soluble
Ethanol	Insoluble
Chloroform	Insoluble

pH (56 mg/mL in water): 7.5 to 8.4

CLINICAL TRIALS

Malignant Pleural Mesothelioma: Pemetrexed/Cisplatin versus Cisplatin

The safety and efficacy of pemetrexed were evaluated in chemonaive patients with malignant pleural mesothelioma (MPM) in combination with cisplatin.

Study Demographics and Trial Design

Table 11: Patient Demographics - Clinical Trials Supporting Efficacy of pemetrexed in the Treatment of Malignant Pleural Mesothelioma (MPM)

Study #	Trial Design	Dosage, route of administration and duration	Study subjects and Gender (N=number)	Median age (Range)
H3E-MC-JMCH	international, single-blind, multi-centre, randomized, parallel-arm study	Pemetrexed 500 mg/m^2 intravenous injection Cisplatin 75 mg/m^2 intravenous injection Treatment Duration: 21-day cycle 6 cycles of therapy	Enrolled: 456 Treated: 448 Pemetrexed/Cisplatin: 226 (Male: 184; Female: 42) Cisplatin: 222 (Male 181; Female: 41) Vitamin supplemented (FS): 331 Pemetrexed/Cisplatin: 168 Cisplatin: 163 Nonvitamin supplemented (PS+NS): 117 Pemetrexed/Cisplatin: 58 Cisplatin: 59	Pemetrexed/Cisplatin arm Median age=61 Age range=29-85 Cisplatin arm Median age=60 Age range=19-84

Randomized Trial

A Phase 3 multi-centre, randomized, single-blind study in 448 chemonaive patients with MPM compared median survival in patients treated with pemetrexed in combination with cisplatin to those patients receiving cisplatin alone. Pemetrexed (n = 226) was administered intravenously over 10 minutes at a dose of 500 mg/m^2 and cisplatin (n = 222) was administered intravenously over 2 hours at a dose of 75 mg/m^2 beginning approximately 30 minutes after the end of the pemetrexed infusion. Both drugs were given on Day 1 of a 21-day cycle. Folic acid and vitamin B_{12} supplementation were added to both treatment arms to reduce white cell and GI toxicity observed in the first 117 treated patients. All patients received prophylactic dexamethasone as part of the treatment regimen to prevent/reduce skin toxicities. Patient demographics are shown in Table 12.

Table 12: Summary of Patient Characteristics

Patient Characteristic	Randomized and Treated Patients		Fully Supplemented Patients	
	Pemetrexed/ Cisplatin (N=226)	Cisplatin (N=222)	Pemetrexed/ Cisplatin (N=168)	Cisplatin (N=163)
Age (yrs)				
Median (range)	61 (29-85)	60 (19-84)	60 (29-85)	60 (19-82)
Gender (%)				
Male	184 (81.4)	181 (81.5)	136 (81.0)	134 (82.2)
Female	42 (18.6)	41 (18.5)	32 (19.0)	29 (17.8)
Origin (%)				
Caucasian	204 (90.3)	206 (92.8)	150 (89.3)	153 (93.9)
Hispanic	11 (4.9)	12 (5.4)	10 (6.0)	7 (4.3)
Asian	10 (4.4)	4 (1.9)	7 (4.2)	3 (1.8)
African descent	1 (0.4)	0	1 (0.6)	0
Stage at Entry (%)				
I	16 (7.1)	14 (6.3)	15 (8.9)	12 (7.4)
II	35 (15.6)	33 (15.0)	27 (16.2)	27 (16.8)
III	73 (32.4)	68 (30.6)	51 (30.5)	49 (30.4)
IV	101 (44.9)	105 (47.2)	74 (44.3)	73 (45.3)
Unspecified	1 (0.4)	2 (0.9)	1 (0.6)	2 (1.2)
Diagnosis/Histology[a] (%)				
Epithelial	154 (68.1)	152 (68.5)	117 (69.6)	113 (69.3)
Mixed	37 (16.4)	36 (16.2)	25 (14.9)	25 (15.3)
Sarcomatoid	18 (8.0)	25 (11.3)	14 (8.3)	17 (10.4)
Other	17 (7.5)	9 (4.1)	12 (7.1)	8 (4.9)
Baseline KPS[b] (%)				
70-80	109 (48.2)	97 (43.7)	83 (49.4)	69 (42.3)
90-100	117 (51.8)	125 (56.3)	85 (50.6)	94 (57.7)

[a] Only 67% of the patients had the histologic diagnosis of malignant mesothelioma confirmed by independent review.
[b] Karnofsky Performance Scale.

Table 13 summarizes the number of cycles of treatment completed by all randomized and treated patients and fully supplemented patients. The fully supplemented patients completed a median of 6 cycles in the pemetrexed plus cisplatin treatment arm and 4 cycles in the cisplatin treatment arm. Patients who never received folic acid and vitamin B_{12} during study therapy received a median of 2 cycles in both treatment arms.

Table 13: Summary of Cycles Given in Randomized and Treated MPM Patients

Cycle Statistics	All Patients*		Fully Supplemented Patients		Never Supplemented	
	Pemetrexed/ Cisplatin (N=226)	Cisplatin (N=222)	Pemetrexed/ Cisplatin (N=168)	Cisplatin (N=163)	Pemetrexed/ Cisplatin (N= 32)	Cisplatin (N= 38)
Median Cycles Completed	6	4	6	4	2	2
Range	(1-12)	(1-9)	(1-12)	(1-9)	(1-6)	(1-6)
Total Cycles Completed	1066	877	825	650	-	-
Cycles given at full dosage	1030	874	802	648	-	-
(%)	(96.6%)	(99.7%)	(97.2%)	(99.7%)	-	-

* All Patients (N=448) include all randomized and treated patients regardless of supplementation status

Table 14 summarizes the dose intensity administered to the treatment groups. Patients in both arms received more than 90% of the planned dose intensity.

Table 14: Summary of Dose Intensity (DI) in Randomized and Treated MPM Patients

	All Patients*			Fully Supplemented Patients		
	Pemetrexed/Cisplatin (N=226)		Cisplatin (N=222)	Pemetrexed/Cisplatin (N=168)		Cisplatin (N=163)
	Pemetrexed	Cisplatin	Cisplatin	Pemetrexed	Cisplatin	Cisplatin
Planned Mean/Patient (mg/m^2/week)	166.7	25	25	166.7	25	25
Delivered Mean/Patient (mg/m^2/week)	153.4	23.2	24.1	154.6	23.4	24.1
Percent of planned DI (delivered/planned)	92.0%	92.8%	96.4%	92.7%	93.6%	96.4%

* All Patients (N=448) include all randomized and treated patients regardless of supplementation status

Study Results

Table 15 summarizes the efficacy results for all randomized and treated patients regardless of vitamin supplementation status and those patients receiving vitamin supplementation from the time of enrollment in the trial (fully supplemented patients). In the population of all treated patients regardless of supplementation status (primary analysis), patients receiving the combination of pemetrexed plus cisplatin had a significantly higher median survival time than the patients in the cisplatin monotherapy arm (Table 15; Figure 1). The 2.8-month difference in median survival (12.1 versus 9.3 months), was statistical significant (p-value 0.020).

Table 15: Efficacy of Pemetrexed plus Cisplatin versus Cisplatin in Randomized and Treated MPM Patients

Efficacy Parameter	All Patients*		Fully Supplemented Patients	
	Pemetrexed/ Cisplatin (N=226)	Cisplatin (N=222)	Pemetrexed/ Cisplatin (N=168)	Cisplatin (N=163)
Median Overall Survival	12.1 months	9.3 months	13.3 months	10.0 months
(95% CI)	(10.0-14.4)	(7.8-10.7)	(11.4-14.9)	(8.4-11.9)
Hazard ratio	0.77		0.75	
Log Rank p-value**	0.02		0.051	
Percent censored	35.8	28.4	43.5	36.8

* All Patients (N=448) include all randomized and treated patients regardless of supplementation status
** p-value refers to comparison between arms.

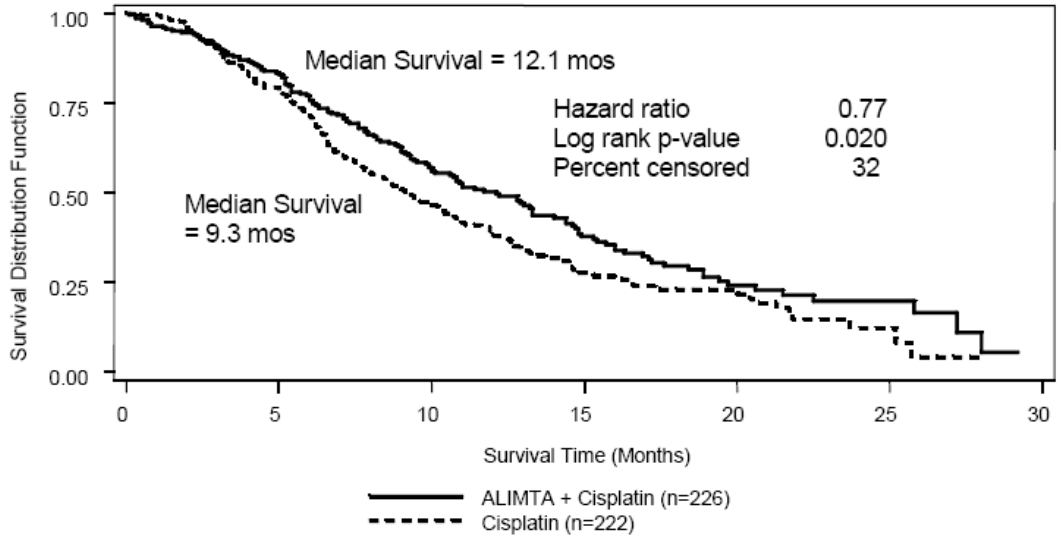


Figure 1: Kaplan-Meier Estimates of Survival Time

Objective tumour response criteria for malignant pleural mesothelioma is difficult to assess and response criteria are not universally agreed upon. However, based on a prospectively defined criteria, the objective tumour response rate for pemetrexed plus cisplatin was greater than the response rate for cisplatin alone (41.3% vs. 16.7%; p = 0.001), as were the measures of time to progressive disease (5.7 vs. 3.9 months) and time to treatment failure (4.5 vs. 2.7 months; p = 0.001). Vitamin supplementation was associated with further improvement in the objective tumour response rate for the pemetrexed plus cisplatin compared to cisplatin alone patients (45.5% vs. 19.6%) as was time to progressive disease (6.1 vs. 3.9 months; p = 0.008) and time to treatment failure (4.7 vs. 2.7 months; p = 0.001).

Quality of Life was measured using the Lung Cancer Symptom Scale (LCSS) which assessed 6 symptoms (anorexia, fatigue, pain, cough, hemoptysis, and dyspnea); 3 summary scales (symptom distress, interference with activity level, and global QoL); and an average of all the individual scales (Total LCSS). LCSS data had to be present at both baseline and at least one post-baseline assessment between cycle 1-6, to be included in the analysis and were available for

93.8% of the pemetrexed plus cisplatin patients and for 98.1% of the cisplatin monotherapy patients. At cycle 6, there was a significant difference in favour of the pemetrexed plus cisplatin patients for dyspnea, fatigue, symptom distress, interference with activity, and total LCSS. Pain scores improved for pemetrexed plus cisplatin patients and these scores were statistically different than those for cisplatin patients for cycles 3 through 6. Cycle 3 LS mean, (model-based mean from the repeated measures analysis) was -3.51 for pemetrexed/cisplatin and -3.27 for cisplatin; p=0.005. Cycle 6 LS Mean was -1.23 for pemetrexed/cisplatin and 5.8 for cisplatin (p = 0.009).

Pulmonary function tests were used to provide objective measures of lung function. Results for slow vital capacity (SVC), forced vital capacity (FVC), and forced expiratory volume in one second (FEV_1) in absolute and percentage of predicted normal were assessed at baseline and repeated up to Cycle 6 for each treatment arm. For each parameter (SVC, FVC, and FEV_1), lung volumes in the pemetrexed/cisplatin arm at Cycle 6 were higher than the cisplatin alone arm throughout treatment period. Similar results were seen when analyzed as changes from baseline. Averaging over the entire treatment period, the pemetrexed/cisplatin arm had statistically significantly greater pulmonary function for all three parameters [SVC ($p = 0.001$), FVC ($p = 0.002$), and FEV_1 ($p < 0.001$)].

First Line – Nonsquamous Non-Small Cell Lung Cancer - Pemetrexed/Cisplatin versus Gemcitabine/Cisplatin

Study Demographics and Trial Design

Table 16: **Patient Demographics - Clinical Trial Supporting Efficacy of Pemetrexed/Cisplatin versus Gemcitabine/Cisplatin in the Treatment of NSCLC**

Study #	Trial Design	Dosage, route of administration and duration	Study subjects and Gender (N=number)	Median age (Range)
H3E-MC-JMDB	Phase 3, randomized, open-label, controlled, initial treatment of Stage IIIb or IV NSCLC	Pemetrexed 500 mg/m^2 plus cisplatin 75 mg/m^2 on Day 1 of a 21-day cycle vs. gemcitabine 1250 mg/m^2 on Day 1 and Day 8 plus cisplatin 75 mg/m^2 on Day 1 of a 21-day cycle	Entered: 1833 Randomized: 1725 Pemetrexed/Cisplatin: 862 (Male:605; Female:257) Gemcitabine/Cisplatin: 863 (Male 605; Female:258)	Pemetrexed/Cisplatin arm Median age=61 Age range=29-83 Gemcitabine/Cisplatin arm Median age=61 Age range=26-79

Approval of pemetrexed in combination with cisplatin in first line NSCLC is based on a single non-inferiority trial.

A multi-centre, randomized, Phase 3 study in 1725 chemonaive patients with 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/m^2 with cisplatin administered intravenously at a dose of 75 mg/m^2 after pemetrexed administration, on Day 1 of each 21-day cycle. Gemcitabine was administered at a dose of 1250 mg/m^2 on Day 1 and Day 8, and cisplatin was administered intravenously at a dose of 75 mg/m^2 after administration of gemcitabine, on

Day 1 of each 21-day cycle. Patients in both treatment arms received folic acid, vitamin B12, and dexamethasone. The study was designed to show non-inferiority of survival of pemetrexed and cisplatin to gemcitabine and cisplatin. Patient demographics of the intent to treat (ITT) population are shown in Table 17. The demographics and disease characteristics were well balanced. All patients had a good performance status of ECOG 0 or 1. The results of the protocol qualified (PQ) population analysis (N = 1666) were consistent with those of the ITT population analysis.

Table 17: Summary of Patient Characteristics

Patient Characteristic	Pemetrexed plus Cisplatin (N=862)	Gemcitabine plus Cisplatin (N=863)
Age (yrs)		
Median age, years (range)	61.05 (28.8-83.2)	60.95 (26.4-79.4)
Gender (%)		
Female	257 (29.8)	258 (29.9)
Male	605 (70.2)	605 (70.1)
Origin (%)		
African Decent	18 (2.1)	18 (2.1)
Caucasian	669 (77.6)	680 (78.8)
East/Southeast Asian	116 (13.5)	104 (12.1)
Hispanic	27 (3.1)	23 (2.7)
Western Asian	30 (3.5)	37 (4.3)
Other	2 (0.2)	1 (0.1)
Smoking Status (%)[a]		
Ever Smoker	629 (73.0)	637 (73.8)
Never Smoker	128 (14.8)	122 (14.1)
Unknown	105 (12.2)	104 (12.1)
Performance Status (%)[b]		
ECOG PS 0	305 (35.4)	307 (35.6)
ECOG PS 1	556 (64.5)	554 (64.2)
Unknown	1 (0.1)	2 (0.2)
Basis for Diagnosis		
Cytological	289 (33.5)	288 (33.4)
Histological	573 (66.5)	575 (66.6)
Stage of Disease (%)		
Stage IIIb	205 (23.8)	210 (24.3)
Stage IV disease	657 (76.2)	653 (75.7)
Histology (%)		
Adenocarcinoma	436 (50.6)	411 (47.6)
Squamous	244 (28.3)	229 (26.5)
Large Cell	76 (8.8)	77 (8.9)
Unknown	106 (12.3)	146 (16.9)

Abbreviations: ECOG PS = Eastern Cooperative Oncology Group performance status; N = number of patients enrolled; n = number of patients in groups.

a Smoking history was not recorded for all treated patients. Percentages are representative of N = 757 for the pemetrexed plus cisplatin arm and N = 759 for the gemcitabine plus cisplatin arm.

b ECOG PS was not reported for all treated patients. Percentages are representative of N=861 for the pemetrexed plus cisplatin arm, and N = 861 for the gemcitabine plus cisplatin arm.

Treatment was administered up to a total of 6 cycles of therapy as per study protocol. A median of 5 cycles of treatment was administered on both treatment arms. Patients treated with pemetrexed plus cisplatin received a relative dose intensity of 94.8% of the protocol-specified pemetrexed dose intensity and 95.0% of the protocol-specified cisplatin dose intensity. Patients treated with gemcitabine plus cisplatin received a relative dose intensity of 85.8% of the protocol-specified gemcitabine dose intensity and 93.5% of the protocol-specified cisplatin dose intensity.

Study Results

The primary endpoint of noninferior overall survival was met for pemetrexed plus cisplatin compared to gemcitabine plus cisplatin in the intent-to-treat (ITT) study population. The median survival time was 10.3 months in both treatment arms, with an adjusted hazard ratio of 0.94 (95% confidence interval 0.84 – 1.05), based on a noninferiority margin of 1.17647. This margin was derived from a single study (Sandler 2000). Progression-free survival (PFS) and objective response rate (ORR) were similar between treatment arms. Table 18 summarizes the study results in the overall study population.

Table 18: Efficacy of Pemetrexed **plus Cisplatin versus Gemcitabine plus Cisplatin in First-line Non-Small Cell Lung Cancer - ITT Population**

	Pemetrexed plus Cisplatin (N=862)	**Gemcitabine plus Cisplatin (N=863)**
Median overall survival (95% CI)	10.3 months (9.8-11.2)	10.3 months (9.6-10.9)
Adjusted hazard ratio (HR) a, b (95% CI)	0.94c (0.84-1.05)	
Unadjusted hazard ratio (HR) b (95% CI)	0.93c (0.83-1.04)	
Log rank p-value	0.209	
12 month survival (95% CI)	43.5% (40.1-46.9)	41.9 % (38.5-45.4)
Median progression-free survival (95% CI)	4.8 months (4.6-5.3)	5.1 months (4.6-5.5)
Overall response rate d (95% CI)	30.6% (27.3-33.9)	28.2% (25.0-31.4)

Abbreviations: CI = confidence interval; HR = hazard ratio; ITT = intent to treat; n = total population size.

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.

c Statistically significant for non-inferiority.

d Number of qualified patients on the AC arm (N = 762) and GC arm (N = 755).

Figure 2 displays the Kaplan-Meier survival curve for the ITT population.

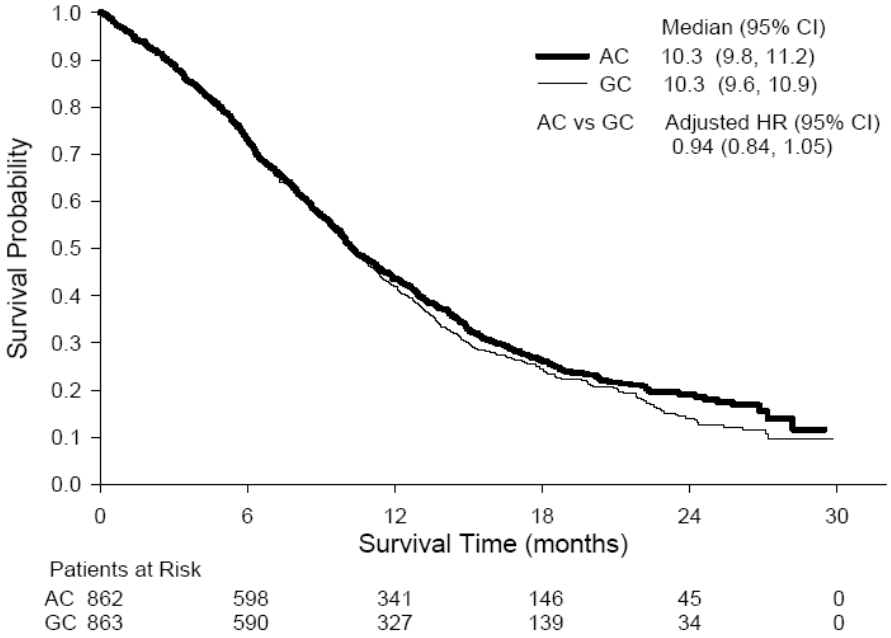


Figure 2: Kaplan-Meier Curves for Overall Survival Pemetrexed **plus Cisplatin (AC) versus Gemcitabine plus Cisplatin (GC) in Non-Small Cell Lung Cancer - ITT Population**

Subsets of patients were examined in planned secondary analyses. The results of these analyses are shown in Figure 3.

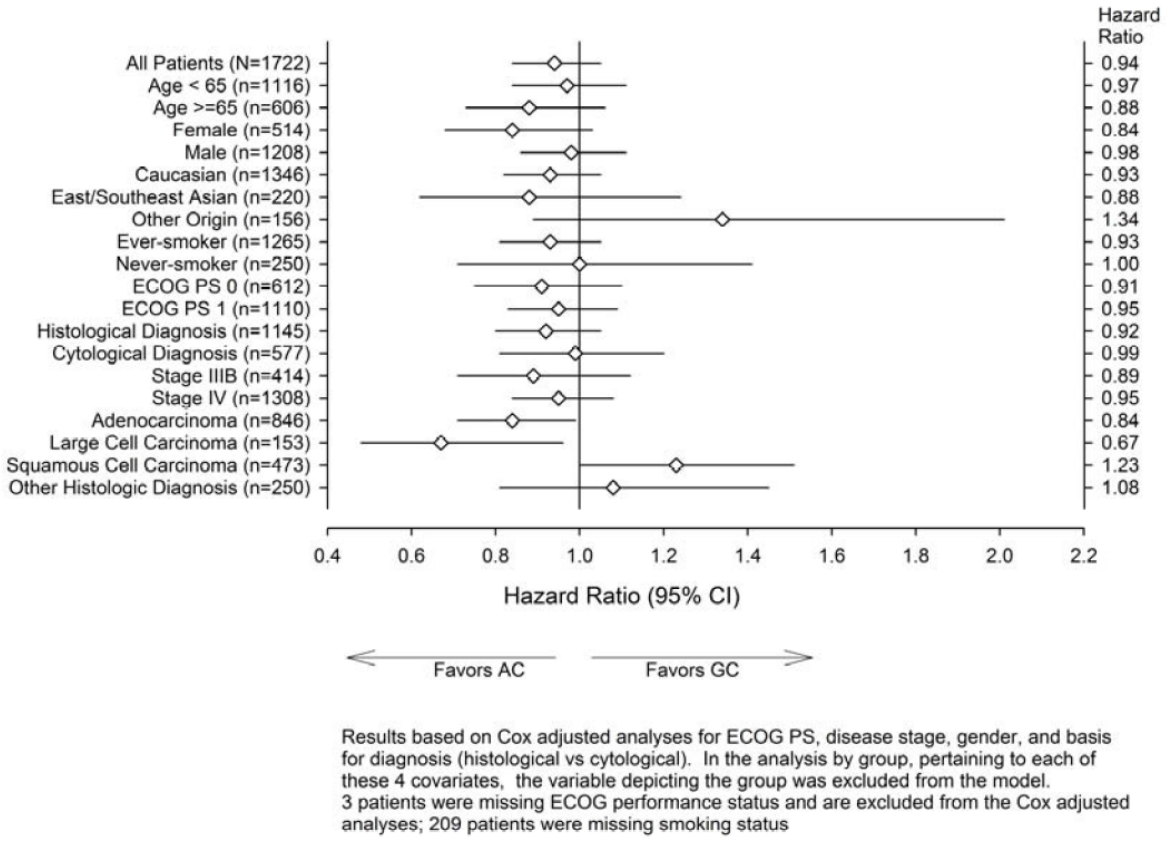


Figure 3: Forest Plot for Overall Survival Adjusted Hazard Ratios of Subgroups Pemetrexed+ **Cisplatin versus Gemcitabine + Cisplatin in First-line Non- Small Cell Lung Cancer – ITT Population**

The effect of pemetrexed plus cisplatin on survival was similar regardless of age, gender, ethnic origin, smoking status, and performance status (0 or 1). A prespecified subgroup analysis of the impact of NSCLC histology on overall survival demonstrated clinically relevant differences in survival according to histology (see Table 19 below). In the subgroup analysis of patients with squamous cell histology, pemetrexed plus cisplatin was not shown to be non-inferior to the comparator, suggesting it may not be effective in patients with squamous cell histology NSCLC (see INDICATIONS AND CLINICAL USE).

Table 19: Overall Survival of Pemetrexed plus Cisplatin versus Gemcitabine plus Cisplatin in Non-Small Cell Lung Cancer - Histologic Subgroups, ITT Population

Histology Subgroup	Median Overall Survival in Months (95% CI)				Hazard Ratio (HR)[a] (95% CI)
	Pemetrexed plus Cisplatin		Gemcitabine plus Cisplatin		
Adenocarcinoma (N=847)	12.6 (10.7 - 13.6)	N=436	10.9 (10.2 - 11.9)	N=411	0.84 [b] (0.71 - 0.98)
Large Cell (N=153)	10.4 (8.6 - 14.1)	N=76	6.7 (5.5 - 9.0)	N=77	0.68 [b] (0.48 - 0.97)
Squamous Cell (N=473)	9.4 (8.4 - 10.2)	N=244	10.8 (9.5 - 12.1)	N=229	1.22 (0.99 - 1.50)
Other (N=252)	8.6 (6.8 - 10.2)	N=106	9.2 (8.1 - 10.6)	N=146	1.12 (0.84 - 1.49)

a HR was based on unadjusted analyses. 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.

b Log rank $p < 0.05$ unadjusted for multiple comparisons.

Figure 4 displays the Kaplan-Meier curves for histology subgroups (adenocarcinoma and squamous cell carcinoma) in the ITT population.

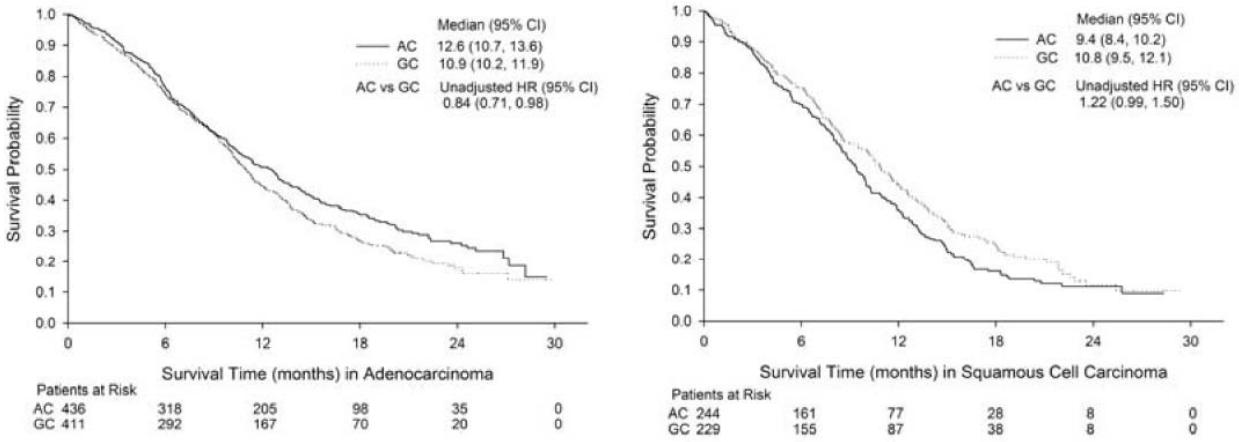


Figure 4: Kaplan-Meier Curves for Overall Survival Pemetrexed plus Cisplatin (AC) versus Gemcitabine plus Cisplatin (GC) in First-line Non-Small Cell Lung Cancer - Histology Subgroups: Adenocarcinoma and Squamous Cell Carcinoma, ITT Population

No formal Quality of Life assessment was conducted during the trial. Patients treated with pemetrexed and cisplatin required fewer transfusions (16.4% versus 28.9%), red blood cell transfusions (16.1% versus 27.3%) and platelet transfusions (1.8% versus 4.5%). Patients also required lower administration of erythropoietin/darbopoietin (10.4% versus 18.1%), G-CSF/ GM-CSF (3.1% versus 6.1%), and iron preparations (4.3% versus 7.0%). The incidence of hospitalization for a drug-related adverse event was 17.9% for patients treated with pemetrexed/cisplatin versus 16.9% for patients treated with gemcitabine/cisplatin.

Maintenance Therapy – Nonsquamous Non-Small Cell Lung Cancer - Monotherapy

Study Demographics and Trial Design

The safety and efficacy of pemetrexed as a single-agent have been evaluated in 2 randomized controlled trials immediately following first-line platinum-based chemotherapy, for the maintenance treatment of patients with locally advanced or metastatic (Stage IIIb or IV) non-small cell lung cancer (NSCLC).

Table 20: **Patient Demographics - Clinical Trials Supporting Efficacy of Pemetrexed in NSCLC Maintenance Therapy**

Study #	Trial Design	Dosage, route of administration and duration	Study subjects and Gender (N=number)	Median age (Range)
H3E-MC-JMEN (JMEN)	Phase 3, double-blind, placebo-controlled study of maintenance pemetrexed plus BSC immediately following non-pemetrexed containing induction therapy for Stage IIIb or IV NSCLC	Pemetrexed 500 mg/m^2 on Day 1 of a 21-day cycle plus BSC	Entered: 741 Randomized: 663 Pemetrexed: 441 (Male:322; Female:119) Placebo: 222 (Male 161; Female:61)	Pemetrexed arm Median age=60.6 Age range= 25.6-82.6 Placebo arm Median age=60.4 Age range= 35.4-78.5
H3E-EW-S124 (PARAMOUNT)	Phase 3, double-blind, placebo-controlled study of continuation maintenance Pemetrexed plus BSC immediately following induction therapy with Pemetrexed plus Cisplatin for Stage IIIb or IV NSCLC	Pemetrexed 500 mg/m^2 on Day 1 of a 21-day cycle plus BSC	Entered: 939 Randomized: 539 Pemetrexed: 359 (Male:201; Female:158) Placebo: 180 (Male 112; Female:68)	Pemetrexed arm Median age=60.9 Age range= 31.9-78.7 Placebo arm Median age=62.4 Age range= 34.9-83.3

Abbreviations: BSC = best supportive care

JMEN

A multi-centre, randomized, double-blind, placebo-controlled, Phase 3 study was conducted in 663 patients with Stage IIIb/IV NSCLC who did not progress after four cycles of first-line platinum-based doublet chemotherapy containing cisplatin or carboplatin with gemcitabine, paclitaxel, or docetaxel. First line doublet therapy containing pemetrexed was not included. Patients who did not progress were randomized 2:1 to receive pemetrexed or placebo immediately following platinum-based chemotherapy. The minimization principle adopted for randomization did not include histology. Pemetrexed was administered intravenously over 10 minutes at a dose of 500 mg/m^2 on Day 1 of each 21-day cycle, until disease progression. Patients in both study arms received folic acid, vitamin B_{12}, and dexamethasone.

The study was designed to demonstrate superior progression-free survival and overall survival (OS) of pemetrexed over placebo. Progression free survival (PFS) was assessed by independent review. Patient characteristics of the intent to treat (ITT) population are shown in Table 21. The demographics and baseline disease characteristics were well balanced between study arms.

Table 21: Summary of Patient Characteristics in Study of NSCLC – Maintenance Therapy Following non- Pemetrexed -containing Platinum-Based Induction

Patient characteristic	Pemetrexed (N=441)	Placebo (N=222)
Age (yrs)		
Median (range)	60.6 (25.6-82.6)	60.4 (35.4-78.5)
Gender		
Male/Female	73.0%/27.0%	72.5%/27.5%
Ethnic Origin		
Caucasian	279 (63.3%)	149 (67.1%)
East Asian	104 (23.6%)	50 (22.5%)
Other	58 (13.2%)	23 (10.4%)
Stage at Entry[a]		
IIIb/IV	18.0%/82.0%	21.2%/78.8%
Histology (%)		
Nonsquamous NSCLC[b]	325 (73.7%)	156 (70.3%)
Adenocarcinoma	222 (50.3%)	106 (47.7%)
Large cell	10 (2.3%)	10 (4.5%)
Other[c]	93 (21.1%)	40 (18.0%)
Squamous	116 (26.3%)	66 (29.7%)
ECOG PS[d]		
0/1	40.1%/59.9%	38.3%/61.7%
Smoking History[e]		
Ever/never smoker	74.1%/25.9%	71.5%/28.5%
Time from start of induction therapy to study randomization (months)		
Median (range)	3.25 (1.6-4.8)	3.29 (2.7-5.1)

a Stage at Entry was not reported for all randomized patients. Percentages are representative of N=440 for the pemetrexed arm and N = 222 for the placebo arm.

b Includes patients with adenocarcinoma, large cell, and other histologic diagnoses.

c The subgroup of "Other" represents patients with a primary diagnosis of NSCLC whose disease did not clearly qualify as adenocarcinoma, large cell carcinoma, or squamous cell carcinoma.

d Eastern Cooperative Oncology Group Performance Status (ECOG PS) was not reported for all randomized patients. Percentages are representative of N=439 for the pemetrexed arm, and N = 222 for the placebo arm.

e Smoking history was not reported for all randomized patients. Percentages are representative of N=437 for the pemetrexed arm and N = 221 for the placebo arm.

Patients received a median of 5 cycles of pemetrexed and 3.5 cycles of placebo. Patients randomized to pemetrexed received a relative dose intensity of 95.7%. A total of 213 patients (48.3%) completed ≥ 6 cycles and a total of 98 patients (22.6%) completed ≥ 10 cycles of treatment with pemetrexed. The percentage of patients that received post discontinuation systemic therapy was 51.5% of pemetrexed and 67.1% of placebo patients.

Study Results

In the overall study population, Pemetrexed was statistically superior to placebo in terms of overall survival (OS) (13.4 months versus 10.6 months, HR=0.79 (95% CI 0.65 - 0.95, pvalue= 0.012)) and PFS (4.0 months versus 2.0 months, HR=0.60 (95% CI 0.49 - 0.73, pvalue< 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 (15.5 months versus 10.3 months, HR=0.70 (95% CI 0.56 – 0.88, p-value=0.002)) and PFS (4.4 months versus 1.8 months, HR=0.47 (95% CI 0.37 – 0.60; pvalue < 0.00001)). For the population of patients with squamous NSCLC, Pemetrexed did not improve OS compared to placebo (median 9.9 months vs 10.8 months, HR=1.07 (95% CI 0.77 – 1.50) or PFS (median 2.4 months vs 2.5 months, HR=1.03 (95% CI 0.71 – 1.49)). Efficacy results for the

overall patient population are presented in Table 22, and efficacy results by pre-specified histologic subgroups are presented in Table 23, below.

Table 22: Maintenance Therapy Following non- Pemetrexed -containing Platinum-Based Induction:
Efficacy of Pemetrexed versus Placebo in NSCLC - ITT Population

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[b] (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<0.00001	

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.

Table 23: Maintenance Therapy following non-Pemetrexed-containing Platinum-Based Induction:
Efficacy of Pemetrexed versus Placebo in NSCLC – Prespecified Histologic Subgroups[a]

	Overall Survival		**Progression-Free Survival[b]**	
	Pemetrexed	**Placebo**	**Pemetrexed**	**Placebo**
	Median (months)	**Median (months)**	**Median (months)**	**Median (months)**
	HR[c] (95% CI)		**HR[c] (95% CI)**	
Nonsquamous NSCLC[d]	**15.5**	**10.3**	**4.4**	**1.8**
N=481	**0.70 (0.56-0.88)**		**0.47 (0.37-0.60)**	
p-value	**p=0.002**		**p<0.00001**	
Adenocarcinoma	16.8	11.5	4.6	2.7
N=328	0.73 (0.56-0.96)[e]		0.51 (0.38-0.68)[e]	
Large cell carcinoma	8.4	7.9	4.5	1.5
N=20	0.98 (0.36-2.65)		0.40 (0.12-1.29)	
Other[f]	11.3	7.7	4.1	1.6
N=133	0.61 (0.40-0.94)[e]		0.44 (0.28-0.68)[e]	
Squamous cell	**9.9**	**10.8**	**2.4**	**2.5**
N=182	**1.07 (0.77-1.50)**		**1.03 (0.71-1.49)**	
p-value	**p=0.678**		**p=0.896**	

a PFS and OS were calculated from time of randomization, after completion of 4 cycles of induction platinum-based chemotherapy. All results unadjusted for multiple comparisons.
b Values for PFS are 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. A HR >1.0 indicates that the result is better in the placebo arm than in the pemetrexed arm.
d Includes patients with adenocarcinoma, large cell carcinoma, and other histology.
e p<0.05 unadjusted for multiple comparisons.
f The subgroup of "Other" represents patients with a primary diagnosis of NSCLC whose disease did not clearly qualify as adenocarcinoma, large cell carcinoma, or squamous cell carcinoma.

Figures 5 and 6 display the Kaplan-Meier survival curves for the overall patient population and the histologic subgroups (nonsquamous NSCLC and squamous cell NSCLC), respectively.

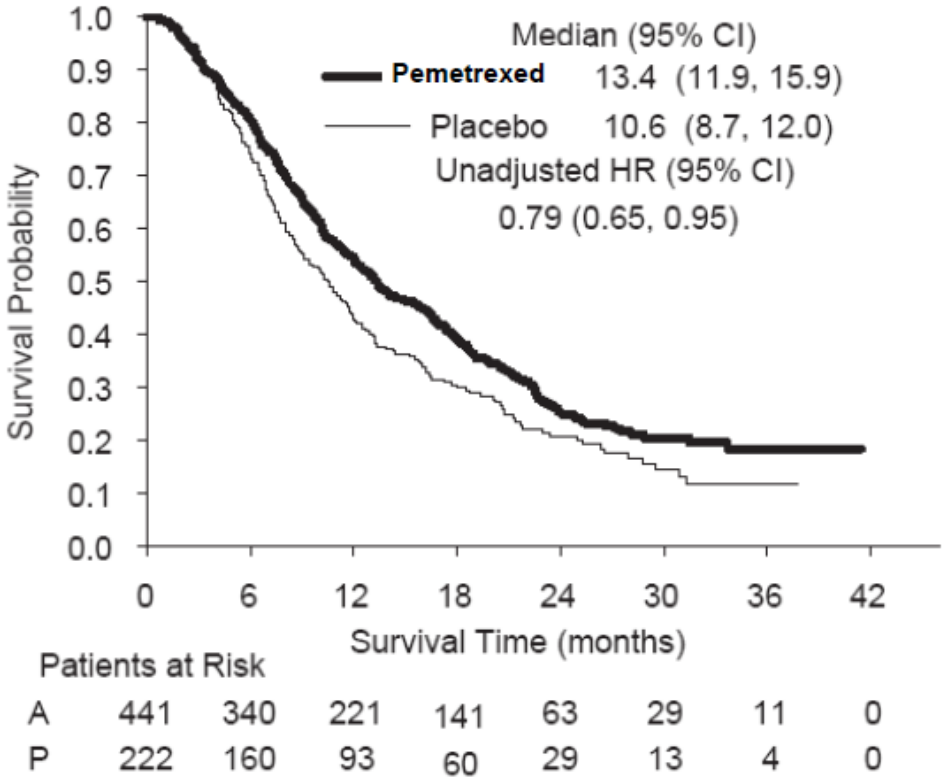


Figure 5: Kaplan-Meier Curve for Overall Survival Pemetrexed (A) versus Placebo (P) in NSCLC - ITT Population.

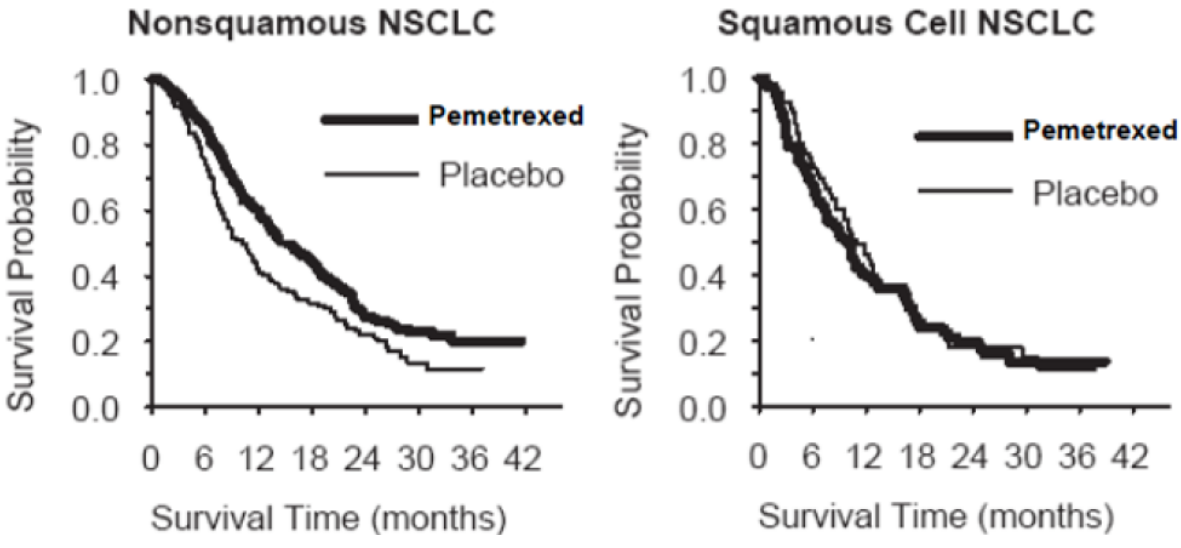
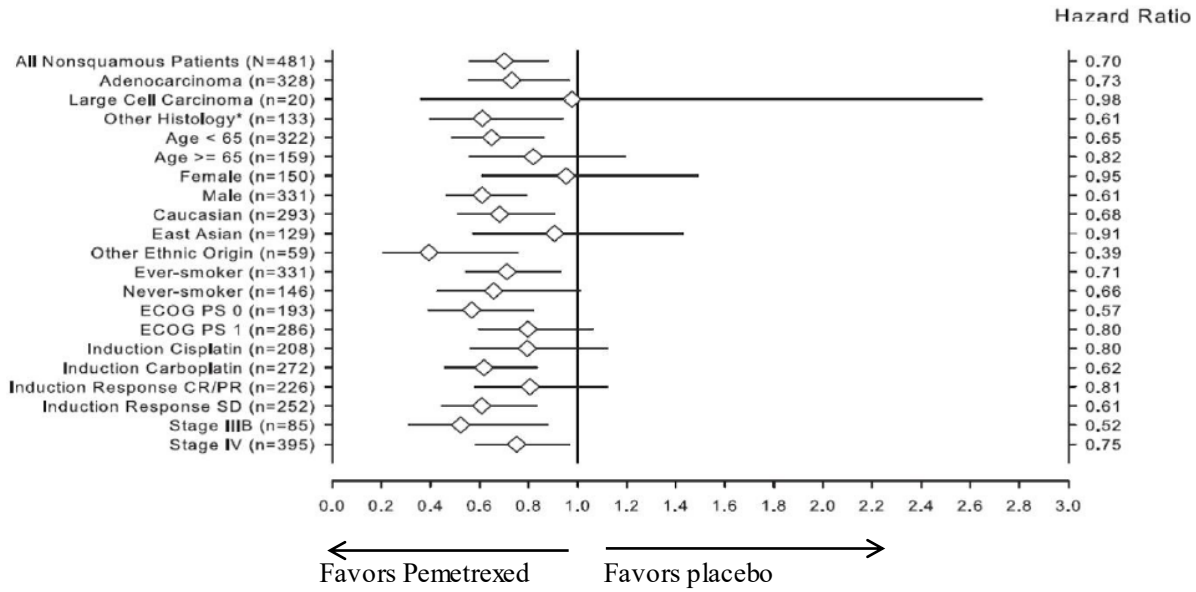


Figure 6: Kaplan-Meier Curves for Overall Survival Pemetrexed versus Placebo in NSCLC - Nonsquamous NSCLC and Squamous Cell NSCLC.

Subsets of patients were examined according to baseline characteristics in pre-specified efficacy analyses. The results of these analyses are shown in Figure 7.



*Patients with a primary diagnosis of NSCL whose disease did not clearly quality as adenocarcinoma, large cell carcinoma, or squamous cell carcinoma.

Figure 7: Forest Plot for Overall Survival Hazard Ratios Pemetrexed versus Placebo – Nonsquamous NSCLC.

Supportive care measures were similar between treatment arms, except: RBC transfusions (pemetrexed9.5% vs placebo 3.2%); erythropoiesis stimulating agents (pemetrexed5.9% vs placebo 1.8%); hospitalizations for a drug-related adverse event (pemetrexed5% vs placebo 0%); enteral/parenteral nutritional support (pemetrexed5% vs placebo 1%).

PARAMOUNT

A multi-centre, randomized, double-blind, placebo-controlled Phase 3 study was conducted to evaluate continuation of pemetrexed in patients with Stage IIIb/IV nonsquamous NSCLC who did not progress after 4 cycles of first line doublet therapy of pemetrexed(500 mg/m^2) in combination with cisplatin (75 mg/m^2). Patients completing induction treatment with a best response of stable disease or better and PS 0/1 were eligible for maintenance treatment. Of the 939 patients treated with pemetrexed plus cisplatin induction, 539 patients were randomized (2:1) to receive maintenance treatment with pemetrexed or placebo. Of the randomized patients, 51.9% had a response of stable disease, 44.7% had a partial response, and 0.2% had a complete response to pemetrexed plus cisplatin induction. The median time from the start of pemetrexed plus cisplatin induction therapy to the start of maintenance treatment was 2.96 months on both the pemetrexed arm and the placebo arm. Efficacy and safety were measured from the time of randomization after completion of first line (induction) therapy. Pemetrexed was administered intravenously over 10 minutes at a dose of 500 mg/m^2 on Day 1 of each 21-day cycle, and continued until disease progression or unacceptable toxicity. Patients in both study arms received folic acid, vitamin B12, and dexamethasone.

The study was designed to demonstrate superior progression-free survival and overall survival of pemetrexed plus best supportive care (BSC) continuation maintenance over placebo plus BSC. Patient demographics of the intent to treat (ITT) population are shown in Table 24.
The demographics and baseline disease characteristics were well balanced between study arms.

Table 24: Maintenance Therapy Following Pemetrexed plus Cisplatin Induction: Summary of Patient Characteristics in Study of Nonsquamous NSCLC

Patient characteristic	Pemetrexed (N=359)	Placebo (N=180)
Age (yrs)		
Median (range)	60.95 (31.9-78.7)	62.35 (34.9-83.3)
Gender		
Male/Female	56.0%/44.0%	62.2%/37.8%
Ethnic Origin		
Caucasian	339 (94.4%)	171 (95.0%)
Asian	16 (4.5%)	8 (4.4%)
African	4 (1.1%)	1 (0.6%)
Stage at Entry[a]		
IIIb/IV	8.6%/91.4%	10.6%/89.4%
Histology (%)		
Nonsquamous NSCLC[b]		
Adenocarcinoma Large cell	310 (86.4%)	161 (89.4%)
Large cell	24 (6.7%)	12 (6.7%)
Other[c]	25 (7.0%)	7 (3.9%)
ECOG PS		
0/1	32.0%/67.7%	30.6%/68.3%
Smoking History[d]		
Ever/never smoker	76.6%/22.8%	80%/18.9%

[a] Stage at Entry was not reported for all randomized patients. Percentages are representative of N = 359 for the pemetrexed arm and N = 180 for the placebo arm.
[b] Histological or cytological diagnosis of NSCLC defined as other than predominantly squamous cell histology (squamous cell and/or mixed small cell, non-small cell histology were not permitted on this study).
[c] The subcategory of "Other" represents patients with a primary diagnosis of NSCLC whose disease did not clearly qualify as adenocarcinoma or large-cell carcinoma.
[d] Smoking history was not reported for all randomized patients. Percentages are representative of N = 359 for the pemetrexed arm, and N = 180 for the placebo arm.

Patients received a median of 4 cycles of maintenance treatment with pemetrexed (range 1-44 cycles) and 4 cycles of placebo (range 1-38 cycles). Patients randomized to continue pemetrexed received a relative dose intensity of 93.7%. A total of 169 patients (47.1%) completed ≥ 6 cycles maintenance treatment with pemetrexed, representing at least 10 total cycles of pemetrexed. The percentage of patients that received post study treatment was 64.3% for pemetrexed and 71.7% for placebo.

Study Results
Efficacy results are presented in Table 25 and Figure 8. Following pemetrexed plus cisplatin induction (4 cycles), treatment with pemetrexed maintenance was statistically superior to placebo for overall survival (OS) (median 13.9 months versus 11.0 months, HR = 0.78 [95% CI: 0.64-0.96], p-value = 0.0195). The investigator assessment of PFS showed that pemetrexed was

statistically superior to placebo (median 4.1 months versus 2.8 months, HR = 0.62 [95% CI: 0.49-0.79], p-value < 0.0001).

Table 25: Maintenance Therapy Following Pemetrexed Plus Cisplatin Induction: Efficacy of Pemetrexed versus Placebo in Nonsquamous NSCLC

Efficacy Parameter[a,b]	**Pemetrexed (N=359)**	**Placebo (N=180)**
Median overall survival[c] (95% CI)	13.9 mos (12.8-16.0)	11.0 mos (10.0-12.5)
Hazard ratio (HR)[c] (95% CI)	0.78 (0.64-0.96)	
p-value	p=0.0195	
1-year survival	58%	45%
2-year survival	32%	21%
Median progression-free survival (95% CI)	4.1 (3.2 – 4.6)	2.8 (2.6 – 3.1)
Hazard ratio (HR)[c] (95% CI)	0.62 (0.49 – 0.79)	
p-value	p<0.0001	

[a] PFS and OS were calculated from time of randomization, after completion of 4 cycles of pemetrexed plus cisplatin induction therapy.
[b] Values for PFS given based on investigator assessment.
[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

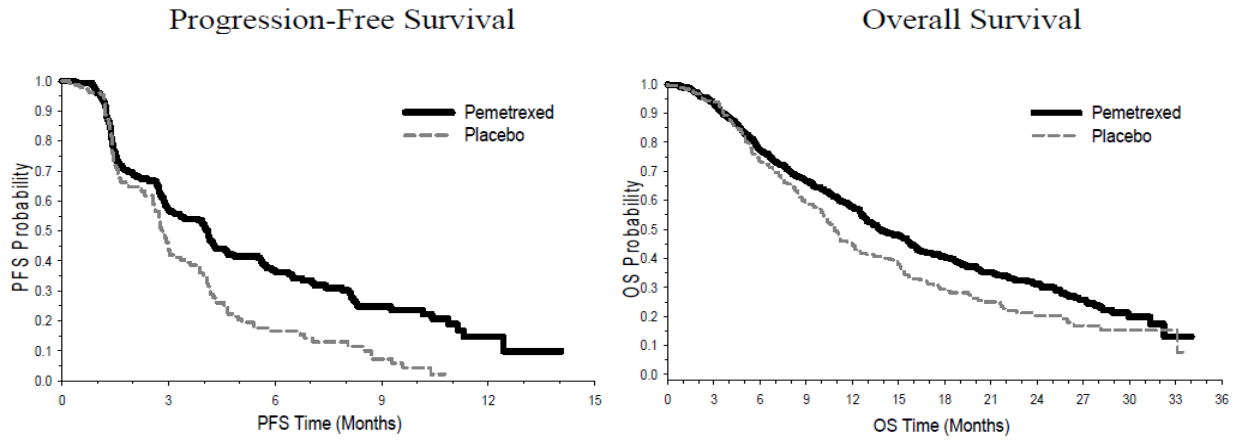
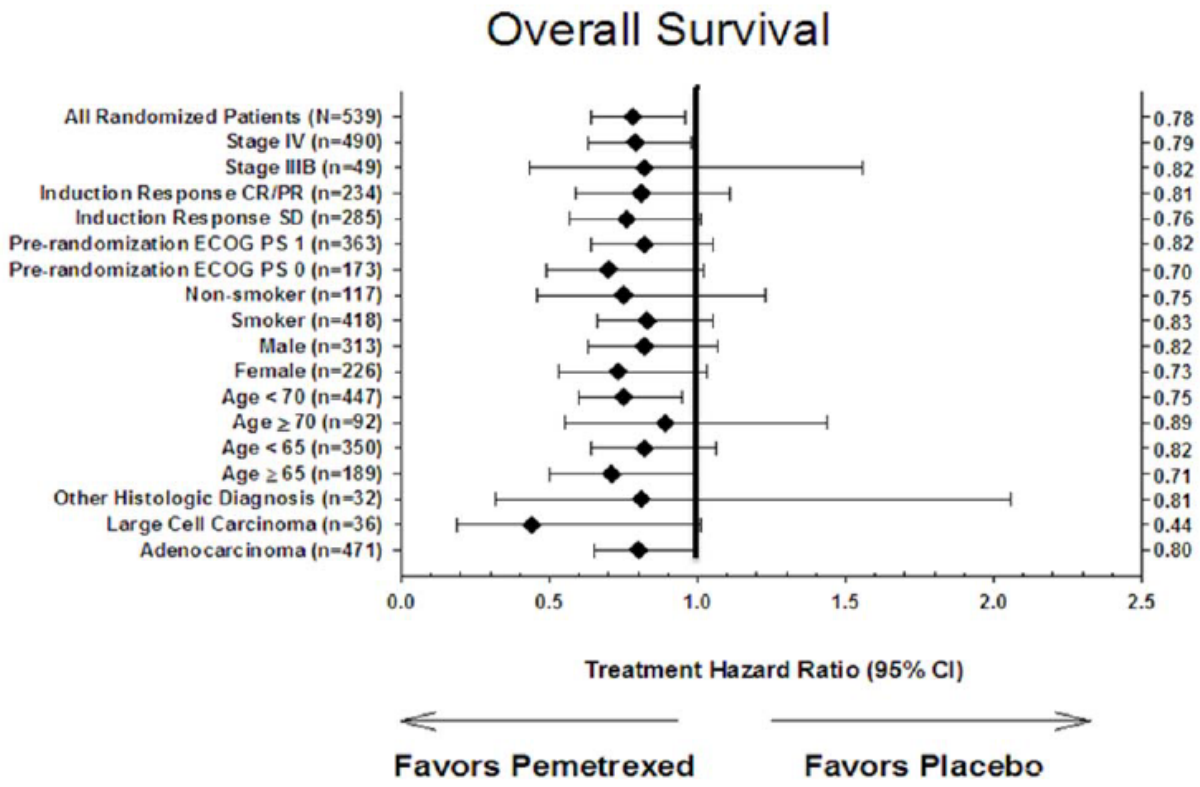


Figure 8: Maintenance Therapy Following Pemetrexed Plus Cisplatin Induction: Kaplan Meier Curve for Progression-Free Survival and Overall Survival for Pemetrexed versus Placebo in Nonsquamous NSCLC (measured from randomization)

For randomized patients, as measured from the start of pemetrexed plus cisplatin first line induction treatment, the median investigator-assessed PFS was 6.9 months for the pemetrexed arm and 5.6 months for the placebo arm (HR = 0.59, 95% CI = 0.47-0.74). The median OS was 16.9 months for the pemetrexed arm and 14.0 months for the placebo arm (HR = 0.78, 95% CI = 0.64-0.96).

The relative treatment effect of pemetrexed across subgroups (including disease stage, induction response, ECOG PS, smoking status, gender, histology, and age) is presented in Figure 9 below.



Abbreviations: CI = confidence interval; CR = complete response; ECOG PS = Eastern Cooperative Oncology Group performance status; N = number of randomized patients; n = number of patients in category; PR = partial response; SD = stable disease.

Figure 9: Overall Survival Hazard Ratios (Pemetrexed over placebo) in Subgroups According to Baseline Characteristics for All Randomized Patients, PARAMOUNT.

A total of 25 patients randomized in this study received reduced dose pemetrexed during the induction phase, 18 of whom continued with the reduced dose in the maintenance phase. Clinical efficacy and safety of the pemetrexed maintenance therapy in this subgroup is unclear (post-hoc analysis). However, patient number is small and definitive conclusion cannot be established.

Second Line – Nonsquamous Non-Small Cell Lung Cancer - Pemetrexed versus Docetaxel

Study Demographics and Trial Design

Table 26: Patient Demographics - Clinical Trial Supporting Efficacy of Pemetrexed versus Docetaxel in the Treatment of NSCLC after Prior Chemotherapy

Study #	Trial Design	Dosage, route of administration and duration	Study subjects and Gender (N=number)	Median age (Range)
H3E-MC-JMEI	randomized, Phase 3, controlled, open-label, multicentre study	Pemetrexed 500 mg/m^2 10-minute iv infusion Docetaxel 75 mg/m^2 1-hour iv infusion Treatment Duration: 21-day cycle median of 4 cycles of therapy for both arms (Pemetrexed: 1 to 20 cycles; Docetaxel: 1 to 14 cycles)	Entered: 698 Randomized: 571 Pemetrexed: 283 (Male:194; Female:89) Docetaxel: 288 (Male 217; Female:71)	Pemetrexed arm Median age=59 Age range=22-81 Docetaxel arm Median age=57 Age range=28-87

A single, Phase 3 multi-center, randomized, open label study was conducted to compare the safety and efficacy of pemetrexed to docetaxel in patients with locally advanced or metastatic (Stage III or IV) NSCLC after prior chemotherapy. The study was intended to show either an overall survival superiority or non-inferiority of pemetrexed to docetaxel. Pemetrexed was administered intravenously over 10 minutes at a dose of 500 mg/m^2 and docetaxel was administered at 75 mg/m^2 as a 1-hour intravenous infusion. Both drugs were given on Day 1 of each 21-day cycle. All patients treated with Pemetrexed received vitamin supplementation with folic acid and vitamin B_{12}. A summary of the patient demographics and characteristics are shown in Tables 26 and 27, respectively.

Table 27: Summary of Patient Characteristics

Patient Characteristic	Pemetrexed (N=283)	Docetaxel (N=288)
Age (yrs)		
Median age, years (range)	59 (22-81)	57 (28-87)
Gender (%)		
Female	31.4	24.7
Male	68.6	75.3
ECOG PS 0 or 1 (%)[a]	88.6	87.6
Stage III/IV disease (%)	25.1/74.9	25.3/74.7
Homocysteine level <12 mcm (%)	71.4	68.9
Diagnosis/Histology (%)		
Adenocarcinoma	54.4	49.3
Squamous	27.6	32.3
Best response to prior chemotherapy (%)		
CR/PR	35.6	36.5
Time since last chemotherapy (%)		
<3 mo	50.4	48.1
>3 mo	49.6	51.9
Prior therapy (%)		
Prior paclitaxel	25.8	27.8
Prior platinum	92.6	89.9

Abbreviations: CR = complete response; ECOG = Eastern Cooperative Oncology Group; ITT = intent to treat; N = number of patients; PR = partial response; PS = performance status.
a Performance status was not reported for all treated patients. Percentages are representative of N=264 for the pemetrexed and N=274 for the docetaxel arm.

Baseline demographic and disease characteristics were similar between the two treatment arms. Approximately three-quarters of the patients were men, reflecting the gender ratio of this disease observed in the general population. The median age of 58 years with a wide age range (22 to 87 years) corresponds with the expected demographics of the general NSCLC patient population. Approximately half of the patients had adenocarcinoma, and approximately 30% had squamous cell carcinoma. About three-quarters of patients presented with Stage IV disease at study entry, as would be expected for patients who experienced a relapse of a previously treated disease. Eighty-eight percent had good performance status. Approximately 90% of the patients had received prior platinum-containing regimens.

Table 28 presents a summary of reported prior therapies for the intent to treat (ITT) population. The two treatment arms were well balanced with respect to all prior therapy categories.

Table 28: Summary of Reported Prior Therapies

	Pemetrexed (N=283) n (%)	**Docetaxel (N=288) n (%)**
Prior surgery	64 (22.6)	67 (23.3)
Prior radiotherapy	125 (44.2)	131 (45.5)
Prior immunotherapy	1 (0.4)	1 (0.3)
Prior chemotherapy	283 (100)	288 (100)
Adjuvant setting	21 (7.4)	18 (6.3)
Neoadjuvant setting	26 (9.2)	23 (8.0)
Locally advanced setting	101 (35.7)	111 (38.5)
Metastatic setting	147 (51.9)	148 (51.4)
One line of therapy	143 (50.5)	146 (50.7)
Two lines of therapy	4 (1.4)	2 (0.7)
Drug therapy needing classification	1 (0.4)	0

Abbreviations: n = number of patients who received specified prior therapy; N = number of intent to treat (ITT) patients

Study Results

The primary endpoint was overall survival. The median survival time was 8.3 months in the pemetrexed treatment arm and 7.9 months in the docetaxel arm, with a hazard ratio of 0.99. The study did not achieve overall survival superiority of pemetrexed over docetaxel. Non-inferiority of pemetrexed to docetaxel could not be demonstrated because a reliable and consistent survival effect of docetaxel required for a non-inferiority analyses could not be estimated from historical trials. However, the similarity of the response rate, median survival rate and 1-year survival rate between pemetrexed and docetaxel was sufficient evidence to consider pemetrexed as a treatment option for patients with NSCLC after prior chemotherapy. See Table 29.

Table 29: Efficacy of Pemetrexed versus Docetaxel in Non-Small Cell Lung Cancer

	Pemetrexed (N=283)	Docetaxel (N=288)
Median overall survival (95% CI)	8.3 mos (7.0-9.4)	7.9 mos (6.3-9.2)
Fixed Margin Method Hazard ratio (HR) (95% CI) Non-inferiority p-value	0.99 (0.82-1.20) 0.226	
Log rank p-value	0.93	
1-year survival (95% CI)	29.7% (23.7-35.6)	29.7% (23.9-35.5)
Overall response rate* (95% CI)	9.1% (5.9-13.2)	8.8% (5.7-12.8)
p-value	>0.999	

Abbreviations: CI = confidence interval; HR = hazard ratio; N = number of intent to treat (ITT) patients
* Number of qualified patients on the pemetrexed arm (N=264) and docetaxel arm (N = 274).

Figure 10 displays the Kaplan-Meier (K-M) survival time graph for the ITT population. Graphs of survival distributions for pemetrexed and docetaxel arms are superimposable.

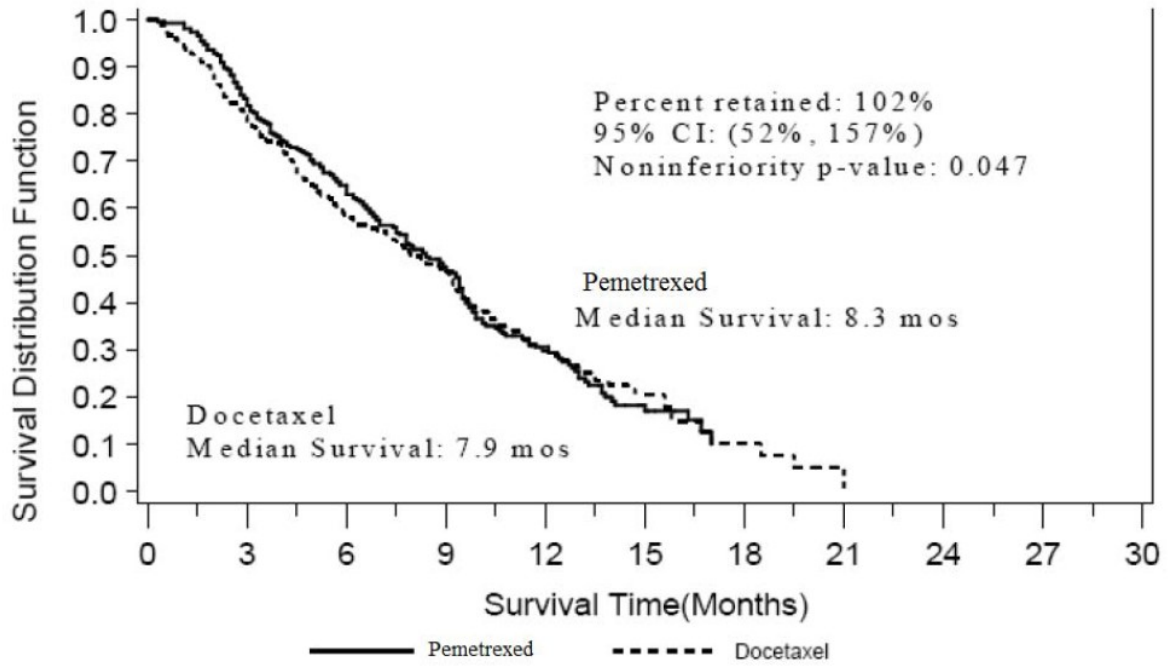


Figure 10: Kaplan-Meier Estimates of Survival Time for Pemetrexed versus Docetaxel.

A retrospective analysis of the impact of NSCLC histology on the treatment effect on overall survival was in favour of pemetrexed versus docetaxel for patients with nonsquamous NSCLC (n = 399, 9.3 versus 8.0 months, adjusted HR = 0.78; 95% CI =0 .61-1.00, p =0.047) and was in favour of docetaxel for patients with squamous cell carcinoma (n = 172, 6.2 versus 7.4 months, adjusted HR = 1.56; 95% CI =1.08-2.26, p =0.018).

There were no significant differences in the results of the secondary endpoints between patients on the pemetrexed arm and docetaxel arm. See Table 30.

Table 30: Secondary Efficacy Endpoints – Pemetrexed versus Docetaxel in Non-Small Cell Lung Cancer

	Pemetrexed		Docetaxel
Progression-free Survival (months)			
No. of patients evaluated	283		288
Median	2.9		2.9
HR (95% CI)		0.97 (0.82–1.16)	
Wald p-value		0.759	
Time to Progressive Disease (months)			
No. of patients evaluated	283		288
Median	3.4		3.5
HR (95% CI)		0.97 (0.80–1.17)	
Wald p-value		0.721	
Time to Treatment Failure (months)			
No. of patients evaluated	282		288
Median	2.3		2.1
HR (95% CI)		0.84 (0.71–0.997)	
Wald p-value		0.046	
Time to Tumour Response (months)			
No. of patients evaluated	24		24
Median	2.9		1.7
ANOVA p-value		0.105	
Duration of Clinical Response (months)			
No. of patients evaluated	24		24
Median	4.6		5.3
HR (95% CI)		0.77 (0.40–1.47)	
Wald p-value		0.427	
Duration of Clinical Benefit (months)			
No. of patients evaluated	145		151
Median	5.4		5.2
HR (95% CI)		0.91 (0.71–1.16)	
Wald p-value		0.450	

No differences were identified between the two treatment arms in any of the patient Lung Cancer Symptom Scales (LCSS). Both treatment arms reported initial increases in average symptom burden index, symptom distress, and interference with activity level that subsequently stabilized. Both arms reported initial deterioration in global quality of life and total LCSS, which subsequently stabilized.

DETAILED PHARMACOLOGY

Pharmacodynamics:

Preclinical studies have shown that pemetrexed inhibited, although with different potency (Table 31) the *in vitro* growth of multiple cell lines, including mesothelioma (MSTO-211H, NCI-H2052), non-small cell lung (A549, LX-1), breast (MCF7, ZR-75-1), colorectal (GC3, HT8, WiDr), leukemia (CCRF-CEM, L1210), and ovarian (IGROV1, SKOV3) carcinomas, as well as cells of these tumor types derived from fresh patient specimens. Additionally, these *in vitro* studies have shown that in certain cell lines, additive or greater than additive growth inhibitory activity could possibly be obtained when pemetrexed was optimally combined with radiation (WiDr colon, MCF7 breast, HeLa cervix, and LX1 lung carcinomas) as well as other

antineoplastic agents, such as cisplatin (NCI-H23 and NCI-H460 lung carcinoma), carboplatin (NCI-H23 lung, SKOV3 ovarian, HT29 colorectal carcinomas), oxaliplatin (HT29 colon carcinoma), doxorubicin (ZR-75-1 breast carcinoma), gemcitabine (HCT8 and HT29 colorectal carcinoma), docetaxel and paclitaxel (NCI-H460 lung carcinoma). In particular, studies with the MSTO-211H mesothelioma cell line showed synergistic effects when pemetrexed was combined concurrently with cisplatin. However, the ratios pemetrexed/cisplatin used in these experiments were different than the ratio used in humans. *In vitro* studies have also suggested that pemetrexed may be active against certain tumor cells that are resistant to methotrexate, 5-fluorouracil, and raltitrexed. Additionally, preclinical animal studies have suggested that folic acid can reduce the severity of the drug-induced toxicity with preservation of the antitumor activity of pemetrexed on several cell lines. Furthermore, folic acid and vitamin B_{12} were shown not to have negative impact on the antitumor activity of pemetrexed in mice. However, no studies of this type have been done on mesothelioma bearing animals.

Table 31: IC_{50} Values of Pemetrexed for Representative Tumor Cell Lines

Tumor Type[a]	IC_{50} (nM)
Mesothelioma MSTO-211H	30
Mesothelioma NCI-H2052	209
NSCLC LX-1	4
NSCLS A549	156
CCRF CEM leukemia	23 to 54
L1210 murine leukemia	14
Colon carcinoma GC3	34
Colon carcinoma HCT8	220
Breast carcinoma MCF7	8.1 to 31
Breast carcinoma ZR-75-1	110
Ovarian carcinoma IGROV-1	44

[a] Examples included here are for commonly available cell lines that have not undergone drug selection or been subjected to genetic alterations.

Absolute neutrophil counts (ANC) following single-agent administration of pemetrexed to non-vitamin-supplemented patients were characterized using a population pharmacodynamic analyses. Severity of hematologic toxicity, as measured by the depth of the ANC nadir, is influenced primarily by the magnitude of systemic exposure (AUC). A 5- to 6-fold increase in pemetrexed AUC produces a 5- to 6-fold lowering of the ANC nadir. Though less pronounced than AUC, increased cystathionine or homocysteine concentrations correlate with a lowering of the ANC nadir, supporting the use of vitamin supplementation. There is no cumulative effect of pemetrexed exposure on ANC nadir over multiple treatment cycles.

Time to ANC nadir also correlates with pemetrexed systemic exposure (AUC), and varied from 8 to 9.6 days after pemetrexed administration over a range of exposures from 38.3 to 316.8 mcg.hr/mL. Return to baseline ANC occurs from 4.2 to 7.5 days following the nadir over the same range of exposures.

TOXICOLOGY

Pemetrexed has been evaluated in a comprehensive series of toxicology studies (see Table 32).

Table 32: Toxicology Program for Pemetrexed Disodium

Study Type and Duration	Route of Administration	Species
Single-dose toxicity	Intravenous	Mouse, rat, dog
Repeat-dose toxicity		
2-weeks (daily)	Intraperitoneal	Mouse
6-weeks (daily, twice/week, once/week)	Intraperitoneal	Mouse
6-month (once/week)	Intraperitoneal	Mouse
2-weeks (daily; twice/week)	Intravenous	Dog
6-weeks (daily, twice/week, once/week)	Intravenous	Dog
1-month (once/week), 3 weeks reversibility	Intravenous	Dog
6-month (once/week or once every 3 weeks)	Intravenous	Dog
9-month (once every 3 weeks)	Intravenous	Dog
Genotoxicity		
Bacterial mutation (Ames)	*In vitro*	*S. typhimurium, E. coli*
Forward mutation	*In vitro*	HGPRT+ CHO cells
Chromosome aberration	*In vitro*	CHO cells
Micronucleus	Intravenous	Mouse
Reproductive and Developmental Toxicity		
Male fertility study	Intraperitoneal	Mouse
Embryo-fetal study	Intravenous	Mouse
Other Toxicity Studies		
Leucovorin rescue	Intravenous	Dog
Thymidine rescue	Intravenous	Dog
Ocular irritation	Conjunctival sac of eye	Rabbit
Dermal irritation	Dermal	Rabbit

Intravenous dosing is the route of administration in humans. All toxicology studies in dogs were conducted by intravenous administration of pemetrexed. The intraperitoneal route was used to assess its repeat-dose toxicity in mice. Pharmacokinetic studies indicated that pemetrexed was rapidly absorbed when administered by the intraperitoneal route, with overall pharmacokinetic profile comparable to the intravenous route. The route of administration of pemetrexed was changed from intraperitoneal to intravenous in the developmental toxicity study in mice to avoid potential damage to the pregnant uterus by the injection needle.

Single-dose toxicity studies with pemetrexed have been performed in mice rats and dogs by the intravenous route of administration. Pemetrexed demonstrated low acute toxicity in mice at the

dose of 4722 mg/m^2, and in male rats, the MLD was 7922 mg/m^2. Dogs' MLD was not determined.

The toxicologic profile of pemetrexed following repeat dosing in dogs and mice is consistent with the known anti proliferative activities of folate antimetabolites. Lesions of mucositis, enteropathy, lymphoid and bone marrow hypocellularity, and effects on spermatogenesis are commonly encountered with folate antimetabolites and other oncolytic agents. The major pathologic effects associated with pemetrexed administration occurred in the intestinal tract and lymphoid tissues; the bone marrow was only minimally affected in dogs and mice given repeated doses up to 6 weeks. However, hematotoxicity was the dose-limiting effect in dogs treated for longer than 6 weeks. Clinical manifestations of toxicity were delayed approximately 1 week from the time of dose administration, with individual animal variability in response to the compound. Modest signs of toxicity were generally reversible with supportive care and interruption of pemetrexed treatment. Supportive care included parenteral fluid therapy, nutritional supplementation, and antibiotics, when clinically appropriate.

Dogs were more sensitive to the toxic effects of pemetrexed than mice. This finding was expected, as mice have a "self-rescue" mechanism in a circulating thymidine moiety that can serve as a replacement source in folate-antagonized cells. Additionally, dogs are generally more predictive of systemic toxicity in man than are mice. Mice tolerated daily doses of 26.2 mg/kg (78.6 mg/m^2) for 6 weeks and 700 mg/kg once weekly for 6 months without any compound-related deaths or clinical signs of toxicity. Most dogs (5 of 6) completed 6 weeks of daily doses of 0.11 mg/kg (2.2 mg/m^2) with minimal clinicopathologic effects. The 1 dog that failed to complete the treatment period had become progressively anorectic, which accentuated the inherent toxicity of the folate antagonism. Higher daily doses were not tolerated for more than 3 weeks. Prominent toxicity was generally more evident in the daily dose schedule, even though the weekly dose was a much larger total dose of pemetrexed. The maximum tolerated dose (MTD) for mice given pemetrexed once weekly for 6 weeks was 314.8 mg/kg (944.4 mg/m^2). The minimally toxic dose for dogs following four doses of pemetrexed given once per week was 25 mg/kg (500 mg/m^2). Four doses of pemetrexed (25 mg/kg) given once per week caused slight-to-moderate decreases in neutrophils, lymphocytes, platelets, and reticulocytes. Primary histopathologic observation was minimal-to- slight enteropathy throughout the gastrointestinal tract. All changes except for the decreased platelet count fully or partially reversed within the 3-week recovery period.

A 6-month repeat dose study in beagle dog was designed to evaluate the chronic toxicity of pemetrexed at doses of 0, 10, or 25 mg/kg (0, 200, or 500 mg/m^2) given intravenously once per week, which bridges directly to the 1-month study described above. However, after approximately 3 months, the dosing frequency was changed to once every 3 weeks for the dogs in the 10-mg/kg group and dosing was discontinued for the 25-mg/kg group due to hematotoxicity. Therefore, hematotoxicity was the dose-limiting effect in this study, and weekly administration of 10 or 25 mg/kg exceeded a tolerated dose. Hematotoxicity was reversible as demonstrated during a 3-month drug holiday in the dogs that had been given 25 mg/kg. Further, even when the10-mg/kg group reached critically low platelet and neutrophil levels, a 3-week period without treatment was sufficient for hematology parameters to completely recover.

An additional chronic study was conducted in which dogs were given pemetrexed intravenously at doses of 0, 10, or 25 mg/kg (0, 200, or 500 mg/m^2) once every 3 weeks for 9 months. The

observed effects were similar to those in the 6-month repeat-dose study in dogs, however, the hematotoxicity was not as severe due to the change in dosing regimen from once a week in the 6-month study to once every 3 weeks in the 9-month study. Additional changes observed in the 9-month study included decreased testes weight with degeneration/necrosis of the seminiferous epithelium and minimal-to-slight renal tubular karyomegaly and degeneration with no organ weight or clinical pathology correlates. This was observed in male dogs only. The effects on the testes, although not seen in previous studies (possibly due to the age of the dogs), were not unexpected based on the effects in the mouse and the cytotoxic nature of pemetrexed.

Pemetrexed was positive in an *in vivo* mouse micronucleus assay. This finding was not unexpected with a compound that causes accumulation of deoxyuridine monophosphate through the inhibition of thymidylate synthase. Therefore, pemetrexed may be a potential clastogenic hazard for man.

In studies on mice, pemetrexed was found to be embryotoxic at a dose of 30 mg/m^2 (1/17 the recommended human dose) and all litters were entirely resorbed at a dose of 150 mg/m^2 (1/3 the recommended human dose) when given in gestation days 6 through 15. Incomplete ossification was observed at a dose of 0.6 mg/m^2 (1/833 of the human dose). Pemetrexed was also fetotoxic (cleft palate) at a dose of 15 mg/m^2 (1/33 the recommended human dose).

Administration of pemetrexed to pregnant mice resulted in decreased fetal weight at doses $\geq$ 0.6 mg/m^2, incomplete ossification of some skeletal structures at doses $\geq$ 3 mg/m^2, and cleft palate at 15 mg/m^2. These observations were not unexpected findings for this class of compound (folic acid antimetabolite) and were consistent with previously reported findings with folic acid antagonists and folic acid deficiency. Administration of pemetrexed at doses of 0.3 to 30 mg/m^2 resulted in male reproductive toxicity characterized by slightly reduced fertility rates and testicular atrophy and epididymal hypospermia.

Two studies were conducted to evaluate potential rescue agents (leucovorin and thymidine) for treatment of severe toxicity due to pemetrexed administration. In the leucovorin rescue study, both clinical signs of toxicity and hematological alterations were reversed by coadministration of leucovorin, a reduced form of folate. In the thymidine rescue study, subsequent administration of thymidine as a continuous infusion for 3 days was successful in rescuing dogs from life-threatening toxicity associated with pemetrexed.

Pemetrexed was found to be a mild ocular irritant and a moderate dermal irritant when evaluated in rabbits. These studies were done to ensure workplace safety.

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PART III: CONSUMER INFORMATION

[Pr]Pemetrexed for Injection

This leaflet is part III of a three-part "Product Monograph" published when Pemetrexed for Injection was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Pemetrexed for Injection. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

Pemetrexed for Injection is used in the treatment of the following types of cancers:

- Malignant pleural mesothelioma (cancer of the lining of the chest cavity) in combination with cisplatin (another anti-cancer drug).
- Nonsquamous locally advanced or metastatic non-small cell lung cancer as:
  - Initial treatment in combination with cisplatin.
  - Maintenance treatment given alone immediately after four cycles of platinum-based first-line chemotherapy.
  - Second line treatment given alone after prior chemotherapy.

What it does:

Pemetrexed for Injection is an antifolate anticancer agent that works by disrupting the metabolic processes that are essential for cell replication. It helps to stop the cancer cells from multiplying.

When it should not be used:

Do not take Pemetrexed for Injection if you:

- are allergic to pemetrexed disodium or any of the ingredients in Pemetrexed for Injection.
- have received or are going to receive the Yellow Fever vaccine.

What the medicinal ingredient is:

Pemetrexed for Injection contains the active ingredient called pemetrexed disodium.

What the important nonmedicinal ingredients are:

Pemetrexed for Injection contains citric acid, L-methionine, monothioglycerol, and water for injection. Hydrochloric acid and/or sodium hydroxide, may have been added to adjust pH.

What dosage forms it comes in:

Pemetrexed for Injection is supplied as sterile solution in single dose vials for intravenous infusion. Each single dose vial supplied in following strengths and fill volume.

STRENGTH / FILL VOLUME	PACK STYLE
100 mg/4 mL (25 mg/mL)	1 single dose vial in a carton
500 mg/20 mL (25 mg/mL)	1 single dose vial in a carton
850 mg/34 mL (25 mg/mL)	1 single dose vial in a carton
1000 mg/40 mL (25 mg/mL)	1 single dose vial in a carton

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- Pemetrexed for Injection should be administered under the supervision of a qualified physician experienced in the use of anticancer agents.
- Liver toxicity and rare cases of fatal liver failure have been reported in clinical trial patients treated with Pemetrexed for Injection alone or in combination with other anticancer drugs.

To lower your chances of side effects of Pemetrexed for Injection, you must also take folic acid and vitamin B_{12} injections prior to and during your treatment with Pemetrexed for Injection.

BEFORE you receive Pemetrexed for Injection talk to your doctor or pharmacist if:

- you have a severe hypersensitivity reaction to Pemetrexed for Injection or to any other ingredient used in the formulation.
- you are pregnant or planning to get pregnant (Pemetrexed for Injection may cause harm to an unborn child).
- you plan to father a child. (Pemetrexed for Injection may cause irreversible infertility).
- you are breast feeding.
- you are under 18 years old.
- you have a kidney disease.
- you have a liver disease.
- you have a heart problem.
- you have ever had radiation therapy.
- you have recently received or are planning on receiving a
- vaccine against Yellow Fever or any live vaccines.

You should discuss effective birth control methods with your doctor. Male patients should not father a child during the treatment and up to 6 months after stopping the treatment.

INTERACTIONS WITH THIS MEDICATION

Tell your doctor or pharmacist if you are taking or have taken other medications, including prescription and nonprescription medicines, vitamins, and natural health products.

Drugs that may interact with Pemetrexed for Injection include:

- NSAIDs (nonsteroidal anti-inflammatory drugs, e.g. ibuprofen): you should stop taking them for at least 5 days before, the day of, and at least 2 days after Pemetrexed for Injection treatment. If it is necessary to take NSAIDs inform your doctor and you will be monitored accordingly.

PROPER USE OF THIS MEDICATION

Usual dose:
Pemetrexed for Injection is slowly infused (injected) into a vein. The injection or infusion will last about 10 minutes. You will usually receive Pemetrexed for Injection once every 21 days (3 weeks).

You may receive Pemetrexed for Injection alone or in combination with cisplatin, another anti-cancer agent. Your doctor will determine your treatment plan, be sure to ask your doctor or health care team if you have any questions.

If your doctor has prescribed cisplatin, it will be infused in your vein for about 2 hours starting about 30 minutes after your treatment with Pemetrexed for Injection.

Pre-Medications
To lower your chances of experiencing harmful side effects, it is important for you to take the following medication and vitamins prior to and/or during your treatment with Pemetrexed for Injection.

Corticosteroid
Your doctor will prescribe a medicine called a "corticosteroid" to take the day before, the day of, and the day after Pemetrexed for Injection treatment. Corticosteroid medicines lower your chances for getting skin reactions with Pemetrexed for Injection.

Folic Acid Tablets
You must start taking 350- 600 micrograms of folic acid every day for at least 5 days out of the 7 days before your first dose of Pemetrexed for Injection. You must keep taking folic acid every day during the time you are getting treatment with Pemetrexed for Injection and for 21 days after your last treatment.

You can get folic acid vitamins over-the-counter. Folic acid is also found in many multivitamin pills. Ask your doctor or pharmacist for help if you are not sure how to choose a folic acid product.

Vitamin B_{12} Injection
Your doctor will give you vitamin B12 injections while you are getting treatment with Pemetrexed for Injection. You will get your first vitamin B_{12} injection during the week before your first dose of Pemetrexed for Injection, and then about every 9 weeks during treatment until 3 weeks after the last dose of Pemetrexed for Injection.

Contact your doctor if you forget to take your pre-medications.

You will have regular blood tests before and during your treatment with Pemetrexed for Injection. Your doctor may adjust your dose of Pemetrexed for Injection or delay treatment based on the results of your blood tests and on your general condition.

Overdose:

If you think you have taken too much Pemetrexed for Injection, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:
Contact your physician immediately for further instructions.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Most patients taking Pemetrexed for Injection will have side effects. Sometimes it is not possible to tell whether Pemetrexed for Injection, another medicine, or the cancer itself is causing these side effects. **Call your doctor right away if you have a fever, chills, diarrhea, or mouth sores.** These symptoms could mean you have an infection.

The most common side effects of Pemetrexed for Injection when taken alone or with cisplatin are:

- Stomach upset, including nausea, vomiting, diarrhea, and constipation.
- Low blood cell counts
  - Low red blood cells may make you feel tired, get tired easily, appear pale, and become short of breath.
  - Low white blood cells may give you a greater chance for infection. If you have a fever (temperature above 38°C) or other signs of infection, call your doctor right away.
  - Low platelets give you a greater chance for bleeding. Your doctor will do blood tests to check your blood counts before and during treatment with Pemetrexed for Injection.
- Tiredness. You may feel tired or weak for a few days after your Pemetrexed for Injection treatments. If you have severe weakness or tiredness, call your doctor.
- Mouth, throat, or lip sores (stomatitis, pharyngitis). You may get redness or sores in your mouth, throat, or on your lips. These symptoms may happen a few days after Pemetrexed for Injection treatment. Talk with your doctor about proper mouth and throat care.

- Loss of appetite. You may lose your appetite and lose weight during your treatment.
- Kidney. Your kidney function may be decreased, sometimes seriously, which may make you feel unwell. Your doctor may do blood tests to monitor your kidney function.
- Rash. You may get a rash or itching during treatment. These usually appear between treatments with Pemetrexed for Injection and usually go away before the next treatment. Sometimes you may get severe skin reactions. Call your doctor if you get a severe rash or itching.
- Fever.

Effects on heart and brain have been reported uncommonly in clinical studies. Severe effects on stomach and intestine including bleeding has been uncommonly reported in clinical studies. Sometimes the effect on intestine are worse after radiation. In clinical studies, severe effects on lung and breathing have been reported. Blood flow disturbance leading to tissue damage has been reported.

Rare cases of unusual swelling in the legs or the face (edema) have been reported.

A small number of patients have reported changes in mood/ depression.

Be sure to tell your doctor if your breathing gets worse while you are on Pemetrexed for Injection.

Talk with your doctor, nurse, or pharmacist about any side effect that bothers you or that doesn't go away. It is important that you continue to take your folic acid and vitamin B_{12} supplements even if you experience serious side effects.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

	Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist*
		Only if severe	In all cases	
Common	Allergic reaction		√	
	Bleeding		√	
	Breathing (Any change)		√	
	Chest pain (new or worsening)		√	
	Diarrhea		√	
	Fever	√		
	Mouth, throat or lip sores		√	
	Nausea	√		
	Skin rash	√		
	Swallowing difficulty		√	
	Tiredness	√		
	Vomiting	√		

*Continue taking your folic acid and vitamin B_{12} injections even if you have serious side effects. Common = 1% to <10%

This is not a complete list of side effects. For any unexpected effects while taking Pemetrexed for Injection, contact your doctor or pharmacist.

HOW TO STORE IT

PEMETREXED FOR INJECTION should be stored at 20 - 25°C, excursions permitted between 15°C and 30°C. Keep vial in the carton until use and protect from light.

Keep out of reach and sight of children.

REPORTING SIDE EFFECTS

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

If you want more information about Pemetrexed for Injection:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Consumer Information by visiting the Health Canada website (https://health-products.canada.ca/dpd-bdpp/index-eng.jsp); or by calling the sponsor Accord Healthcare Inc. at 1-866-296-0354.

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