HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use PEMETREXED INJECTION safely and effectively. See full prescribing information for PEMETREXED INJECTION.

PEMETREXED injection, for intravenous use
Initial U.S. Approval: 2004

---------- INDICATIONS AND USAGE ----------
Pemetrexed Injection is a folate analog metabolic inhibitor indicated:
- as a single agent for the maintenance treatment of patients with locally advanced or metastatic, non-squamous NSCLC whose disease has not progressed after four cycles of platinum-based first-line chemotherapy. (1.1)
- as a single agent for the treatment of patients with recurrent, metastatic non-squamous, NSCLC after prior chemotherapy. (1.1)

Limitations of Use:
Pemetrexed Injection is not indicated for the treatment of patients with squamous cell, non-small cell lung cancer. (1.1)

----------DOSAGE AND ADMINISTRATION ----------
- The recommended dose of Pemetrexed Injection, administered as a single agent, in patients with creatinine clearance of 45 mL/minute or greater is 500 mg/m^2 as an intravenous infusion over 10 minutes on Day 1 of each 21-day cycle. (2.1)
- Initiate folic acid 400 mcg to 1000 mcg orally, once daily, beginning 7 days prior to the first dose of Pemetrexed Injection and continue until 21 days after the last dose of Pemetrexed Injection. (2.3)
- Administer vitamin B_{12}, 1 mg intramuscularly, 1 week prior to the first dose of Pemetrexed Injection and every 3 cycles. (2.3)
- Administer dexamethasone 4 mg orally, twice daily the day before, the day of, and the day after Pemetrexed Injection administration. (2.3)

----------DOSAGE FORMS AND STRENGTHS----------
Injection: 100 mg/4 mL, 500 mg/20 mL or 1 g/40 mL solution in single-dose vials (3)

---------- CONTRAINDICATIONS ----------
History of severe hypersensitivity reaction to pemetrexed. (4)

---------- WARNINGS AND PRECAUTIONS ----------
- Myelosuppression: Can cause severe bone marrow suppression resulting in cytopenia and an increased risk of infection. Do not administer pemetrexed when the absolute neutrophil count is less than 1500 cells/mm^3 and platelets are less than 100,000 cells/mm^3. Initiate supplementation with oral folic acid and intramuscular vitamin B_{12} to reduce the severity of hematologic and gastrointestinal toxicity of pemetrexed. (2.3, 5.1)
- Renal Failure: Can cause severe, and sometimes fatal, renal failure. Do not administer when creatinine clearance is less than 45 mL/min. (2.2, 5.2)
- Bullous and Exfoliative Skin Toxicity: Permanently discontinue for severe and life-threatening bullous, blistering or exfoliating skin toxicity. (5.3)
- Interstitial Pneumonitis: Withhold for acute onset of new or progressive unexplained pulmonary symptoms. Permanently discontinue if pneumonitis is confirmed. (5.4)
- Radiation Recall: Can occur in patients who received radiation weeks to years previously; permanently discontinue for signs of radiation recall. (5.5)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise patients of the potential risk to a fetus and to use effective contraception. (5.7, 8.1, 8.3)

---------- ADVERSE REACTIONS ----------
- The most common adverse reactions (incidence ≥20%) of pemetrexed, when administered as a single agent are fatigue, nausea, and anorexia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Actavis at 1-800-432-8534 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- DRUG INTERACTIONS ----------
Ibuprofen increased risk of pemetrexed toxicity in patients with mild to moderate renal impairment. Modify the ibuprofen dosage as recommended for patients with a creatinine clearance between 45 mL/min and 79 mL/min. (2.4, 5.6, 7)

----------USE IN SPECIFIC POPULATIONS----------
Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 8/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Non-Squamous Non-Small Cell Lung Cancer (NSCLC)

Pemetrexed Injection is indicated:

- as a single agent for the maintenance treatment of patients with locally advanced or metastatic, non-squamous NSCLC whose disease has not progressed after four cycles of platinum-based first-line chemotherapy.
- as a single agent for the treatment of patients with recurrent, metastatic non-squamous, NSCLC after prior chemotherapy.

Limitations of Use: Pemetrexed Injection is not indicated for the treatment of patients with squamous cell, non-small cell lung cancer *[see Clinical Studies (14.1)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage for Non-Squamous NSCLC

- The recommended dose of Pemetrexed Injection for maintenance treatment of non-squamous NSCLC in patients with a creatinine clearance (calculated by Cockcroft-Gault equation) of 45 mL/min or greater is 500 mg/m^2 as an intravenous infusion over 10 minutes on Day 1 of each 21-day cycle until disease progression or unacceptable toxicity after four cycles of platinum-based first-line chemotherapy.
- The recommended dose of Pemetrexed Injection for treatment of recurrent non-squamous NSCLC in patients with a creatinine clearance (calculated by Cockcroft-Gault equation) of 45 mL/min or greater is 500 mg/m^2 as an intravenous infusion over 10 minutes on Day 1 of each 21-day cycle until disease progression or unacceptable toxicity.

2.2 Renal Impairment

- Pemetrexed Injection dosing recommendations are provided for patients with a creatinine clearance (calculated by Cockcroft-Gault equation) of 45 mL/min or greater *[see Dosage and Administration (2.1)]*. There is no recommended dose for patients whose creatinine clearance is less than 45 mL/min *[see Use in Specific Populations (8.6)]*.

2.3 Premedication and Concomitant Medications to Mitigate Toxicity

Vitamin Supplementation

- Initiate folic acid 400 mcg to 1000 mcg orally once daily, beginning 7 days before the first dose of Pemetrexed Injection and continuing until 21 days after the last dose of Pemetrexed Injection *[see Warnings and Precautions (5.1)]*.

- Administer vitamin B_{12}, 1 mg intramuscularly, 1 week prior to the first dose of Pemetrexed Injection and every 3 cycles thereafter. Subsequent vitamin B_{12} injections may be given the same day as treatment with Pemetrexed Injection *[see Warnings and Precautions (5.1)]*. **Do not substitute oral vitamin B_{12} for intramuscular vitamin B_{12}.**

Corticosteroids

- Administer dexamethasone 4 mg orally twice daily for three consecutive days, beginning the day before each Pemetrexed Injection administration.

2.4 Dosage Modification of Ibuprofen in Patients with Mild to Moderate Renal Impairment Receiving Pemetrexed Injection

In patients with creatinine clearances between 45 mL/min and 79 mL/min, modify administration of ibuprofen as follows *[see Warnings and Precautions (5.6), Drug Interactions (7) and Clinical Pharmacology (12.3)]*:

- Avoid administration of ibuprofen for 2 days before, the day of, and 2 days following administration of Pemetrexed Injection.
- Monitor patients more frequently for myelosuppression, renal, and gastrointestinal toxicity, if concomitant administration of ibuprofen cannot be avoided.

2.5 Dosage Modifications for Adverse Reactions

Obtain complete blood count on Days 1, 8, and 15 of each cycle. Assess creatinine clearance prior to each cycle. Do not administer Pemetrexed Injection if the creatinine clearance is less than 45 mL/min.

Delay initiation of the next cycle of Pemetrexed Injection until:

- recovery of non-hematologic toxicity to Grade 0-2,
- absolute neutrophil count (ANC) is 1500 cells/mm^3 or higher, and
- platelet count is 100,000 cells/mm^3 or higher.

Upon recovery, modify the dosage of Pemetrexed Injection in the next cycle as specified in Table 1.

Table 1: Recommended Dosage Modifications for Adverse Reactions[a]

Toxicity in Most Recent Treatment Cycle	**Pemetrexed Injection Dose Modification for Next Cycle**
Myelosuppressive toxicity *[see Warnings and Precautions (5.1)]*	
ANC less than 500/mm^3 **and** platelets greater than or equal to 50,000/mm^3 OR Platelet count less than 50,000/mm^3 without bleeding.	75% of previous dose
Platelet count less than 50,000/mm^3 with bleeding	50% of previous dose
Recurrent Grade 3 or 4 myelosuppression after 2 dose reductions	Discontinue
Non-hematologic toxicity	
Any Grade 3 or 4 toxicities EXCEPT mucositis or neurologic toxicity OR Diarrhea requiring hospitalization	75% of previous dose
Grade 3 or 4 mucositis	50% of previous dose
Renal toxicity *[see Warnings and Precautions (5.2)]*	Withhold until creatinine clearance is 45 mL/min or greater
Grade 3 or 4 neurologic toxicity	Permanently discontinue
Recurrent Grade 3 or 4 non-hematologic toxicity after 2 dose reductions	Permanently discontinue
Severe and life-threatening Skin Toxicity *[see Warnings and Precautions (5.3)]*	Permanently discontinue
Interstitial Pneumonitis *[see Warnings and Precautions (5.4)]*	Permanently discontinue

[a] National Cancer Institute Common Toxicity Criteria for Adverse Events version 2 (NCI CTCAE v2).

2.6 Preparation for Administration

- Pemetrexed Injection is a cytotoxic drug. Follow applicable special handling and disposal procedures.[1]
- Calculate the dose of Pemetrexed Injection and determine the number of vials needed.
- Withdraw the calculated dose of Pemetrexed Injection from the vial(s) and discard vial with any unused portion.
- Dilute Pemetrexed Injection with 5% Dextrose Injection, USP to achieve a total volume of 100 mL for intravenous infusion.
- Administer diluted solution via an 0.2 µm in-line filter.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If particulate matter is observed, do not administer.

Store diluted solution under refrigerated conditions [2° to 8°C (36° to 46°F)] for no more than 14 days from the time of dilution and at room temperature for not more than 8 hours from the time of dilution.

3 DOSAGE FORMS AND STRENGTHS

Injection: Pemetrexed Injection is a clear, colorless to slightly yellowish or slightly yellow-greenish solution available in sterile single-dose vials containing 100 mg/4 mL, 500 mg/20 mL, and 1 g/40 mL of pemetrexed.

4 CONTRAINDICATIONS

Pemetrexed is contraindicated in patients with a history of severe hypersensitivity reaction to pemetrexed *[see Adverse Reactions (6.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Myelosuppression and Increased Risk of Myelosuppression without Vitamin Supplementation

Pemetrexed can cause severe myelosuppression resulting in a requirement for transfusions and which may lead to neutropenic infection. The risk of myelosuppression is increased in patients who do not receive vitamin supplementation.

Initiate supplementation with oral folic acid and intramuscular vitamin B_{12} prior to the first dose of Pemetrexed Injection; continue vitamin supplementation during treatment and for 21 days after the last dose of Pemetrexed Injection to reduce the severity of hematologic and gastrointestinal toxicity of Pemetrexed Injection *[see Dosage and Administration (2.3)]*. Obtain a complete blood count at the beginning of each cycle. Do not administer Pemetrexed Injection until the ANC is at least 1500 cells/mm^3 and platelet count is at least 100,000 cells/mm^3. Permanently reduce Pemetrexed Injection in patients with an ANC of less than 500 cells/mm^3 or platelet count of less than 50,000 cells/mm^3 in previous cycles *[see Dosage and Administration (2.5)]*.

In Studies JMEN, PARAMOUNT, and JMEI, where all patients received vitamin supplementation, incidence of Grade 3-4 neutropenia ranged from 3% to 5%, and incidence of Grade 3-4 anemia ranged from 3% to 5%.

5.2 Renal Failure

Pemetrexed can cause severe, and sometimes fatal, renal toxicity. The incidence of renal failure in clinical studies in which patients received pemetrexed as a single agent ranged from 0.4% to 0.6% (Studies JMEN, PARAMOUNT, and JMEI *[see Adverse Reactions (6.1)]*. Determine creatinine clearance before each dose and periodically monitor renal function during treatment with pemetrexed. Withhold pemetrexed in patients with a creatinine clearance of less than 45 mL/minute *[see Dosage and Administration (2.2)]*.

5.3 Bullous and Exfoliative Skin Toxicity

Serious and sometimes fatal, bullous, blistering and exfoliative skin toxicity, including cases suggestive of Stevens- Johnson Syndrome/Toxic epidermal necrolysis can occur with pemetrexed. Permanently discontinue pemetrexed for severe and life-threatening bullous, blistering or exfoliating skin toxicity.

5.4 Interstitial Pneumonitis

Serious interstitial pneumonitis, including fatal cases, can occur with Pemetrexed Injection treatment. Withhold pemetrexed for acute onset of new or progressive unexplained pulmonary symptoms such as dyspnea, cough, or fever pending diagnostic evaluation.

If pneumonitis is confirmed, permanently discontinue Pemetrexed Injection.

5.5 Radiation Recall

Radiation recall can occur with Pemetrexed Injection in patients who have received radiation weeks to years previously. Monitor patients for inflammation or blistering in areas of previous radiation treatment. Permanently discontinue Pemetrexed Injection for signs of radiation recall.

5.6 Increased Risk of Toxicity with Ibuprofen in Patients with Renal Impairment

Exposure to pemetrexed is increased in patients with mild to moderate renal impairment who take concomitant ibuprofen, increasing the risks of adverse reactions of Pemetrexed Injection. In patients with creatinine clearances between 45 mL/min and 79 mL/min, avoid administration of ibuprofen for 2 days before, the day of, and 2 days following administration of Pemetrexed Injection.

If concomitant ibuprofen use cannot be avoided, monitor patients more frequently for pemetrexed adverse reactions, including myelosuppression, renal, and gastrointestinal toxicity *[see Dosage and Administration (2.4), Drug Interactions (7), and Clinical Pharmacology (12.3)]*.

5.7 Embryo-Fetal Toxicity

Based on findings from animal studies and its mechanism of action, pemetrexed can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, intravenous administration of pemetrexed to pregnant mice during the period of organogenesis was teratogenic, resulting in developmental delays and increased malformations at doses lower than the recommended human dose of 500 mg/m^2. Advise pregnant women of the potential risk to the fetus. Advise females of reproductive potential to use effective contraception during treatment with Pemetrexed Injection and for 6 months after the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with Pemetrexed Injection and for 3 months after the final dose *[see Use in Specific Populations (8.1, 8.3) and Clinical Pharmacology (12.1)]*.

6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the labeling:

- Myelosuppression *[see Warnings and Precautions (5.1)]*
- Renal failure *[see Warnings and Precautions (5.2)]*
- Bullous and exfoliative skin toxicity *[see Warning and Precautions (5.3)]*
- Interstitial pneumonitis *[see Warnings and Precautions (5.4)]*
- Radiation recall *[see Warnings and Precautions (5.5)]*

6.1 Clinical Trials Experience

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

In clinical trials, the most common adverse reactions (incidence ≥20%) of pemetrexed, when administered as a single agent, are fatigue, nausea, and anorexia.

Non-Squamous NSCLC

Maintenance Treatment Following First-line Non- Pemetrexed Containing Platinum-Based Chemotherapy

In Study JMEN, the safety of pemetrexed was evaluated in a randomized (2:1), placebo-controlled, multicenter trial conducted in patients with non-progressive locally advanced or metastatic NSCLC following four cycles of a first-line, platinum-based chemotherapy regimen. Patients received either pemetrexed 500 mg/m^2 or matching placebo intravenously every 21 days until disease progression or unacceptable toxicity. Patients in both study arms were fully supplemented with folic acid and vitamin B_{12}.

Study JMEN excluded patients with an ECOG (Eastern Cooperative Oncology Group)performance status (PS) of 2 or greater, uncontrolled third-space fluid retention, inadequate bone marrow reserve and organ function, or a calculated creatinine clearance (CLcr) < 45 mL/min. Patients unable to stop using aspirin or other non-steroidal anti-inflammatory drugs (NSAIDS) or unable to take folic acid, vitamin B_{12} or corticosteroids were also excluded from the study.

The data described below reflect exposure to pemetrexed in 438 patients in Study JMEN. Median age was 61 years (range 26 to 83 years), 73% of patients were men; 65% were White, 31% were Asian, 2.9% were Hispanic or Latino, and <2% were other ethnicities; 39% had an ECOG PS 0. Patients received a median of 5

cycles of pemetrexed and a relative dose intensity of pemetrexed of 96%. Approximately half the patients (48%) completed at least six, 21-day cycles and 23% completed ten or more 21-day cycles of pemetrexed.

Table 2 provides the frequency and severity of adverse reactions reported in ≥5% of the 438 pemetrexed-treated patients in Study JMEN.

Table 2: Adverse Reactions Occurring in ≥5% of Patients Receiving Pemetrexed in Study JMEN

Adverse Reaction[a]	Pemetrexed (N=438)		Placebo (N=218)	
	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
All adverse reactions	66	16	37	4
Laboratory				
Hematologic				
Anemia	15	3	6	1
Neutropenia	6	3	0	0
Hepatic				
Increased ALT	10	0	4	0
Increased AST	8	0	4	0
Clinical				
Constitutional symptoms				
Fatigue	25	5	11	1
Gastrointestinal				
Nausea	19	1	6	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				
Sensory neuropathy	9	1	4	0
Dermatology/Skin				
Rash/desquamation	10	0	3	0

[a] NCI CTCAE version 3.0.

The requirement for transfusions (9.5% versus 3.2%), primarily red blood cell transfusions, and for erythropoiesis stimulating agents (5.9% versus 1.8%) were higher in the pemetrexed arm compared to the placebo arm.

The following additional adverse reactions were observed in patients who received pemetrexed.

Incidence 1% to<5%
Dermatology/Skin — alopecia, pruritus/itching
Gastrointestinal — constipation
General Disorders — edema, fever
Hematologic — thrombocytopenia
Eye Disorder — ocular surface disease (including conjunctivitis), increased lacrimation

Incidence <1%
Cardiovascular — supraventricular arrhythmia

Dermatology/Skin — erythema multiforme
General Disorders — febrile neutropenia, allergic reaction/hypersensitivity
Neurology — motor neuropathy
Renal — renal failure

Maintenance Treatment Following First-line Pemetrexed Plus Platinum Chemotherapy
The safety of pemetrexed was evaluated in PARAMOUNT, a randomized (2:1), placebo-controlled study conducted in patients with non-squamous NSCLC with non-progressive (stable or responding disease) locally advanced or metastatic NSCLC following four cycles of pemetrexed in combination with platinum-based chemotherapy as first-line therapy for NSCLC. Patients were randomized to receive pemetrexed 500 mg/m^2 or matching placebo intravenously on Day 1 of each 21-day cycle until disease progression or unacceptable toxicity. Patients in both study arms received folic acid and vitamin B_{12} supplementation.

PARAMOUNT excluded patients with an ECOG PS of 2 or greater, uncontrolled third-space fluid retention, inadequate bone marrow reserve and organ function, or a calculated creatinine clearance less than 45 mL/min. Patients unable to stop using aspirin or other non-steroidal anti-inflammatory drugs or unable to take folic acid, vitamin B_{12} or corticosteroids were also excluded from the study.

The data described below reflect exposure to pemetrexed in 333 patients in PARAMOUNT. Median age was 61 years (range 32 to 83 years); 58% of patients were men; 94% were White, 4.8% were Asian, and <1% were Black or African American; 36% had an ECOG PS 0. The median number of maintenance cycles was 4 for pemetrexed and placebo arms. Dose reductions for adverse reactions occurred in 3.3% of patients in the pemetrexed arm and 0.6% in the placebo arm. Dose delays for adverse reactions occurred in 22% of patients in the pemetrexed arm and 16% in the placebo arm.

Table 3 provides the frequency and severity of adverse reactions reported in ≥5% of the 333 pemetrexed-treated patients in PARAMOUNT.

Table 3: Adverse Reactions Occurring in ≥5% of Patients Receiving Pemetrexed in PARAMOUNT

Adverse Reaction[a]	Pemetrexed (N=333)		Placebo (N=167)	
	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grades 3-4 (%)
All adverse reactions	53	17	34	4.8
Laboratory				
Hematologic				
Anemia	15	4.8	4.8	0.6
Neutropenia	9	3.9	0.6	0
Clinical				
Constitutional symptoms				
Fatigue	18	4.5	11	0.6
Gastrointestinal				
Nausea	12	0.3	2.4	0
Vomiting	6	0	1.8	0
Mucositis/stomatitis	5	0.3	2.4	0
General disorders				
Edema	5	0	3.6	0

[a] NCI CTCAE version 3.0.

The requirement for red blood cell (13% versus 4.8%) and platelet (1.5% versus 0.6%) transfusions, erythropoiesis stimulating agents (12% versus 7%), and granulocyte colony stimulating factors (6% versus 0%) were higher in the pemetrexed arm compared to the placebo arm.

The following additional Grade 3 or 4 adverse reactions were observed more frequently in the pemetrexed arm.

Incidence 1% to <5%
Blood/Bone Marrow — thrombocytopenia
General Disorders — febrile neutropenia

Incidence <1%
Cardiovascular — ventricular tachycardia, syncope
General Disorders — pain
Gastrointestinal — gastrointestinal obstruction
Neurologic — depression
Renal — renal failure
Vascular — pulmonary embolism

Treatment of Recurrent Disease After Prior Chemotherapy
The safety of pemetrexed was evaluated in Study JMEI, a randomized (1:1), open-label, active-controlled trial conducted in patients who had progressed following platinum-based chemotherapy. Patients received pemetrexed 500 mg/m^2 intravenously or docetaxel 75 mg/m^2 intravenously on Day 1 of each 21-day cycle. All patients on the pemetrexed arm received folic acid and vitamin B_{12} supplementation.

Study JMEI excluded patients with an ECOG PS of 3 or greater, uncontrolled third-space fluid retention, inadequate bone marrow reserve and organ function, or a calculated creatinine clearance less than 45 mL/min. Patients unable to discontinue aspirin or other non-steroidal anti-inflammatory drugs or unable to take folic acid, vitamin B_{12} or corticosteroids were also excluded from the study.

The data described below reflect exposure to pemetrexed in 265 patients in Study JMEI. Median age was 58 years (range 22 to 87 years); 73% of patients were men; 70% were White, 24% were Asian, 2.6% were Black or African American, 1.8% were Hispanic or Latino, and <2% were other ethnicities; 19% had an ECOG PS 0.

Table 4 provides the frequency and severity of adverse reactions reported in ≥5% of the 265 pemetrexed-treated patients in Study JMEI. Study JMEI is not designed to demonstrate a statistically significant reduction in adverse reaction rates for pemetrexed, as compared to the control arm, for any specified adverse reaction listed in the Table 4 below.

Table 4: Adverse Reactions Occurring in ≥5% of Fully Supplemented Patients Receiving Pemetrexed in Study JMEI

Adverse Reaction[a]	Pemetrexed (N=265)		Docetaxel (N=276)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Laboratory				
Hematologic				
Anemia	19	4	22	4
Neutropenia	11	5	45	40
Thrombocytopenia	8	2	1	0
Hepatic				
Increased ALT	8	2	1	0

Increased AST	7	1	1	0
Clinical				
Gastrointestinal				
Nausea	31	3	17	2
Anorexia	22	2	24	3
Vomiting	16	2	12	1
Stomatitis/pharyngitis	15	1	17	1
Diarrhea	13	0	24	3
Constipation	6	0	4	0
Constitutional symptoms				
Fatigue	34	5	36	5
Fever	8	0	8	0
Dermatology/Skin				
Rash/desquamation	14	0	6	0
Pruritus	7	0	2	0
Alopecia	6	1	38	2

[a] NCI CTCAE version 2.0.

The following additional adverse reactions were observed in patients assigned to receive pemetrexed.

Incidence 1% to <5%
Body as a Whole — abdominal pain, allergic reaction/hypersensitivity, febrile neutropenia, infection
Dermatology/Skin — erythema multiforme
Neurology — motor neuropathy, sensory neuropathy

Incidence <1%
Cardiovascular — supraventricular arrhythmias
Renal — renal failure

The following adverse reactions occurred more frequently in patients who were fully vitamin supplemented than in patients who were never supplemented:

- hypertension (11% versus 3%),
- chest pain (8% versus 6%),
- thrombosis/embolism (6% versus 3%).

Additional Experience Across Clinical Trials
Sepsis, with or without neutropenia, including fatal cases: 1%
Severe esophagitis, resulting in hospitalization: <1%

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of pemetrexed. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and Lymphatic System — immune-mediated hemolytic anemia
Gastrointestinal — colitis, pancreatitis
General Disorders and Administration Site Conditions — edema
Injury, poisoning, and procedural complications — radiation recall
Respiratory — interstitial pneumonitis

Skin — Serious and fatal bullous skin conditions, Stevens-Johnson syndrome, and toxic epidermal necrolysis

7 DRUG INTERACTIONS

Effects of Ibuprofen on Pemetrexed

Ibuprofen increases exposure (AUC) of pemetrexed *[see Clinical Pharmacology (12.3)]*. In patients with creatinine clearance between 45 mL/min and 79 mL/min:

- Avoid administration of ibuprofen for 2 days before, the day of, and 2 days following administration of Pemetrexed Injection *[see Dosage and Administration (2.4)]*.
- Monitor patients more frequently for myelosuppression, renal, and gastrointestinal toxicity, if concomitant administration of ibuprofen cannot be avoided.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings from animal studies and its mechanism of action, pemetrexed can cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1)]*. There are no available data on pemetrexed use in pregnant women. In animal reproduction studies, intravenous administration of pemetrexed to pregnant mice during the period of organogenesis was teratogenic, resulting in developmental delays and malformations at doses lower than the recommended human dose of 500 mg/m^2 *[see Data]*. Advise pregnant women of the potential risk to a fetus *[see Use in Special Populations (8.3)]*.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Animal Data

Pemetrexed was teratogenic in mice. Daily dosing of pemetrexed by intravenous injection to pregnant mice during the period of organogenesis increased the incidence of fetal malformations (cleft palate; protruding tongue; enlarged or misshaped kidney; and fused lumbar vertebra) at doses (based on BSA) 0.03 times the human dose of 500 mg/m^2. At doses, based on BSA, greater than or equal to 0.0012 times the 500 mg/m^2 human dose, pemetrexed administration resulted in dose-dependent increases in developmental delays (incomplete ossification of talus and skull bone; and decreased fetal weight).

8.2 Lactation

Risk Summary

There is no information regarding the presence of pemetrexed or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production. Because of the potential for serious adverse reactions in breastfed infants from pemetrexed, advise women not to breastfeed during treatment with pemetrexed and for one week after last dose.

8.3 Females and Males of Reproductive Potential

Based on animal data pemetrexed can cause malformations and developmental delays when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*.

Pregnancy Testing

Verify pregnancy status of females of reproductive potential prior to initiating Pemetrexed Injection [see Use in Specific Populations (8.1)].

Contraception

Females
Because of the potential for genotoxicity, advise females of reproductive potential to use effective contraception during treatment with pemetrexed for at least 6 months after the final dose of pemetrexed.

Males
Because of the potential for genotoxicity, advise males with female partners of reproductive potential to use effective contraception during treatment with pemetrexed and for 3 months after the final dose *[see Nonclinical Toxicology (13.1)]*.

Infertility
Males
Pemetrexed may impair fertility in males of reproductive potential. It is not known whether these effects on fertility are reversible *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use
The safety and effectiveness of pemetrexed in pediatric patients have not been established. The safety and pharmacokinetics of pemetrexed were evaluated in two clinical studies conducted in pediatric patients with recurrent solid tumors. pemetrexed was administered at doses ranging from 400 to 2480 mg/m^2 intravenously over 10 minutes on Day 1 of a 21-day cycle to 32 pediatric patients with recurrent solid tumors in a dose-finding study. The maximum tolerated dose (MTD) was determined to be 1910 mg/m^2 (60 mg/kg for patients <12 months old). Pemetrexed was administered at the MTD every 21 days in an activity-estimating study enrolling 72 patients with relapsed or refractory osteosarcoma, Ewing sarcoma/peripheral primitive neural ectodermal tumor (PNET), rhabdomyosarcoma, neuroblastoma, ependymoma, medulloblastoma/supratentorial PNET, or non-brainstem high grade glioma. Patients in both studies received concomitant vitamin B_{12} and folic acid supplementation and dexamethasone.

No tumor responses were observed. Adverse reactions observed in pediatric patients were similar to those observed in adults.

Single-dose pharmacokinetics of pemetrexed administered at doses ranging from 400 to 2480 mg/m^2 were evaluated in 22 patients (13 males and 9 females) age 4 to 18 years (average age 12 years). Pemetrexed exposure (AUC and C_{max}) appeared to increase proportionally with dose. Average clearance (2.30 L/h/m^2) and half-life (2.3 hours) were similar in pediatric patients compared to adults.

8.5 Geriatric Use
Of the 3,946 patients enrolled in clinical studies of pemetrexed, 34% were 65 and over and 4% were 75 and over. No overall differences in effectiveness were observed between these patients and younger patients. The incidences of Grade 3-4 anemia, fatigue, thrombocytopenia, hypertension, and neutropenia were higher in patients 65 years of age and older as compared to younger patients in at least one of five randomized clinical trials *[see Adverse Reactions (6.1) and Clinical Studies (14.1)]*.

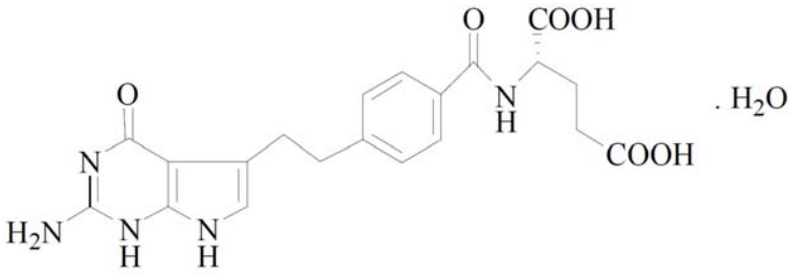
8.6 Patients with Renal Impairment
Pemetrexed is primarily excreted by the kidneys. Decreased renal function results in reduced clearance and greater exposure (AUC) to pemetrexed compared with patients with normal renal function *[Warnings and Precautions (5.2, 5.6) and Clinical Pharmacology (12.3)]*. No dose is recommended for patients with creatinine clearance less than 45 mL/min *[see Dosage and Administration (2.2)]*.

10 OVERDOSAGE

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

11 DESCRIPTION

Pemetrexed is a folate analog metabolic inhibitor. The drug substance, pemetrexed diacid monohydrate, has the chemical name N-[4-[2-(2-amino-4,7-dihydro-4-oxo-1H-pyrrolo[2,3-*d*] pyrimidin-5-yl)ethyl]benzoyl]-L-glutamic acid, monohydrate with a molecular formula of $C_{20}H_{21}N_5O_6 \cdot H_2O$ and a molecular weight of 445.43. It is practically insoluble in water. The structural formula is as follows:



Pemetrexed Injection is supplied as a sterile solution for intravenous infusion available in single-dose vials. The product is a clear to slightly yellowish or slightly yellow-greenish solution. Each mL contains 25 mg pemetrexed, 35 mg tromethamine, 10 mg citric acid anhydrous, 0.5 mg methionine and water for injection. Tromethamine may have been added to adjust pH.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Pemetrexed Injection is a folate analog metabolic inhibitor that disrupts folate-dependent metabolic processes essential for cell replication. *In vitro* studies show that pemetrexed inhibits thymidylate synthase (TS), dihydrofolate reductase, and glycinamide ribonucleotide formyltransferase (GARFT), which are folate-dependent enzymes involved in the de novo biosynthesis of thymidine and purine nucleotides. Pemetrexed is taken into cells by membrane carriers such as the reduced folate carrier and membrane folate binding protein transport systems. Once in the cell, pemetrexed is converted to polyglutamate forms by the enzyme folylpolyglutamate synthetase. The polyglutamate forms are retained in cells and are inhibitors of TS and GARFT.

12.2 Pharmacodynamics

Based on population pharmacodynamic analyses, the depth of the absolute neutrophil counts (ANC) nadir correlates with the systemic exposure to pemetrexed and supplementation with folic acid and vitamin B_{12}. There is no cumulative effect of pemetrexed exposure on ANC nadir over multiple treatment cycles.

12.3 Pharmacokinetics

The pharmacokinetics of pemetrexed were evaluated in patients with cancer at doses ranging from 0.2 to 838 mg/m^2 [0.0004 to 1.7 times the recommended dosage] infused over a 10-minutes. Pemetrexed total systemic exposure (AUC) and maximum plasma concentration (C_{max}) increased proportionally with increase of dose. The pharmacokinetics of pemetrexed did not change over multiple treatment cycles.

Distribution

Pemetrexed has a steady-state volume of distribution of 16.1 liters. In vitro pemetrexed is 81% bound to plasma proteins.

Elimination

The total systemic clearance of pemetrexed is 91.8 mL/min and the elimination half-life of pemetrexed is 3.5 hours in patients with normal renal function (creatinine clearance of 90 mL/min). As renal function decreases, the clearance of pemetrexed decreases and exposure (AUC) of pemetrexed increases.

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. *In vitro* studies indicated that pemetrexed is a substrate of OAT3 (organic anion transporter 3), a transporter that is involved in the active secretion of pemetrexed.

Specific Populations

Age (26 to 80 years) and sex had no clinically meaningful effect on the systemic exposure of pemetrexed based on population pharmacokinetic analyses.

Racial Groups

The pharmacokinetics of pemetrexed were similar in Whites and Blacks or African Americans. Insufficient data are available for other ethnic groups.

Patients with Hepatic Impairment

Pemetrexed has not been formally studied in patients with hepatic impairment. No effect of elevated AST, ALT, or total bilirubin on the PK of pemetrexed was observed in clinical studies.

Patients with Renal Impairment

Pharmacokinetic analyses of pemetrexed included 127 patients with impaired renal function. Plasma clearance of pemetrexed decreases as renal function decreases, with a resultant increase in systemic exposure. Patients with creatinine clearances of 45, 50, and 80 mL/min had 65%, 54%, and 13% increases, respectively in systemic exposure (AUC) compared to patients with creatinine clearance of 100 mL/min *[see Dosage and Administration (2.2) and Warnings and Precautions (5.2)]*.

Third-Space Fluid

The pemetrexed plasma concentrations in patients with various solid tumors with stable, mild to moderate third-space fluid were comparable to those observed in patients without third space fluid collections. The effect of severe third space fluid on pharmacokinetics is not known.

Drug Interaction Studies

Drugs Inhibiting OAT3 Transporter

Ibuprofen, an OAT3 inhibitor, administered at 400 mg four times a day decreased the clearance of pemetrexed and increased its exposure (AUC) by approximately 20% in patients with normal renal function (creatinine clearance >80 mL/min).

In Vitro Studies

Pemetrexed is a substrate for OAT3. Ibuprofen, an OAT3 inhibitor inhibited the uptake of pemetrexed in OAT3-expressing cell cultures with an average $[I_u]/IC_{50}$ ratio of 0.38. *In vitro* data predict that at clinically relevant concentrations, other NSAIDs (naproxen, diclofenac, celecoxib) would not inhibit the uptake of pemetrexed by OAT3 and would not increase the AUC of pemetrexed to a clinically significant extent. *[see Drug Interactions (7)]*.

Pemetrexed is a substrate for OAT4. *In vitro*, ibuprofen and other NSAIDs (naproxen, diclofenac, celecoxib) are not inhibitors of OAT4 at clinically relevant concentrations.

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

Vitamins
Neither folic acid nor vitamin B_{12} affect the pharmacokinetics of pemetrexed.

Drugs Metabolized by Cytochrome P450 Enzymes
In vitro studies suggest that pemetrexed does not inhibit the clearance of drugs metabolized by CYP3A, CYP2D6, CYP2C9, and CYP1A2.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity studies have been conducted with pemetrexed. Pemetrexed was clastogenic in an in vivo micronucleus assay in mouse bone marrow but was not mutagenic in multiple *in vitro* tests (Ames assay, Chinese Hamster Ovary cell assay).

Pemetrexed administered intraperitoneally at doses of ≥0.1 mg/kg/day to male mice (approximately 0.006 times the recommended human dose based on BSA) resulted in reduced fertility, hypospermia, and testicular atrophy.

14 CLINICAL STUDIES

14.1 Non-Squamous NSCLC

Maintenance Treatment Following First-line Non-Pemetrexed Containing Platinum-Based Chemotherapy
The efficacy of pemetrexed as maintenance therapy following first-line platinum-based chemotherapy was evaluated in Study JMEN (NCT00102804), a multicenter, randomized (2:1), double-blind, placebo-controlled study conducted in 663 patients with Stage IIIb/IV NSCLC who did not progress after four cycles of platinum-based chemotherapy. Patients were randomized to receive pemetrexed 500 mg/m^2 intravenously every 21 days or placebo until disease progression or intolerable toxicity. Patients in both study arms received folic acid, vitamin B_{12}, and dexamethasone *[see Dosage and Administration (2.3)]*. Randomization was carried out using a minimization approach [Pocock and Simon (1975)] using the following factors: gender, ECOG PS (0 versus 1), response to prior chemotherapy (complete or partial response versus stable disease), history of brain metastases (yes versus no), non-platinum component of induction therapy (docetaxel versus gemcitabine versus paclitaxel), and disease stage (IIIb versus IV). The major efficacy outcome measures were progression-free survival based on assessment by independent review and overall survival; both were measured from the date of randomization in Study JMEN.

A total of 663 patients were enrolled with 441 patients randomized to pemetrexed and 222 patients randomized to placebo. The median age was 61 years (range 26-83 years); 73% were male; 65% were White, 32% were Asian, 2.9% were Hispanic or Latino, and <2% were other ethnicities; 60% had an ECOG PS of 1; and 73% were current or former smokers. Median time from initiation of platinum-based chemotherapy to randomization was 3.3 months (range 1.6 to 5.1 months) and 49% of the population achieved a partial or complete response to first-line, platinum-based chemotherapy. With regard to tumor characteristics, 81% had Stage IV disease, 73% had non-squamous NSCLC and 27% had squamous NSCLC. Among the 481 patients with non-squamous NSCLC, 68% had adenocarcinoma, 4% had large cell, and 28% had other histologies.

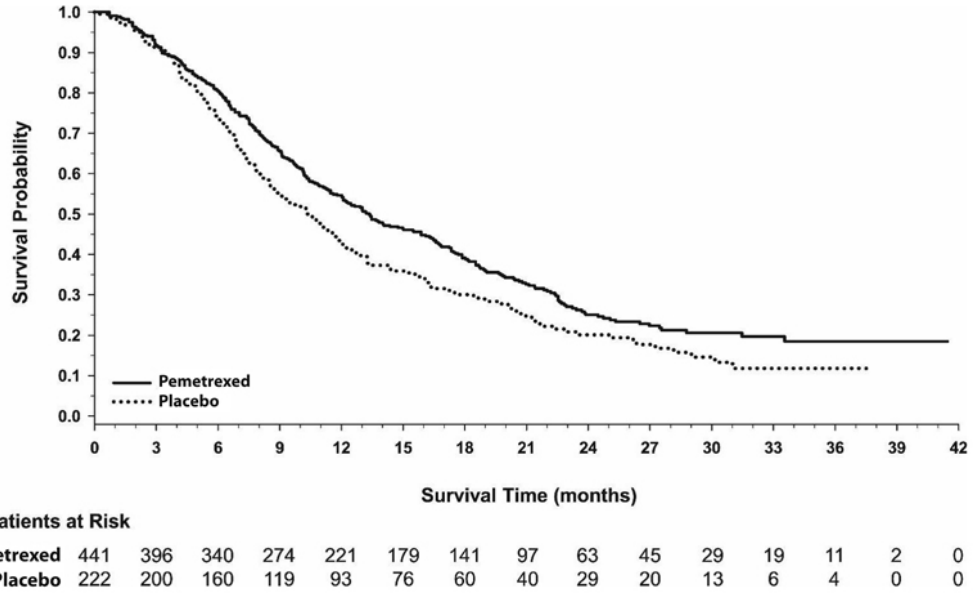
Efficacy results are presented in Table 5 and Figure 1.

Table 5: Efficacy Results in Study JMEN

Efficacy Parameter	Pemetrexed	Placebo
Overall survival	N=441	N=222
Median (months) (95% CI)	13.4 (11.9-15.9)	10.6 (8.7-12.0)
Hazard ratio[a] (95% CI)	0.79 (0.65-0.95)	
p-value	p=0.012	
Progression-free survival per independent review	N=387	N=194
Median (months) (95% CI)	4.0 (3.1-4.4)	2.0 (1.5-2.8)
Hazard ratio[a] (95% CI)	0.60 (0.49-0.73)	
p-value	p<0.00001	

[a] Hazard ratios are adjusted for multiplicity but not for stratification variables.

Figure 1: Kaplan-Meier Curves for Overall Survival in Study JMEN



The results of pre-specified subgroup analyses by NSCLC histology are presented in Table 6 and Figures 2 and 3.

Table 6: Efficacy Results in Study JMEN by Histologic Subgroup

Efficacy Parameter	Overall Survival		Progression-Free Survival Per Independent Review	
	Pemetrexed (N=441)	Placebo (N=222)	Pemetrexed (N=387)	Placebo (N=194)
Non-squamous NSCLC (n=481)				
Median (months)	15.5	10.3	4.4	1.8
HR[a] (95% CI)	0.70 (0.56 to 0.88)		0.47 (0.37 to 0.60)	
Adenocarcinoma (n=328)				
Median (months)	16.8	11.5	4.6	2.7
HR[a]	0.73		0.51	

(95% CI)	(0.56 to 0.96)		(0.38 to 0.68)	
Large cell carcinoma (n=20)				
Median (months)	8.4	7.9	4.5	1.5
HR[a] (95% CI)	0.98 (0.36 to 2.65)		0.40 (0.12 to 1.29)	
Other[b] (n=133)				
Median (months)	11.3	7.7	4.1	1.6
HR[a] (95% CI)	0.61 (0.40 to 0.94)		0.44 (0.28 to 0.68)	
Squamous cell NSCLC (n=182)				
Median (months)	9.9	10.8	2.4	2.5
HR[a] (95% CI)	1.07 (0.77 to 1.50)		1.03 (0.71 to 1.49)	

[a] Hazard ratios are not adjusted for multiplicity
[b] Primary diagnosis of NSCLC not specified as adenocarcinoma, large cell carcinoma, or squamous cell carcinoma.

Figure 2: Kaplan-Meier Curves for Overall Survival in Non-squamous NSCLC in Study JMEN

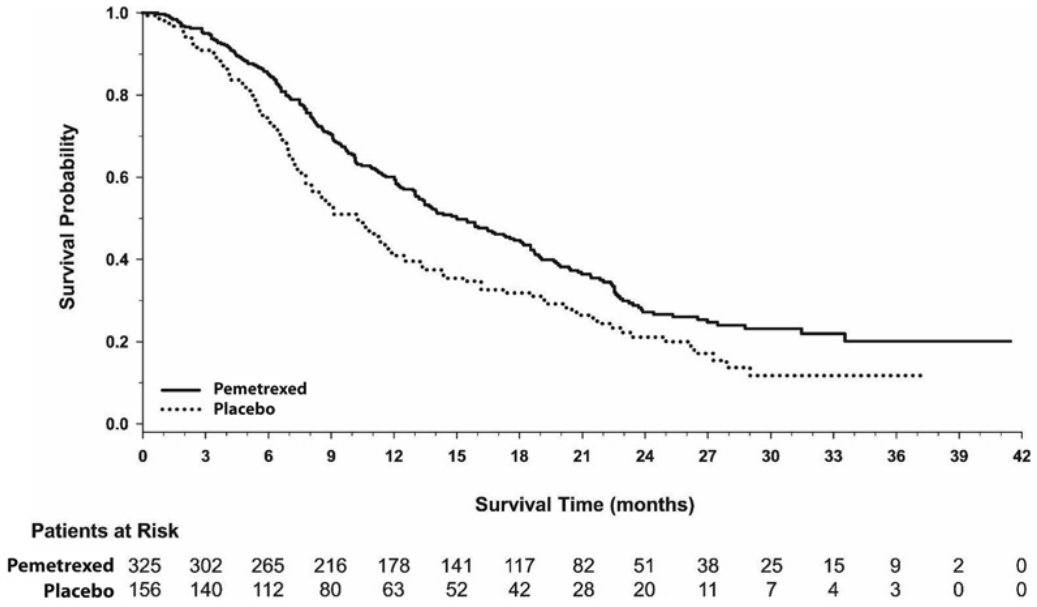
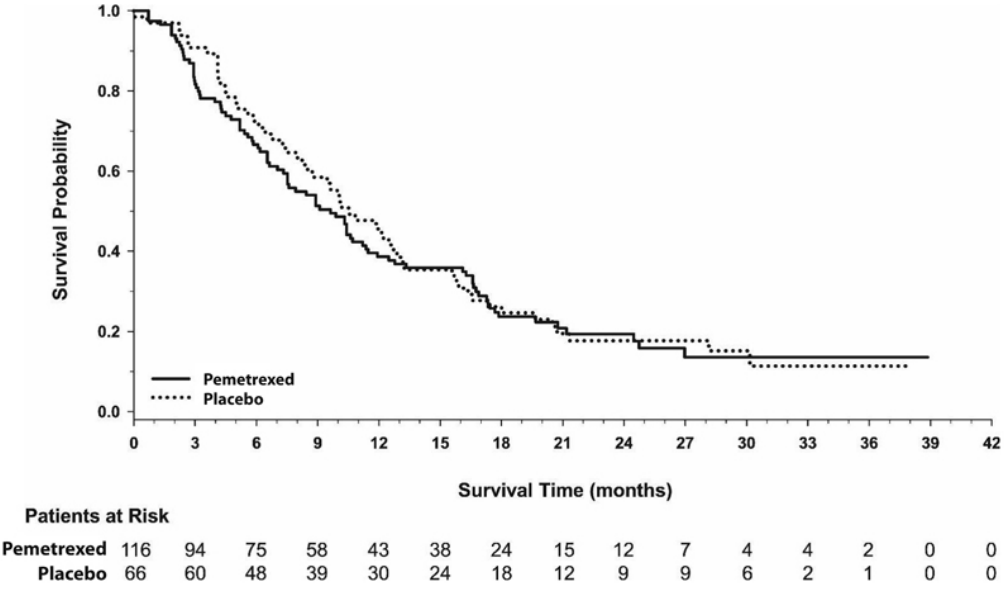


Figure 3: Kaplan-Meier Curves for Overall Survival in Squamous NSCLC in Study JMEN



Maintenance Treatment Following First-line Pemetrexed Plus Platinum Chemotherapy

The efficacy of pemetrexed as maintenance therapy following first-line platinum-based chemotherapy was also evaluated in PARAMOUNT (NCT00789373), a multi-center, randomized (2:1), double-blind, placebo-controlled study conducted in patients with Stage IIIb/IV non-squamous NSCLC who had completed four cycles of pemetrexed in combination with platinum-based first-line chemotherapy and achieved a complete response (CR) or partial response (PR) or stable disease (SD). Patients were required to have an ECOG PS of 0 or 1. Patients were randomized to receive pemetrexed 500 mg/m^2 intravenously every 21 days or placebo until disease progression. Randomization was stratified by response to pemetrexed in combination with platinum-based first-line chemotherapy induction therapy (CR or PR versus SD), disease stage (IIIb versus IV), and ECOG PS (0 versus 1). Patients in both arms received folic acid, vitamin B_{12}, and dexamethasone. The main efficacy outcome measure was investigator-assessed progression- free survival (PFS) and an additional efficacy outcome measure was overall survival (OS); PFS and OS were measured from the time of randomization.

A total of 539 patients were enrolled with 359 patients randomized to pemetrexed and 180 patients randomized to placebo. The median age was 61 years (range 32 to 83 years); 58% were male; 95% were White, 4.5% were Asian, and <1% were Black or African American; 67% had an ECOG PS of 1; 78% were current or former smokers; and 43% of the population achieved a partial or complete response to first-line, platinum-based chemotherapy. With regard to tumor characteristics, 91% had Stage IV disease, 87% had adenocarcinoma, 7% had large cell, and 6% had other histologies.

Efficacy results for PARAMOUNT are presented in Table 7 and Figure 4.

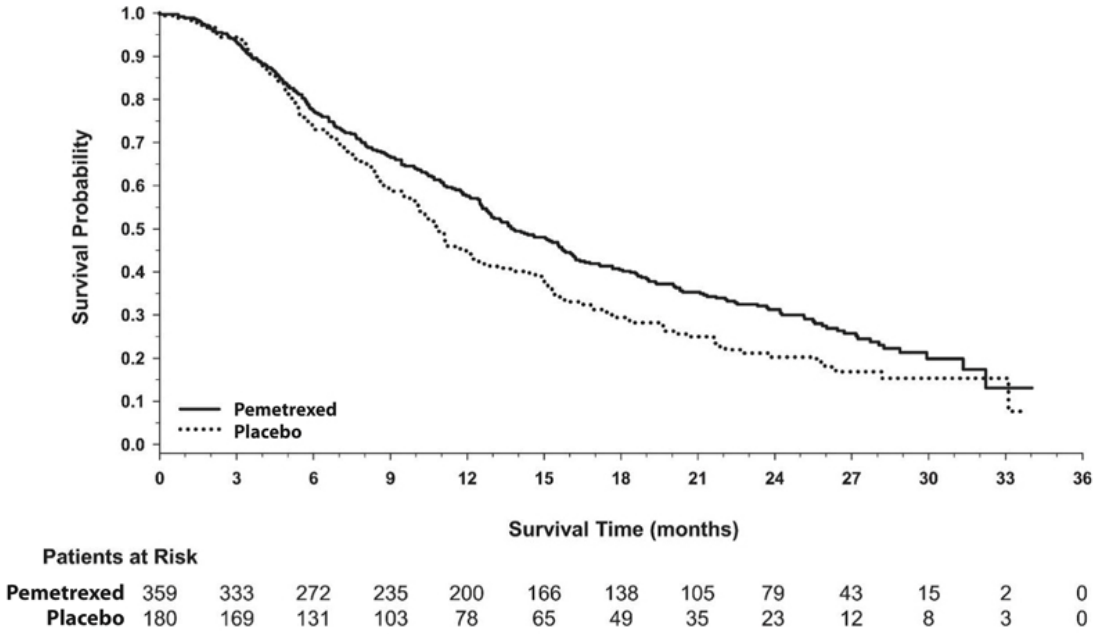
Table 7: Efficacy Results in PARAMOUNT

Efficacy Parameter	**Pemetrexed (N=359)**	**Placebo (N=180)**
Overall survival		
Median (months) (95% CI)	13.9 (12.8 to 16.0)	11.0 (10.0 to 12.5)
Hazard ratio (HR)[a]	0.78	

(95% CI)	(0.64 to 0.96)	
p-value	p=0.02	
Progression-free survival[b]		
Median (months) (95% CI)	4.1 (3.2 to 4.6)	2.8 (2.6 to 3.1)
Hazard ratio (HR)[a] (95% CI)	0.62 (0.49 to 0.79)	
p-value	p<0.0001	

[a] Hazard ratios are adjusted for multiplicity but not for stratification variables.
[b] Based on investigator's assessment.

Figure 4: Kaplan-Meier Curves for Overall Survival in PARAMOUNT



Treatment of Recurrent Disease After Prior Chemotherapy

The efficacy of pemetrexed was evaluated in Study JMEI (NCT00004881), a multicenter, randomized (1:1), open-label study conducted in patients with Stage III or IV NSCLC that had recurred or progressed following one prior chemotherapy regimen for advanced disease. Patients were randomized to receive pemetrexed 500 mg/m^2 intravenously or docetaxel 75 mg/m^2 as a 1-hour intravenous infusion once every 21 days. Patients randomized to pemetrexed also received folic acid and vitamin B_{12}. The study was designed to show that overall survival with pemetrexed was non-inferior to docetaxel, as the major efficacy outcome measure, and that overall survival was superior for patients randomized to pemetrexed compared to docetaxel, as a secondary outcome measure.

A total of 571 patients were enrolled with 283 patients randomized to pemetrexed and 288 patients randomized to docetaxel. The median age was 58 years (range 22 to 87 years); 72% were male; 71% were White, 24% were Asian, 2.8% were Black or African American, 1.8% were Hispanic or Latino, and <2% were other ethnicities; 88% had an ECOG PS of 0 or 1. With regard to tumor characteristics, 75% had Stage IV disease; 53% had adenocarcinoma, 30% had squamous histology; 8% large cell; and 9% had other histologic subtypes of NSCLC.

The efficacy results in the overall population and in subgroup analyses based on histologic subtype are provided in Tables 8 and 9, respectively. Study JMEI did not show an improvement in overall survival in the intent-to-

treat population. In subgroup analyses, there was no evidence of a treatment effect on survival in patients with squamous NSCLC; the absence of a treatment effect in patients with NSCLC of squamous histology was also observed Studies JMEN *[see Clinical Studies (14.1)]*.

Table 8: Efficacy Results in Study JMEI

Efficacy Parameter	**Pemetrexed (N=283)**	**Docetaxel (N=288)**
Overall survival		
Median (months) (95% CI)	8.3 (7.0 to 9.4)	7.9 (6.3 to 9.2)
Hazard ratio[a] (95% CI)	0.99 (0.82 to 1.20)	
Progression-free survival		
Median (months) (95% CI)	2.9 (2.4 to 3.1)	2.9 (2.7 to 3.4)
Hazard ratio[a] (95% CI)	0.97 (0.82 to 1.16)	
Overall response rate (95% CI)	8.5% (5.2 to 11.7)	8.3% (5.1 to 11.5)

[a] Hazard ratios are not adjusted for multiplicity or for stratification variables.

Table 9: Exploratory Efficacy Analyses by Histologic Subgroup in Study JMEI

Histologic Subgroups	**Pemetrexed (N=283)**	**Docetaxel (N=288)**
Non-squamous NSCLC (N=399)		
Median (months) (95% CI)	9.3 (7.8 to 9.7)	8.0 (6.3 to 9.3)
HR[a] (95% CI)	0.89 (0.71 to 1.13)	
Adenocarcinoma (N=301)		
Median (months) (95% CI)	9.0 (7.6 to 9.6)	9.2 (7.5 to 11.3)
HR[a] (95% CI)	1.09 (0.83 to 1.44)	
Large Cell (N=47)		
Median (months) (95% CI)	12.8 (5.8 to 14.0)	4.5 (2.3 to 9.1)
HR[a] (95% CI)	0.38 (0.18 to 0.78)	
Other[b] (N=51)		
Median (months) (95% CI)	9.4 (6.0 to 10.1)	7.9 (4.0 to 8.9)
HR[a] (95% CI)	0.62 (0.32 to 1.23)	
Squamous NSCLC (N=172)		
Median (months) (95% CI)	6.2 (4.9 to 8.0)	7.4 (5.6 to 9.5)
HR[a] (95% CI)	1.32 (0.93 to 1.86)	

[a] Hazard ratio unadjusted for multiple comparisons.

[b] Primary diagnosis of NSCLC not specified as adenocarcinoma, large cell carcinoma, or squamous cell carcinoma.

15 REFERENCES

1. "OSHA Hazardous Drugs." *OSHA. http://www.osha.gov/SLTC/hazardousdrugs/index.html*

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

Pemetrexed Injection is supplied as a clear, colorless to slightly yellowish or slightly yellow-greenish solution available in sterile single-dose vials at a 25 mg/mL concentration in the following package strengths.

Pemetrexed Injection 100 mg/4 mL (25 mg/mL)	NDC 0591-3101-34
Pemetrexed Injection 500 mg/20 mL (25 mg/mL)	NDC 0591-4129-80
Pemetrexed Injection 1 g/40 mL (25 mg/mL)	NDC 0591-5217-49

Storage and Handling

Store under refrigeration between 2° to 8°C (36° to 46°F). Protect from light. Retain in carton until time of use. Pemetrexed Injection is a cytotoxic drug. Follow applicable special handling and disposal procedures.[1]

Do not Freeze.

Sterile, Nonpyrogenic, Preservative-free.
The vial stopper is not made with natural rubber latex.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Premedication and Concomitant Medication: Instruct patients to take folic acid as directed and to keep appointments for vitamin B_{12} injections to reduce the risk of treatment-related toxicity. Instruct patients of the requirement to take corticosteroids to reduce the risks of treatment-related toxicity *[see Dosage and Administration (2.3) and Warnings and Precautions (5.1)]*.

Myelosuppression: Inform patients of the risk of low blood cell counts and instruct them to immediately contact their physician for signs of infection, fever, bleeding, or symptoms of anemia *[see Warnings and Precautions (5.1)]*.

Renal Failure: Inform patients of the risks of renal failure, which may be exacerbated in patients with dehydration arising from severe vomiting or diarrhea. Instruct patients to immediately contact their healthcare provider for a decrease in urine output *[see Warnings and Precautions (5.2)]*.

Bullous and Exfoliative Skin Disorders: Inform patients of the risks of severe and exfoliative skin disorders. Instruct patients to immediately contact their healthcare provider for development of bullous lesions or exfoliation in the skin or mucous membranes *[see Warnings and Precautions (5.3)]*.

Interstitial Pneumonitis: Inform patients of the risks of pneumonitis. Instruct patients to immediately contact their healthcare provider for development of dyspnea or persistent cough *[see Warnings and Precautions (5.4)]*.

Radiation Recall: Inform patients who have received prior radiation of the risks of radiation recall. Instruct patients to immediately contact their healthcare provider for development of inflammation or blisters in an area that was previously irradiated *[see Warnings and Precautions (5.5)]*.

Increased Risk of Toxicity with Ibuprofen in Patients with Renal Impairment: Advise patients with mild to moderate renal impairment of the risks associated with concomitant ibuprofen use and instruct them to avoid use of all ibuprofen containing products for 2 days before, the day of, and 2 days following administration of Pemetrexed Injection *[see Dosage and Administration (2.4), Warnings and Precautions (5.6), and Drug Interactions (7)]*.

Embryo-Fetal Toxicity: Advise females of reproductive potential and males with female partners of reproductive potential of the potential risk to a fetus *[see Warnings and Precautions (5.7) and Use in Specific Populations (8.1)]*. Advise females of reproductive potential to use effective contraception during treatment with Pemetrexed Injection and for 6 months after the final dose. Advise females to inform their prescriber of a known or suspected pregnancy. Advise males with female partners of reproductive potential to use effective contraception during treatment with Pemetrexed Injection and for 3 months after the final dose *[see Warnings and Precautions (5.7) and Use in Specific Populations (8.3)]*.

Lactation: Advise women not to breastfeed during treatment with Pemetrexed Injection and for 1 week after the final dose *[see Use in Specific Populations (8.2)]*.

Manufactured in the United States by:
Teva Pharmaceuticals USA, Inc.
North Wales, PA 19454

Or

Manufactured in Romania by:
Sindan Pharma SRL
Bucharest 1, Romania 011171

Distributed by:
Actavis Pharma, Inc.
Parsippany, NJ 07054 USA

Revised – August 2020

PATIENT INFORMATION
Pemetrexed (pem" e trex' ed) Injection,
for intravenous use

What is Pemetrexed Injection?

Pemetrexed Injection is a prescription medicine used to treat:

- **a kind of lung cancer called non-squamous non-small cell lung cancer (NSCLC).** Pemetrexed Injection is used:
  - alone as maintenance treatment after you have received 4 cycles of chemotherapy that contains platinum for first treatment of your advanced NSCLC and your cancer has not progressed.
  - alone when your lung cancer has returned or spread after prior chemotherapy.

It is not known if Pemetrexed Injection is safe and effective in children.

Do not take Pemetrexed Injection: if you have had a severe allergic reaction to any medicine that contains pemetrexed.

Before taking Pemetrexed Injection, tell your healthcare provider about all of your medical conditions, including if you:

- have kidney problems.
- have had radiation therapy.
- are pregnant or plan to become pregnant. Pemetrexed Injection can harm your unborn baby.
  - **Females** who are able to become pregnant should use effective birth control (contraception) during treatment with Pemetrexed Injection and for 6 months after the final dose. Tell your healthcare provider right away if you become pregnant or think you are pregnant during treatment with Pemetrexed Injection.
  - **Males** with female partners who are able to become pregnant should use effective birth control (contraception) during treatment with Pemetrexed Injection and for 3 months after the final dose.
- are breastfeeding or plan to breastfeed. It is not known if pemetrexed passes into breast milk. Do not breastfeed during treatment with Pemetrexed Injection and for 1 week after the final dose.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Tell your healthcare provider if you have kidney problems and take a medicine that contains ibuprofen. You should avoid taking ibuprofen for 2 days before, the day of, and 2 days after receiving treatment with Pemetrexed Injection.

How is Pemetrexed Injection given?

- **It is very important to take folic acid and vitamin B_{12} during your treatment with Pemetrexed Injection to lower your risk of harmful side effects.**
  - Take folic acid exactly as prescribed by your healthcare provider 1 time a day, beginning 7 days (1 week) before your first dose of Pemetrexed Injection and continue taking folic acid until 21 days (3 weeks) after your last dose of Pemetrexed Injection.
  - Your healthcare provider will give you vitamin B_{12} injections during treatment with Pemetrexed Injection. You will get your first vitamin B_{12} injection 7 days (1 week) before your first dose of Pemetrexed Injection, and then every 3 cycles.
- Your healthcare provider will prescribe a medicine called corticosteroid for you to take 2 times a day for 3 days, beginning the day before each treatment with Pemetrexed Injection.
- Pemetrexed Injection is given to you by intravenous (IV) infusion into your vein. The infusion is given over 10 minutes.
- Pemetrexed Injection is usually given on Day 1 of each 21-day (3 weeks) cycle.

What are the possible side effects of Pemetrexed Injection?

Pemetrexed Injection can cause serious side effects, including:

- **Low blood cell counts.** Low blood cell counts can be severe, including low white blood cell counts (neutropenia), low platelet counts (thrombocytopenia), and low red blood cell counts (anemia). Your

healthcare provider will do blood test to check your blood cell counts regularly during your treatment with Pemetrexed Injection. **Tell your healthcare provider right away if you have any signs of infection, fever, bleeding, or severe tiredness during your treatment with Pemetrexed Injection.**

- **Kidney problems, including kidney failure.** Pemetrexed Injection can cause severe kidney problems that can lead to death. Severe vomiting or diarrhea can lead to loss of fluids (dehydration) which may cause kidney problems to become worse. Tell your healthcare provider right away if you have a decrease in amount of urine.
- **Severe skin reactions.** Severe skin reactions that may lead to death can happen with Pemetrexed Injection. Tell your healthcare provider right away if you develop blisters, skin sores, skin peeling, or painful sores, or ulcers in your mouth, nose, throat or genital area.
- **Lung problems (pneumonitis).** Pemetrexed Injection can cause serious lung problems that can lead to death. Tell your healthcare provider right away if you get any new or worsening symptoms of shortness of breath, cough, or fever.
- **Radiation recall.** Radiation recall is a skin reaction that can happen in people who have received radiation treatment in the past and are treated with Pemetrexed Injection. Tell your healthcare provider if you get swelling, blistering, or a rash that looks like a sunburn in an area that was previously treated with radiation.

The most common side effects of Pemetrexed Injection when given alone are:

- tiredness
- nausea
- loss of appetite

Pemetrexed Injection may cause fertility problems in males. This may affect your ability to father a child. It is not known if these effects are reversible. Talk to your healthcare provider if this is a concern for you.

Your healthcare provider will do blood test to check for side effects during treatment with Pemetrexed Injection. Your healthcare provider may change your dose of Pemetrexed Injection, delay treatment, or stop treatment if you have certain side effects.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the side effects of Pemetrexed Injection. For more information, ask your healthcare provider or pharmacist. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of Pemetrexed Injection.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet.

You can ask your pharmacist or healthcare provider for information about Pemetrexed Injection that is written for health professionals.

What are the ingredients in Pemetrexed Injection?

Active ingredient: pemetrexed

Inactive ingredients: tromethamine, citric acid anhydrous, methionine and water for injection.

Manufactured in the United States by: Teva Pharmaceuticals USA, Inc., North Wales, PA 19454
Or
Manufactured in Romania by: Sindan Pharma SRL, Bucharest 1, Romania 011171
Distributed by: Actavis Pharma, Inc., Parsippany, NJ 07054 USA
For more information, call Actavis at 1-800-432-8534.

This Patient Information has been approved by the U.S. Food and Drug Administration. Issued: August 2020

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

B HARPREET SINGH
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