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

PEMFEXY™ (pemetrexed injection), for intravenous use
Initial U.S. Approval: 2004

----------INDICATIONS AND USAGE----------
PEMFEXY is a folate analog metabolic inhibitor indicated for:
- in combination with cisplatin for the initial treatment of patients with locally advanced or metastatic non-squamous, non-small cell lung cancer (NSCLC). (1.1)
- 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: PEMFEXY is not indicated for the treatment of patients with squamous cell non-small cell lung cancer. (1.1)
- in combination with cisplatin for the initial treatment, of patients with malignant pleural mesothelioma whose disease is unresectable or who are otherwise not candidates for curative surgery. (1.2)

----------DOSAGE AND ADMINISTRATION----------
- The recommended dosage of PEMFEXY, administered as a single agent or with cisplatin, 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, 2.2, 2.3)
- Initiate folic acid 400 mcg to 1000 mcg orally once daily beginning 7 days prior to the first dose of PEMFEXY and continue until 21 days after the last dose. (2.4)
- Administer vitamin B_{12} 1 mg intramuscularly 1 week prior to the first dose of PEMFEXY and every 3 cycles thereafter. (2.4)
- Administer dexamethasone 4 mg orally twice daily the day before, the day of, and the day after PEMFEXY administration. (2.4)

----------DOSAGE FORMS AND STRENGTHS----------
- Injection: 500 mg/20 mL (25 mg/mL) in a single-dose vial (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 PEMFEXY 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 PEMFEXY. (2.4, 5.1)
- Renal Failure: Can cause severe, and sometimes fatal, renal failure. Do not administer when creatinine clearance is less than 45 mL/min. (2.3, 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. (5.6, 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)
- The most common adverse reactions (incidence ≥ 20%) of pemetrexed when administered with cisplatin are vomiting, neutropenia, anemia, stomatitis/pharyngitis, thrombocytopenia, and constipation. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Eagle Pharmaceuticals, Inc. at 1-855-318-2170 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
Ibuprofen: Modify the ibuprofen dosage as recommended for patients with a creatinine clearance between 45 mL/min and 79 mL/min. (2.5, 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: 02/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Non-squamous Non-Small Cell Lung Cancer

PEMFEXY™ is indicated:

- in combination with cisplatin for the initial treatment of patients with locally advanced or metastatic, non-squamous, non-small cell lung cancer (NSCLC).
- 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: PEMFEXY is not indicated for the treatment of patients with squamous cell NSCLC *[see Clinical Studies 14.1]*.

1.2 Mesothelioma

PEMFEXY is indicated in combination with cisplatin for the initial treatment of patients with malignant pleural mesothelioma whose disease is unresectable or who are otherwise not candidates for curative surgery.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage for Non-squamous Non-Small Cell Lung Cancer

- The recommended dosage of PEMFEXY, when administered with cisplatin for initial treatment of locally advanced or metastatic non-squamous NSCLC in patients with a creatinine clearance (calculated by Cockcroft-Gault equation) of 45 mL/min or greater, is 500 mg/m^2 as an intravenous infusion over 10 minutes administered prior to cisplatin on Day 1 of each 21-day cycle for up to six cycles in the absence of disease progression or unacceptable toxicity.
- The recommended dosage of PEMFEXY 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 dosage of PEMFEXY 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 Recommended Dosage for Mesothelioma

The recommended dosage of PEMFEXY, when administered with cisplatin, 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.

2.3 Renal Impairment

PEMFEXY 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, 2.2)]*. There is no recommended dose for patients whose creatinine clearance is less than 45 mL/min *[see Use in Specific Populations (8.6)]*.

2.4 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 PEMFEXY and continuing until 21 days after the last dose *[see Warnings and Precautions (5.1)]*.

Administer vitamin B_{12} 1 mg intramuscularly 1 week prior to the first dose of PEMFEXY and every 3 cycles thereafter. Subsequent vitamin B_{12} injections may be given the same day as treatment with PEMFEXY *[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 PEMFEXY administration.

2.5 Dosage Modification of Ibuprofen in Patients with Mild to Moderate Renal Impairment Receiving PEMFEXY

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 PEMFEXY.
- Monitor patients more frequently for myelosuppression, renal, and gastrointestinal toxicity, if concomitant administration of ibuprofen cannot be avoided.

2.6 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 PEMFEXY if the creatinine clearance is less than 45 mL/min.

Delay initiation of the next cycle of PEMFEXY 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 PEMFEXY in the next cycle as specified in Table 1.

For dosage modifications for cisplatin, refer to the prescribing information for cisplatin.

Table 1: Recommended Dosage Modifications for Adverse Reactions

Toxicity in Most Recent Treatment Cycle	**PEMFEXY Dosage Modifications 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	Permanently 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

Toxicity in Most Recent Treatment Cycle	PEMFEXY Dosage Modifications for Next Cycle
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)

2.7 Preparation and Administration

PEMFEXY is a cytotoxic drug. Follow applicable special handling and disposal procedures.[1]

- Calculate the dose of PEMFEXY and determine the number of vials needed. Withdraw the calculated dose of PEMFEXY from the vial(s) and discard vial with any unused portion. Each vial contains 500 mg pemetrexed per 20 mL (25 mg/mL). The vial contains an excess of pemetrexed to facilitate delivery of labeled amount.
- Dilute PEMFEXY with 5% Dextrose in Water, USP to achieve a total volume of 100 mL for intravenous infusion. **Do not use other diluents, such as Lactated Ringer's Injection, USP or Ringer's Injection, USP.**
- Visually inspect for particulate matter and discoloration prior to administration, whenever solution and container permit. Discard if particulate matter or discoloration is observed.
- Administer PEMFEXY as an intravenous infusion over 10 minutes.
- Store diluted PEMFEXY refrigerated at 2°C to 8°C (36 °F to 46°F) or at ambient room temperature and room lighting for no more than 48 hours. When prepared as directed, infusion solutions of PEMFEXY contain no antimicrobial preservatives. Discard after 48 hours.

PEMFEXY is compatible with polyolefin infusion bags with polyvinyl chloride (PVC) ports.

3 DOSAGE FORMS AND STRENGTHS

Injection: 500 mg pemetrexed per 20 mL (25 mg/mL) as a clear, colorless to yellow or green-yellow solution in a single-dose vial.

4 CONTRAINDICATIONS

PEMFEXY 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. In Study JMCH, incidences of Grade 3-4 neutropenia (38% versus 23%), thrombocytopenia (9% versus 5%), febrile neutropenia (9% versus 0.6%), and neutropenic infection (6% versus 0) were higher in patients who received pemetrexed plus cisplatin without vitamin supplementation as compared to patients who

were fully supplemented with folic acid and vitamin B_{12} prior to and throughout pemetrexed plus cisplatin treatment.

Initiate supplementation with oral folic acid and intramuscular vitamin B_{12} prior to the first dose of PEMFEXY; continue vitamin supplementation during treatment and for 21 days after the last dose of PEMFEXY to reduce the severity of hematologic and gastrointestinal toxicity of pemetrexed *[see Dosage and Administration (2.4)]*.

Obtain a complete blood count at the beginning of each cycle. Do not administer PEMFEXY until the ANC is at least 1500 cells/mm^3 and platelet count is at least 100,000 cells/mm^3. Permanently reduce PEMFEXY 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 (2.6)]*.

In Studies JMDB and JMCH, among patients who received vitamin supplementation, incidence of Grade 3-4 neutropenia was 15% and 23%, the incidence of Grade 3-4 anemia was 6% and 4%, and incidence of Grade 3-4 thrombocytopenia was 4% and 5%, respectively. In Study JMCH, 18% of patients in the pemetrexed arm required red blood cell transfusions compared to 7% of patients in the cisplatin arm *[see Adverse Reactions (6.1)]*. 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 incidences of renal failure in clinical studies in which patients received pemetrexed with cisplatin were: 2.1% in Study JMDB and 2.2% in Study JMCH. 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 PEMFEXY. Withhold PEMFEXY in patients with a creatinine clearance of less than 45 mL/minute *[see Dosage and Administration (2.3)]*.

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 PEMFEXY 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. Withhold PEMFEXY 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 PEMFEXY.

5.5 Radiation Recall

Radiation recall can occur with pemetrexed in patients who have received radiation weeks to years previously. Monitor patients for inflammation or blistering in areas of previous radiation treatment. Permanently discontinue PEMFEXY 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. 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 PEMFEXY. 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 (2.5), Drug Interactions (7), and Clinical Pharmacology (12.3)]*.

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