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RESEARCH**

*APPLICATION NUMBER:*

**209472Orig1s000**

**LABELING**

## 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<sup>2</sup> 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<sub>12</sub> 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<sup>3</sup> and platelets are less than 100,000 cells/mm<sup>3</sup>. Initiate supplementation with oral folic acid and intramuscular vitamin B<sub>12</sub> 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](http://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

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## 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<sup>2</sup> 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<sup>2</sup> 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<sup>2</sup> 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<sup>2</sup> 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<sub>12</sub> 1 mg intramuscularly 1 week prior to the first dose of PEMFEXY and every 3 cycles thereafter. Subsequent vitamin B<sub>12</sub> injections may be given the same day as treatment with PEMFEXY [see *Warnings and Precautions (5.1)*]. **Do not substitute oral vitamin B<sub>12</sub> for intramuscular vitamin B<sub>12</sub>.**

### 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<sup>3</sup> or higher, and
- Platelet count is 100,000 cells/mm<sup>3</sup> 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
<b>Myelosuppressive toxicity</b> [see <i>Warnings and Precautions (5.1)</i> ]	
ANC less than 500/mm <sup>3</sup> <b>and</b> platelets greater than or equal to 50,000/mm <sup>3</sup> <u>OR</u> Platelet count less than 50,000/mm <sup>3</sup> without bleeding.	75% of previous dose
Platelet count less than 50,000/mm <sup>3</sup> with bleeding	50% of previous dose
Recurrent Grade 3 or 4 myelosuppression after 2 dose reductions	Permanently discontinue.
<b>Non-hematologic toxicity</b>	
Any Grade 3 or 4 toxicities EXCEPT mucositis or neurologic toxicity <u>OR</u> 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.<sup>1</sup>

- 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

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