PEMFEXY®
(PEMETREXED INJECTION)

500 mg/20 mL (25 mg/mL)

BILLING AND CODING GUIDE

Information in this guide was obtained from third-party sources and is made available for illustrative purposes only; it is non-exhaustive, subject to change, and does not constitute coding or legal advice regarding the selection of codes to describe a particular service. Health care professionals are responsible for determining which code(s), charge(s), or modifier(s), if any, appropriately reflect a service or diagnosis. It is the health care professional's responsibility to determine medical necessity, supported by adequate documentation. Eagle Pharmaceuticals, Inc. makes no guarantee of coverage or payment for items or services. Payment and coverage vary by payer. Questions about coding, coverage, and payment may be directed to the applicable third-party payer, reimbursement specialist, and/or legal counsel.

Table of Contents

CMS=Centers for Medicare & Medicaid Services; CPT=Current Procedural Terminology; FDA=Food and Drug Administration; HCPCS= Healthcare Common Procedure Coding System; ICD=International Classification of Diseases; POS=Place of Service

Please see Important Safety Information on page 14, and accompanying full Prescribing Information for PEMFEXY®.

PEMFEXY® (PEMETREXED INJECTION)

500 mg/20 mL (25 mg/mL)

INDICATION

PEMFEXY is indicated in combination with pembrolizumab and platinum chemotherapy, for the initial treatment of patients with metastatic non-squamous non-small cell lung cancer (NSCLC), with no EGFR or ALK genomic tumor aberrations.

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).

PEMFEXY is indicated as a single agent for the maintenance treatment of patients with locally advanced or metastatic non-squamous non-small cell lung cancer (NSCLC) whose disease has not progressed after four cycles of platinum-based first-line chemotherapy.

PEMFEXY is indicated as a single agent for the treatment of patients with recurrent, metastatic non-squamous non-small cell lung cancer (NSCLC) after prior chemotherapy.

Limitation of Use: PEMFEXY is not indicated for the treatment of patients with squamous cell non-small cell lung cancer.

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

IMPORTANT SAFETY INFORMATION

(Continued on Page 14)

CONTRAINDICATION

PEMFEXY is contraindicated in patients who have a history of severe hypersensitivity reaction to pemetrexed.

WARNINGS AND PRECAUTIONS

Myelosuppression and Increased Risk of Myelosuppression Without Vitamin Supplementation

PEMFEXY 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.

7 Days prior to treatment with PEMFEXY, patients must be instructed to initiate supplementation with oral folic acid. Intramuscular injections of vitamin B_{12} are also required 7 days prior to PEMFEXY treatment. Continue vitamin supplementation during treatment and for 21 days after the last dose of PEMFEXY to reduce the severity of treatment-related hematologic and gastrointestinal toxicities. 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.

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. 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%.

PEMFEXY®
Ordering Information

Wholesale		
Distributor	Item Number	Telephone Number
AmerisourceBergen	10265697	844.222.2273
Cardinal Health	5774443	800.926.3161
McKesson	2600252	855.625.4677
Morris & Dickson	204560	800.388.3833
Specialty		
Cardinal Health	5774443	800.926.3161
McKesson	5011811	800.482.6700
Oncology Supply	10264556	800.633.7555

PEMFEXY® Packaging Specifications

Specifications	
How Supplied[1]	Multi-Dose Vial, 500 mg/20 mL (25 mg/mL)
NDC[1]	42367-**0**531-33*

*FDA standard NDC has been "zero-filled" to create an 11-digit code that meets HIPAA standards. The zero-fill location is indicated in **bold.**

HIPAA= Health Insurance Portability and Accountability Act; NDC= National Drug Code

Please see Important Safety Information on page 14, and accompanying full Prescribing Information for PEMFEXY®.

PEMFEXY® Billing and Coding Information

ICD Diagnosis Codes[2]

Non-Squamous, Non-Small Cell Lung Cancer (NSCLC)	
ICD-10-CM Code	Description
Malignant neoplasm of bronchus and lung	
C34.00 C34.01 C34.02	Unspecified main bronchus Right main bronchus Left main bronchus
C34.10 C34.11 C34.12	Upper lobe, unspecified bronchus or lung Upper lobe, right bronchus or lung Upper lobe, left bronchus or lung
C34.2	Middle lobe, bronchus or lung
C34.30 C34.31 C34.32	Lower lobe, unspecified bronchus or lung Lower lobe, right bronchus or lung Lower lobe, left bronchus or lung
C34.80 C34.81 C34.82	Overlapping sites of unspecified bronchus and lung Overlapping sites of right bronchus and lung Overlapping sites of left bronchus and lung
C34.90 C34.91 C34.92	Unspecified part of unspecified bronchus and lung Unspecified part of right bronchus and lung Unspecified part of left bronchus and lung

Malignant Pleural Mesothelioma (MPM)	
ICD-10-CM Code	Description
Mesothelioma	
C38.4	Malignant neoplasm of pleura
C45.0	Mesothelioma of pleura

PEMFEXY® Billing and Coding Information, continued

Providers are encouraged to contact third-party payers for specific information on their coverage, coding, and payment policies.

HCPCS Code

Applicable Settings

PEMFEXY® Unique J-Code[3]	Description	Place of Service (POS) Codes[4]
J9304	Injection, pemetrexed (pemfexy), 10 mg	• Physician Office (11) • Off-Campus Outpatient Hospital (19) • On-Campus Outpatient Hospital (22)

PEMFEXY® J-Code Billing Unit Conversion

J9304 Billing Unit[3]	=	10 mg
One Multi-Dose Vial of PEMFEXY® (500 mg/20 mL)[1]	=	50 Units

The total number of mg administered will vary based on patient body surface area, and based on the potential need for dosage modifications.[1]

Is PEMFEXY® (pemetrexed injection) a generic drug?

No. PEMFEXY® is a proprietary formulation of pemetrexed approved via the 505(b)(2) pathway, with no listed therapeutic equivalence rating in the FDA Orange Book.[5]

What's the difference between a generic drug, and a drug approved via the 505(b)(2) pathway? How are they billed differently?

Drugs submitted via a 505(b)(2) New Drug Application (NDA) specify a Listed Drug (LD), but unlike generics, which are approved via an abbreviated regulatory pathway, they are not required to be therapeutically equivalent nor pharmaceutically equivalent to a Reference Listed Drug. Most 505(b)(2) applications consist of changes to a previously approved drug product (ie, a new dosage form, new route of administration, new formulation, etc.).[6] For example, PEMFEXY® was approved via a 505(b)(2) drug application, does not have a therapeutic equivalence rating, and must be billed using a Unique J-Code: J9304.[3,5] Whereas, ALIMTA® and its therapeutically equivalent generic versions share the same J-Code: J9305.[3†]

What is a Unique J-Code?

J-codes are reimbursement codes used by commercial insurance plans, Medicare, Medicare Advantage, and other government payers for physician-administered drugs like PEMFEXY® and are intended to simplify the claims submission and documentation process, facilitating access for patients.[7]

Can discarded units of PEMFEXY® be billed using the JW modifier?

No. PEMFEXY® is supplied in a multi-dose vial, therefore the JW modifier does not apply to PEMFEXY® billing. The JW modifier is only valid when used to identify wasted drugs or biologicals from a single-dose vial or package. Multi-dose vials are not subject to payment for any discarded amounts of the drug.[8]

†ALIMTA® is a registered trademark of Eli Lilly and Company.

Please see Important Safety Information on page 14, and accompanying full Prescribing Information for PEMFEXY®.

PEMFEXY® Billing and Coding Information, continued

CPT Drug Administration Codes[9]

Code	Description
96409	Chemotherapy, intravenous push, single or initial drug‡
96411	Chemotherapy, intravenous push, each additional drug‡
96413	Chemotherapy, intravenous infusion, 1 hour
96415	Chemotherapy, intravenous infusion, each additional hour
96417	Chemotherapy, intravenous infusion, each additional sequential infusion

‡PEMFEXY® is indicated to be administered as an intravenous infusion over 10 minutes[1] by the FDA. However, this code may be appropriate for use for billing purposes only, as CMS's Billing and Coding Guidelines define an intravenous push, in part, as "an infusion of 15 minutes or less." Please see the Important Safety Information on Page 14 and accompanying full Prescribing Information for PEMFEXY®.

National Drug Code for PEMFEXY®[1]

Vial Description	NDC
Multi-Dose Vial, 500 mg/20 mL (25 mg/mL)	**42367-0531-33***

*FDA standard NDC has been "zero-filled" to create an 11-digit code that meets HIPAA standards. The zero-fill location is indicated in **bold.**

Sample Claim Form CMS-1450 (UB-04)[10,11]

Hospital Outpatient

Providers are encouraged to contact third-party payers for specific information on their coverage, coding, and payment policies.

FIELDS 42-43:

Revenue Codes and Description

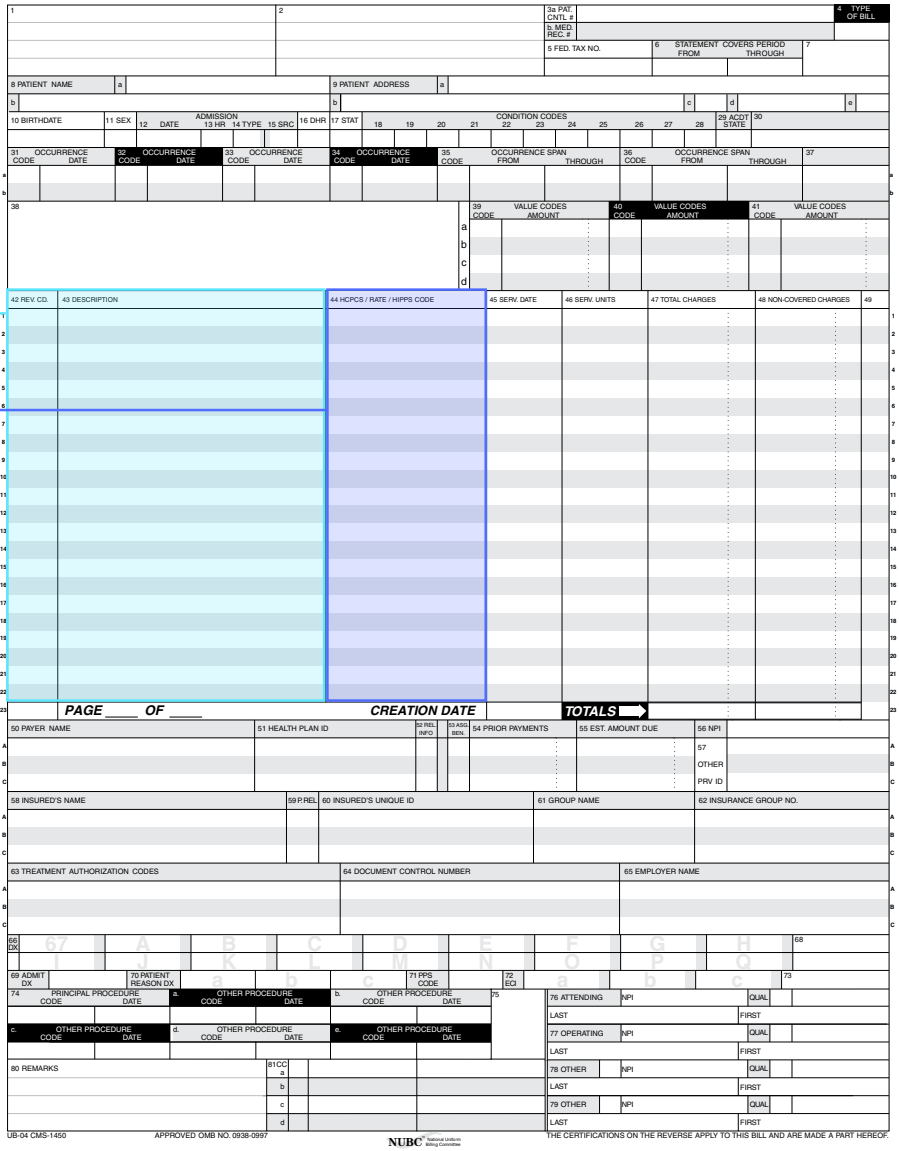
Enter revenue code and description corresponding to HCPCS or CPT codes filled in Field 44.

FIELD 44:

Product and Procedure Coding

Enter HCPCS drug code and CPT code for the administration of PEMFEXY®.

HCPCS[3]:	
J9304	Injection, pemetrexed (pemfexy), 10 mg
CPT[9]:	
96409	Chemotherapy, intravenous push, single or initial drug
96411	Chemotherapy, intravenous push, each additional drug
96413	Chemotherapy, intravenous infusion, 1 hour
96415	Chemotherapy, intravenous infusion, each additional hour
96417	Chemotherapy, intravenous infusion, each additional sequential infusion



Please see additional CMS-1450 claim form information on page 9.

Sample Claim Form CMS-1450 (UB-04), continued [10,11]

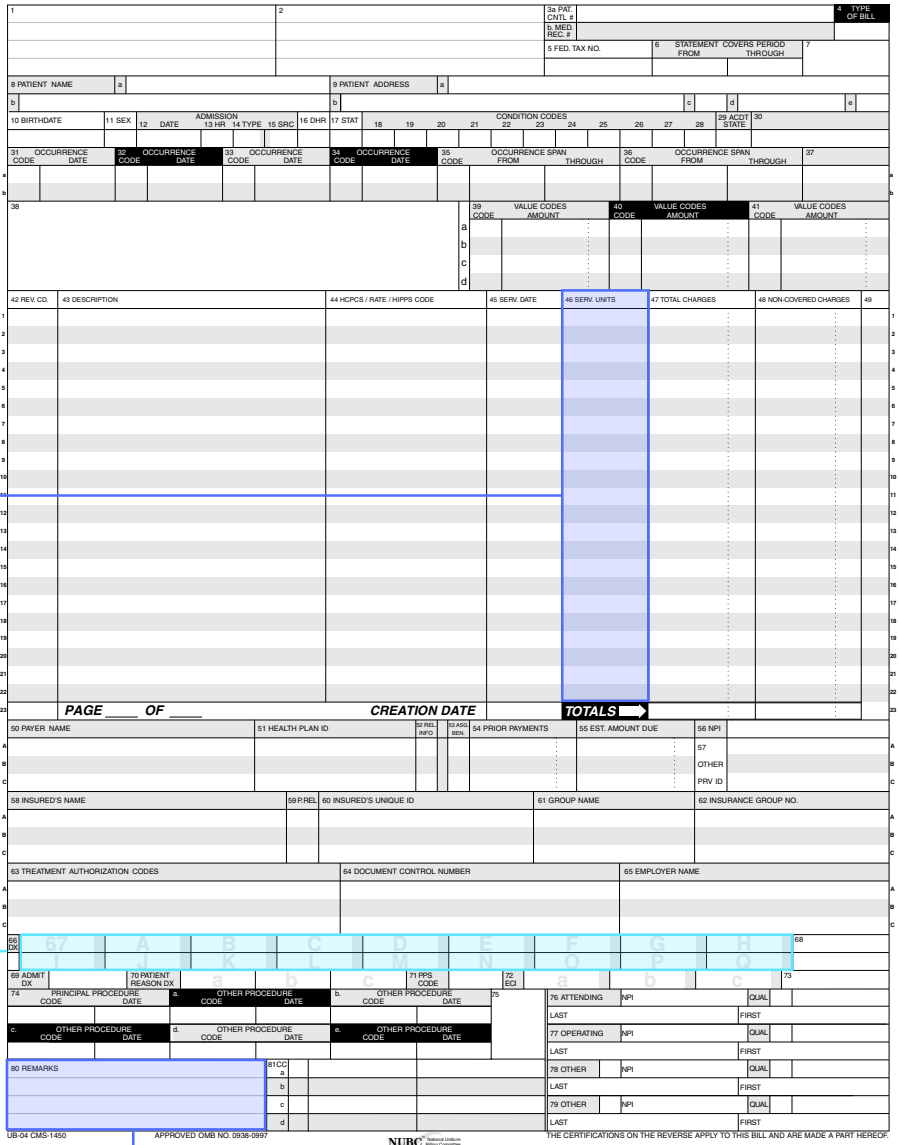
Hospital Outpatient

Providers are encouraged to contact third-party payers for specific information on their coverage, coding, and payment policies.

FIELD 46:

Service Units

Enter the number of service units for PEMFEXY® HCPCS code (J9304).
Billable unit = 10 mg.
One vial = 50 units.



FIELD 67:

Diagnosis Codes

Enter ICD diagnosis code.

See ICD-10-CM codes on page 5.

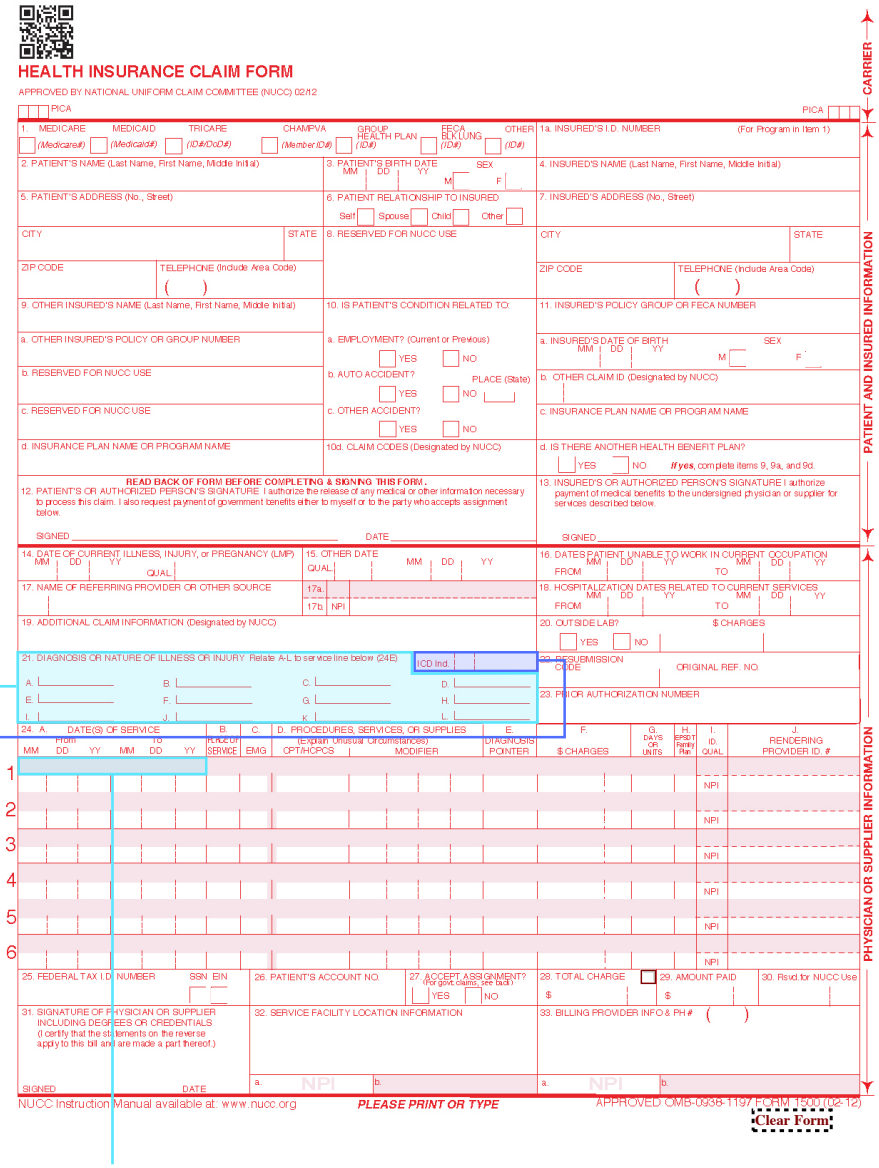
FIELD 80: Remarks

Enter additional information per payer requirements. This may include NDC, date administered, and dosage administered.

Sample Claim Form CMS-1500[4,12]

Physician Office

Providers are encouraged to contact third-party payers for specific information on their coverage, coding, and payment policies.



HEALTH INSURANCE CLAIM FORM

APPROVED BY NATIONAL UNIFORM CLAIM COMMITTEE (NUCC) 02/12

PICA

1. MEDICARE (Medicare#) | MEDICAID (Medicaid#) | TRICARE (ID#/DoD#) | CHAMPVA (Member ID#) | GROUP HEALTH PLAN (ID#) | FECA BLK LUNG (ID#) | OTHER (ID#)

1a. INSURED'S I.D. NUMBER (For Program in Item 1)

2. PATIENT'S NAME (Last Name, First Name, Middle Initial)

3. PATIENT'S BIRTH DATE MM DD YY SEX M F

4. INSURED'S NAME (Last Name, First Name, Middle Initial)

5. PATIENT'S ADDRESS (No., Street)

6. PATIENT RELATIONSHIP TO INSURED Self Spouse Child Other

7. INSURED'S ADDRESS (No., Street)

CITY | STATE | 8. RESERVED FOR NUCC USE | CITY | STATE

ZIP CODE | TELEPHONE (Include Area Code) ( ) | ZIP CODE | TELEPHONE (Include Area Code) ( )

9. OTHER INSURED'S NAME (Last Name, First Name, Middle Initial)

10. IS PATIENT'S CONDITION RELATED TO:

11. INSURED'S POLICY GROUP OR FECA NUMBER

a. OTHER INSURED'S POLICY OR GROUP NUMBER

a. EMPLOYMENT? (Current or Previous) YES NO

a. INSURED'S DATE OF BIRTH MM DD YY SEX M F

b. RESERVED FOR NUCC USE

b. AUTO ACCIDENT? PLACE (State) YES NO

b. OTHER CLAIM ID (Designated by NUCC)

c. RESERVED FOR NUCC USE

c. OTHER ACCIDENT? YES NO

c. INSURANCE PLAN NAME OR PROGRAM NAME

d. INSURANCE PLAN NAME OR PROGRAM NAME

10d. CLAIM CODES (Designated by NUCC)

d. IS THERE ANOTHER HEALTH BENEFIT PLAN? YES NO If yes, complete items 9, 9a, and 9d.

READ BACK OF FORM BEFORE COMPLETING & SIGNING THIS FORM.

12. PATIENT'S OR AUTHORIZED PERSON'S SIGNATURE I authorize the release of any medical or other information necessary to process this claim. I also request payment of government benefits either to myself or to the party who accepts assignment below.

SIGNED DATE

13. INSURED'S OR AUTHORIZED PERSON'S SIGNATURE I authorize payment of medical benefits to the undersigned physician or supplier for services described below.

SIGNED

14. DATE OF CURRENT ILLNESS, INJURY, or PREGNANCY (LMP) MM DD YY QUAL

15. OTHER DATE QUAL MM DD YY

16. DATES PATIENT UNABLE TO WORK IN CURRENT OCCUPATION MM DD YY FROM TO

17. NAME OF REFERRING PROVIDER OR OTHER SOURCE

17a.

17b. NPI

18. HOSPITALIZATION DATES RELATED TO CURRENT SERVICES MM DD YY FROM TO

19. ADDITIONAL CLAIM INFORMATION (Designated by NUCC)

20. OUTSIDE LAB? YES NO $ CHARGES

21. DIAGNOSIS OR NATURE OF ILLNESS OR INJURY Relate A-L to service line below (24E) ICD Ind.

A B C D E F G H I J K L

22. RESUBMISSION CODE ORIGINAL REF. NO.

23. PRIOR AUTHORIZATION NUMBER

24. A. DATE(S) OF SERVICE From MM DD YY	To MM DD YY	B. PLACE OF SERVICE	C. EMG	D. PROCEDURES, SERVICES, OR SUPPLIES (Explain Unusual Circumstances) CPT/HCPCS	MODIFIER	E. DIAGNOSIS POINTER	F. $ CHARGES	G. DAYS OR UNITS	H. EPSDT Family Plan	I. ID. QUAL	J. RENDERING PROVIDER ID. #
1										NPI	
2										NPI	
3										NPI	
4										NPI	
5										NPI	
6										NPI	

25. FEDERAL TAX I.D. NUMBER SSN EIN

26. PATIENT'S ACCOUNT NO.

27. ACCEPT ASSIGNMENT? (For govt. claims, see back) YES NO

28. TOTAL CHARGE $

29. AMOUNT PAID $

30. Rsvd. for NUCC Use

31. SIGNATURE OF PHYSICIAN OR SUPPLIER INCLUDING DEGREES OR CREDENTIALS (I certify that the statements on the reverse apply to this bill and are made a part thereof.)

SIGNED DATE

32. SERVICE FACILITY LOCATION INFORMATION

a. NPI b.

33. BILLING PROVIDER INFO & PH # ( )

a. NPI b.

NUCC Instruction Manual available at: www.nucc.org

PLEASE PRINT OR TYPE

APPROVED OMB-0938-1197 FORM 1500 (02-12)

Clear Form

CARRIER

PATIENT AND INSURED INFORMATION

PHYSICIAN OR SUPPLIER INFORMATION

BOX 21:

Diagnosis or Nature of Illness or Injury

Lines A-L

Enter ICD diagnosis code on lines A-L, one code per line.

ICD Indicator

Enter ICD Indicator in top right corner to identify which version of ICD codes are being used, i.e. “0” for ICD-10-CM codes as shown on page 5.

See ICD-10-CM codes on page 5.

BOX 24A: Date(s) of Service

Enter NDC in the red shaded area.

Please see additional CMS-1500 claim form information on page 11.

Please see Important Safety Information on page 14, and accompanying full Prescribing Information for PEMFEXY®.

Sample Claim Form CMS-1500, continued[4,12]

Physician Office

Providers are encouraged to contact third-party payers for specific information on their coverage, coding, and payment policies.

BOX 24B:

Place of Service

Enter POS code, such as:

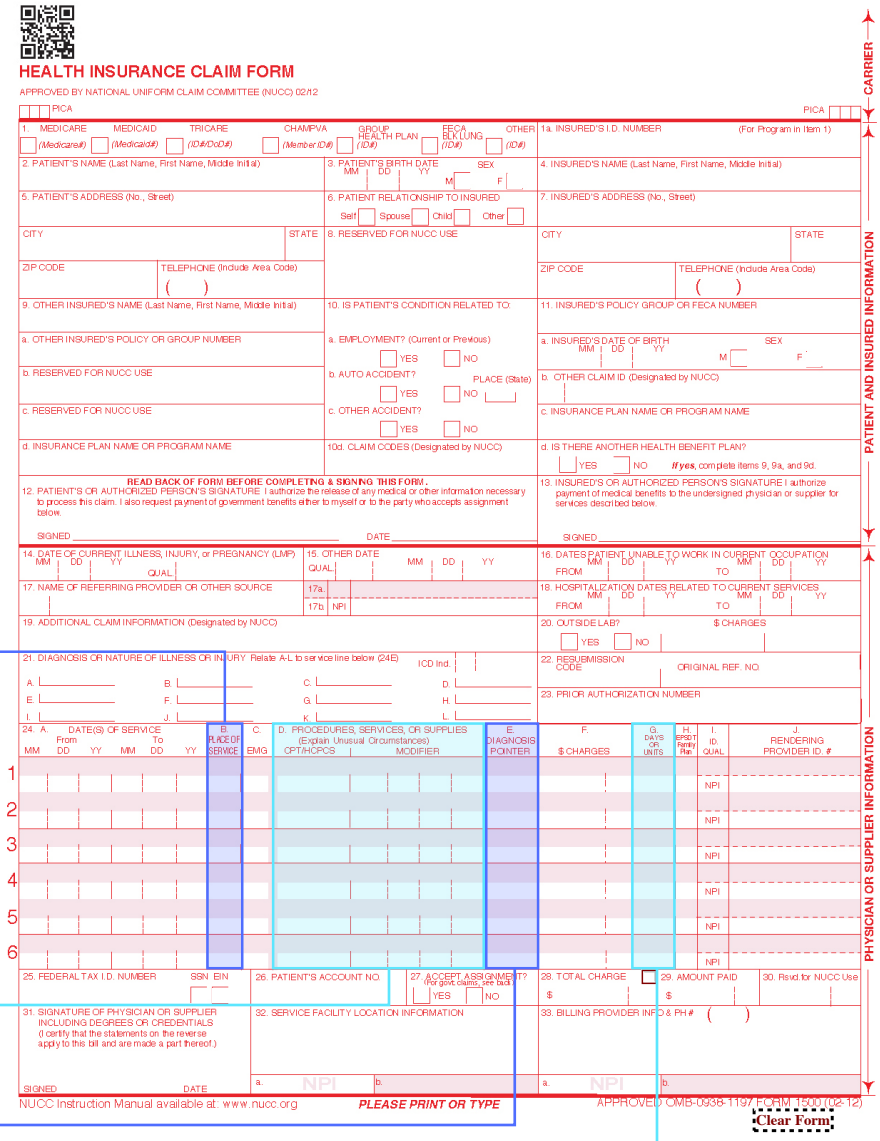
- Physician Office (11)
- Off-Campus Outpatient Hospital (19)
- On-Campus Outpatient Hospital (22)

BOX 24D:

Procedures, Services, or Supplies

Enter HCPCS drug code and CPT code for the administration of PEMFEXY®.

HCPCS[3]:	
J9304	Injection, pemetrexed (pemfexy), 10 mg
CPT[9]:	
96409	Chemotherapy, intravenous push, single or initial drug
96411	Chemotherapy, intravenous push, each additional drug
96413	Chemotherapy, intravenous infusion, 1 hour
96415	Chemotherapy, intravenous infusion, each additional hour
96417	Chemotherapy, intravenous infusion, each additional sequential infusion



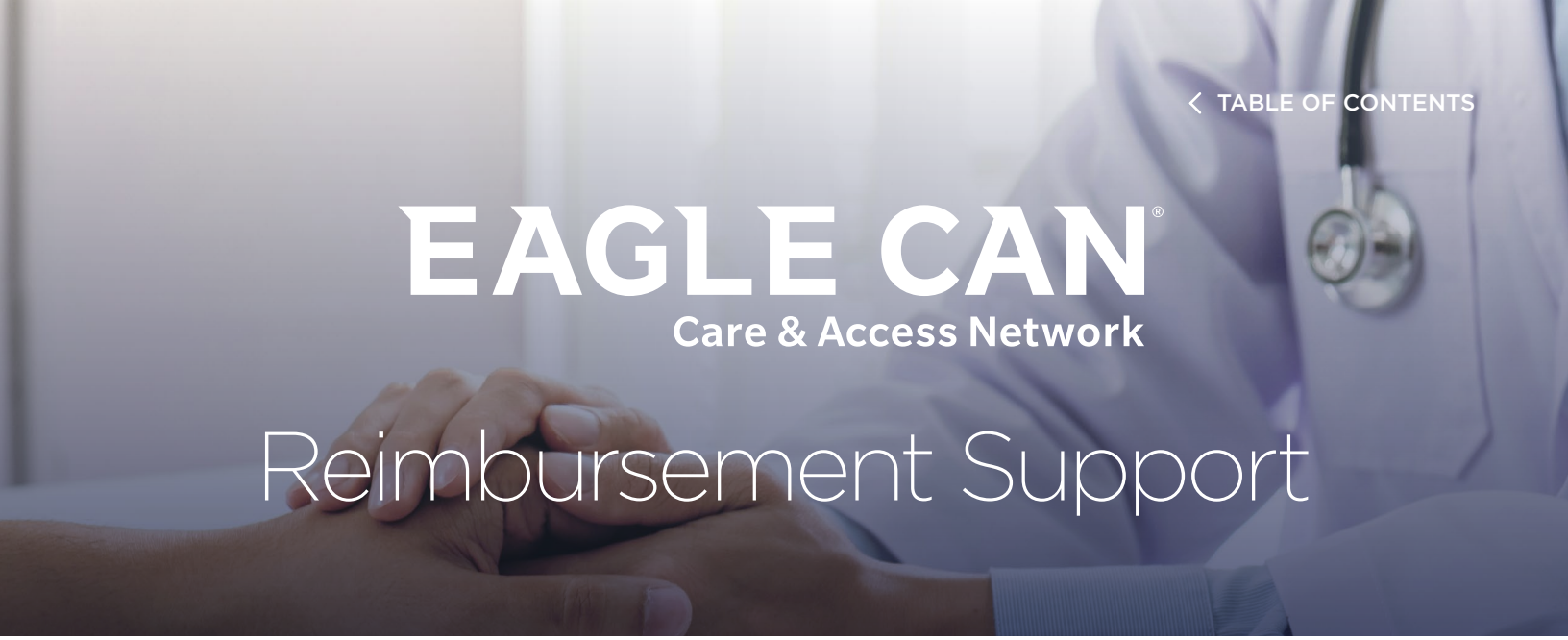
BOX 24E: Diagnosis Pointer

Enter ICD diagnosis code reference letter from Box 21, relative to the date of service and the procedure performed.

BOX 24G: Days or Units

Enter the number of service units for PEMFEXY® HCPCS code (J9304). Billable unit = 10 mg. One vial = 50 units.

See Billing Unit Conversion on page 6.



EAGLE CAN®
Care & Access Network

Reimbursement Support

Providing You and Your Patients Comprehensive Reimbursement and Access Solutions

EAGLE CAN® Program Benefits:

Benefit Verification

Access Support

- Prior authorization assistance
- Coverage counseling
- Reimbursement guidance
- Appeals investigation and counseling

Patient Assistance

- Product access through our Patient Financial Assistance Program[§]
- Product Credit Replacement Program[§]
- Referrals to 501 (c)(3) foundations when applicable

PEMFEXY® Copay Assistance Program

- Patients may pay as little as $0 per dose[¶]
- 12-Month rolling enrollment period[¶]
- Enrollment period maximum benefit of $25,000 per year[§]

Local, Dedicated Field Reimbursement Support

- Contact your regional Field Reimbursement Manager for assistance

For Additional Support, or to Enroll Your Eligible Patients, Contact an EAGLE CAN® Patient Access Specialist Today:

CALL 833-324-5322

Fax: 1-833-324-5346

Monday through Friday
9:00 AM to 5:00 PM ET

Download the EAGLE CAN® Enrollment Form:

VISIT PEMFEXY.COM

[§]For eligibility requirements please contact a program representative.
[¶]Terms and conditions apply; see terms and conditions on the next page.

PEMFEXY® Copay Assistance Program

The PEMFEXY® Copay Assistance Program is for commercially insured, eligible patients whose insurance does not cover the full cost of their PEMFEXY® treatment. Learn more about eligibility requirements in the **Terms and Conditions** on this page.

Patients prescribed PEMFEXY® may pay as little as

$0 per dose

TERMS AND CONDITIONS APPLY

- Patient out-of-pocket cost may be as little as $0 per dose
- 12-Month rolling enrollment period

  Patients and providers must renew enrollment when the active eligibility period ends. There is no limit to how many times a patient may enroll.
- Enrollment period maximum benefit of $25,000 per year

Uninsured patients prescribed PEMFEXY® may qualify for other, separate financial assistance. Speak with an EAGLE CAN® Patient Access Specialist to learn more by calling **833-324-5322.**

Scan to download the Enrollment Form on PEMFEXY.COM

PEMFEXY® COPAY ASSISTANCE PROGRAM TERMS AND CONDITIONS

Patient Eligibility:

1. You must have commercial insurance that covers PEMFEXY but it does not cover the full cost and you are responsible for a portion of the cost.
2. You are not able to receive copay assistance for PEMFEXY if you participate in any state or federal healthcare program, including Medicaid, Medicare, Medigap, CHAMPUS, DoD, VA, TRICARE, or any other state patient or pharmaceutical assistance program.
3. You must immediately notify the EAGLE CAN Program if your insurance situation changes and that you may no longer be eligible to receive copay assistance for PEMFEXY if you begin to participate in one of the programs noted above.
4. You must be 18 years of age or older and receiving PEMFEXY for an FDA approved use. Please ask your doctor for information about FDA approved uses.
5. You must reside in the United States or Puerto Rico.

Program Benefits:

1. You will be eligible to receive up to $25,000 in assistance for your documented out-of-pocket costs for PEMFEXY.
2. You will be responsible for as little as $0 in out-of-pocket costs for each date of service submitted for copay assistance.
3. You must submit documentation of your out-of-pocket costs for PEMFEXY within 180 days of the treatment date.
4. Your healthcare provider can submit documentation for your out-of-pocket costs for PEMFEXY on your behalf.
5. For enrolled patients, the Program may provide support for claims with a date of service that falls within 120 days prior to the date the application is received by the Program.

Program Timing:

1. You will be eligible for 12 months from the approval date and will need to apply again if copay assistance continues to be needed when your eligibility ends.

Additional Terms and Conditions of Program:

1. Copay assistance will only be provided for out-of-pocket costs for PEMFEXY. Copay assistance will not be provided for your out-of-pocket costs related to the administration procedure, office visits, or other expenses.
2. You will not seek reimbursement from any third-party payers, including flexible spending accounts or healthcare savings accounts, for the value of any payment received from the EAGLE CAN Program.
3. Patients are not re-enrolled automatically prior to the end of the current eligibility period. Re-enrollment of the Program is initiated by the provider and patient.
4. This Program is not insurance.
5. Eagle Pharmaceuticals reserves the right to terminate, rescind, revoke, or amend this offer at any time without notice.

IMPORTANT SAFETY INFORMATION
(Continued)

WARNINGS AND PRECAUTIONS (Continued)

Renal Failure

Pemetrexed can cause severe, and sometimes fatal, renal toxicity. Determine creatinine clearance before each dose and periodically monitor renal function during treatment with PEMFEXY. 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).

Withhold PEMFEXY in patients with a creatinine clearance of less than 45 mL/min.

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.

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.

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.

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.

Embryo-Fetal Toxicity

Based on findings from animal studies and its mechanism of action, PEMFEXY 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 PEMFEXY and for 6 months after the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with PEMFEXY and for 3 months after the final dose.

DRUG INTERACTIONS

Ibuprofen increases exposure (AUC) of pemetrexed. 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 PEMFEXY.
- Monitor patients more frequently for myelosuppression, renal, and gastrointestinal toxicity, if concomitant administration of ibuprofen cannot be avoided.

ADVERSE REACTIONS

Severe adverse reactions (Grade 3-4) occurring in ≥20% of patients with metastatic non-squamous non-small cell lung cancer (NSCLC) receiving pemetrexed in combination with pembrolizumab and platinum chemotherapy (carboplatin or cisplatin) versus pemetrexed with platinum chemotherapy + placebo for initial treatment (KEYNOTE-189), respectively, were fatigue (12% vs 6%); diarrhea (5% vs 3%); dyspnea (3.7% vs 5%); vomiting (3.7% vs 3%); nausea (3.5% vs 3.5%); rash (2% vs 2.5%); decreased appetite (1.5% vs 0.5%); constipation (1% vs 0.5%); and pyrexia (0.2% vs 0%).

Common adverse reactions (all grades) occurring in ≥20% of patients with metastatic non-squamous non-small cell lung cancer (NSCLC) receiving pemetrexed in combination with pembrolizumab and platinum chemotherapy (carboplatin or cisplatin) versus pemetrexed with platinum chemotherapy + placebo for initial treatment (KEYNOTE-189), respectively, were nausea (56% vs 52%); fatigue (56% vs 58%); constipation (35% vs 32%); diarrhea (31% vs 21%); decreased appetite (28% vs 30%); rash (25% vs 17%); vomiting (24% vs 23%); cough (21% vs 28%); dyspnea (21% vs 26%); and pyrexia (20% vs 15%).

Severe adverse reactions (Grade 3-4) occurring in fully vitamin supplemented patients with locally advanced or metastatic non-squamous non-small cell lung cancer (NSCLC) receiving pemetrexed in combination with cisplatin versus gemcitabine in combination with cisplatin for initial treatment (JMDB), respectively, were neutropenia (15% vs 27%); fatigue (7% vs 5%); nausea (7% vs 4%); anemia (6% vs 10%); vomiting (6% vs 6%); thrombocytopenia (4% vs 13%); anorexia (2% vs 1%); diarrhea (1% vs 2%); elevated creatinine (1% vs 1%); stomatitis/pharyngitis (1% vs 0%); and constipation (1% vs 0%).

Common adverse reactions (all grades) occurring in ≥5% fully vitamin supplemented patients with locally advanced or metastatic non-squamous non-small cell lung cancer (NSCLC) receiving pemetrexed in combination with cisplatin versus gemcitabine in combination with cisplatin for initial treatment (JMDB), respectively, were nausea (56% vs 53%); fatigue (43% vs 45%); vomiting (40% vs 36%); anemia (33% vs 46%); neutropenia (29% vs 38%); anorexia (27% vs 24%); constipation (21% vs 20%); stomatitis/pharyngitis (14% vs 12%); alopecia (12% vs 21%); diarrhea (12% vs 13%); thrombocytopenia (10% vs 27%); elevated creatinine (10% vs 7%), sensory neuropathy (9% vs 12%); taste disturbance (8% vs 9%); rash/desquamation (7% vs 8%); and dyspepsia/heartburn (5% vs 6%).

Severe adverse reactions (Grade 3-4) occurring in patients with non-progressive locally advanced or metastatic non-squamous non-small cell lung cancer (NSCLC) receiving pemetrexed as a single agent versus placebo as maintenance treatment (JMEN), respectively, following non-pemetrexed containing, platinum-based induction therapy were fatigue (5% vs 1%); anemia (3% vs 1%); neutropenia (3% vs 0%); infection (2% vs 0%); anorexia (2% vs 0%); nausea (1% vs 1%); mucositis/stomatitis (1% vs 0%); diarrhea (1% vs 0%); and sensory neuropathy (1% vs 0%).

Common adverse reactions (all grades) occurring in ≥5% patients with non-progressive locally advanced or metastatic non-squamous non-small cell lung cancer (NSCLC) receiving pemetrexed as a single agent versus placebo as maintenance treatment (JMEN), respectively, following non-pemetrexed containing, platinum-based induction therapy were fatigue (25% vs 11%); nausea (19% vs 6%); anorexia (19% vs 5%); anemia (15% vs 6%); increased ALT (10% vs 4%); rash/desquamation (10% vs 3%); sensory neuropathy (9% vs 4%); vomiting (9% vs 1%); increased AST (8% vs 4%); mucositis/stomatitis (7% vs 2%); neutropenia (6% vs 0%); diarrhea (5% vs 3%); and infection (5% vs 2%).

Severe adverse reactions (Grade 3-4) occurring in patients with non-progressive locally advanced or metastatic non-squamous non-small cell lung cancer (NSCLC) receiving pemetrexed as a single agent versus placebo as maintenance treatment (PARAMOUNT), respectively, following pemetrexed plus cisplatin induction therapy were anemia (4.8% vs 0.6%); fatigue (4.5% vs 0.6%) ; neutropenia (3.9% vs 0%); nausea (0.3% vs 0%); and mucositis/stomatitis (0.3% vs 0%).

Common adverse reactions (all grades) occurring in ≥5% patients with non-progressive locally advanced or metastatic non-squamous non-small cell lung cancer (NSCLC) receiving pemetrexed as a single agent versus placebo as maintenance treatment (PARAMOUNT), respectively, following pemetrexed plus cisplatin induction therapy were fatigue (18% vs 11%); anemia (15% vs 4.8%); nausea (12% vs 2.4%); neutropenia (9% vs 0.6%); vomiting (6% vs 1.8%); edema (5% vs 3.6%); and mucositis/stomatitis (5% vs 2.4%).

Severe adverse reactions (Grade 3-4) occurring in fully supplemented patients with recurrent metastatic non-squamous non-small cell lung cancer (NSCLC) receiving pemetrexed as a single agent versus docetaxel as 2nd-line treatment after prior chemotherapy (JMEI), respectively, were neutropenia (5% vs 40%); fatigue (5% vs 5%); anemia (4% vs 4%); nausea (3% vs 2%); anorexia (2% vs 3%); vomiting (2% vs 1%); thrombocytopenia (2% vs 0%); increased ALT (2% vs 0%); alopecia (1% vs 2%); stomatitis/pharyngitis (1% vs 1%); and increased AST (1% vs 0%).

Common adverse reactions (all grades) occurring in ≥5% of fully supplemented patients with recurrent metastatic non-squamous non-small cell lung cancer (NSCLC) receiving pemetrexed as a single agent versus docetaxel as 2nd-line treatment after prior chemotherapy (JMEI), respectively, were fatigue (34% vs 36%); nausea (31% vs 17%); anorexia (22% vs 24%); anemia (19% vs 22%); vomiting (16% vs 12%); stomatitis/pharyngitis (15% vs 17%); rash/desquamation (14% vs 6%); diarrhea (13% vs 24%); neutropenia (11% vs 45%); fever (8% vs 8%); thrombocytopenia (8% vs 1%); increased ALT (8% vs 1%); pruritus (7% vs 2%); increased AST (7% vs 1%); alopecia (6% vs 38%); and constipation (6% vs 4%).

Severe adverse reactions (Grade 3-4) occurring in fully supplemented subgroup of patients with malignant pleural mesothelioma (MPM) receiving pemetrexed in combination with cisplatin versus cisplatin alone (JMCH), respectively, were neutropenia (23% vs 3%); nausea (12% vs 6%); vomiting (11% vs 4%); fatigue (10% vs 9%); thrombocytopenia (5% vs 0%); dehydration (4% vs 1%); anemia (4% vs 0%); diarrhea (4% vs 0%); stomatitis/pharyngitis (3% vs 0%); decreased creatinine clearance (1% vs 2%); elevated creatinine (1% vs 1%); anorexia (1% vs 1%); constipation (1% vs 1%); dyspepsia (1% vs 0%); and rash (1% vs 0%).

Common adverse reactions (all grades) occurring in ≥5% of fully supplemented subgroup of patients with malignant pleural mesothelioma (MPM) receiving pemetrexed in combination with cisplatin versus cisplatin alone (JMCH), respectively, were nausea (82% vs 77%); vomiting (57% vs 50%); neutropenia (56% vs 13%); fatigue (48% vs 42%); anemia (26% vs 10%); thrombocytopenia (23% vs 9%); stomatitis/pharyngitis (23% vs 6%); anorexia (20% vs 14%); diarrhea (17% vs 8%); decreased creatinine clearance (16% vs 18%);

rash (16% vs 5%); constipation (12% vs 7%); elevated creatinine (11% vs 10%); alopecia (11% vs 6%); sensory neuropathy (10% vs 10%); taste disturbance (8% vs 6%); dehydration (7% vs 1%); conjunctivitis (5% vs 1%); and dyspepsia (5% vs 1%).

USE IN SPECIFIC PATIENT POPULATIONS

Pregnancy

There are no available data on pemetrexed use in pregnant women. Based on findings from animal studies and its mechanism of action, PEMFEXY 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 malformations at doses lower than the recommended human dose of 500 mg/m^2. Advise pregnant women on the potential risk to a fetus.

Lactation

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 PEMFEXY, advise women not to breastfeed during treatment with PEMFEXY and for one week after last dose.

Females and Males of Reproductive Potential

Verify pregnancy status of females of reproductive potential prior to initiating PEMFEXY. PEMFEXY can cause fetal harm when administered to a pregnant woman. Because of the potential for genotoxicity, advise females of reproductive potential to use effective contraception during treatment with PEMFEXY and for 6 months after the final dose. Because of the potential for genotoxicity, advise males with female partners of reproductive potential to use effective contraception during treatment with PEMFEXY and for 3 months after the final dose. PEMFEXY may impair fertility in males of reproductive potential. It is not known whether these effects on fertility are reversible.

Pediatric Use

The safety and effectiveness of PEMFEXY in pediatric patients have not been established. Adverse reactions observed in pediatric patients studied were similar to those observed in adults.

Geriatric Use

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.

Renal Impairment

PEMFEXY 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. No dosage is recommended for patients with creatinine clearance less than 45 mL/min.

For safety and dosing guidelines for PEMFEXY, see complete Warnings and Precautions, Adverse Reactions, and Dosage and Administration sections in the full Prescribing Information.

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.

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PEMFEXY®
(PEMETREXED INJECTION)

500 mg/20 mL (25 mg/mL)

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