AXTLE™
(Pemetrexed for Injection)

BILLING AND CODING GUIDE

If you have additional billing and coding questions, please call your Field Reimbursement Manager or AVYXASSIST™ at 866-939-8927. Our Patient Access Specialists are available to assist Monday through Friday, 8 AM to 8 PM ET.

Please see Important Safety Information on pages 3 and 13-19 and full Prescribing Information for AXTLE™.

AVYXA

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The contents herein provide general coverage, coding, and payment information about AXTLE™. The information within this guide was obtained from third-party sources and is made available for reference only. It is not exhaustive, is subject to change, and does not constitute billing, coding, or legal advice. Healthcare professionals are responsible for determining which code(s), charge(s), or modifie (s), if any, appropriately reflect a service or diagnosis. It is the healthcare professional's responsibility to determine medical necessity and provide adequate documentation. AVYXA™ does not guarantee coverage or payment. 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.

CMS: Centers for Medicare & Medicaid Services; CPT: Current Procedural Terminology; HCPCS: Healthcare Common Procedure Coding System; ICD: International Classification of Diseases; NDC: National Drug Cod

Please see Important Safety Information on pages 3 and 13-19 and full Prescribing Information for AXTLE™.

INDICATIONS AND IMPORTANT SAFETY INFORMATION

INDICATIONS

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

AXTLE™ is indicated for:

- in combination with cisplatin for the initial treatment of patients with locally advanced or metastatic, non-squamous 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 chemotherap
- as a single agent for the treatment of patients with recurrent, metastatic non-squamous, NSCLC after prior chemotherapy

Limitations of Use: AXTLE™ is not indicated for the treatment of patients with squamous cell, non-small cell lung cancer.

Mesothelioma

AXTLE™ 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.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

AXTLE™ is contraindicated in patients with a history of severe hypersensitivity reaction to pemetrexed.

WARNINGS AND PRECAUTIONS

Myelosuppression and Increased Risk of Myelosuppression without Vitamin Supplementation

AXTLE™ 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 AXTLE™; continue vitamin supplementation during treatment and for 21 days after the last dose of AXTLE™ to reduce the severity of hematologic and gastrointestinal toxicity of AXTLE™. Obtain a complete blood count at the beginning of each cycle. Do not administer AXTLE™ until the ANC is at least 1500 cells/mm^3 and platelet count is at least 100,000 cells/mm^3 . Permanently reduce AXTLE™ 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%.

AXTLE™
(Pemetrexed for Injection)

Ordering Information

To order AXTLE™ (Pemetrexed for Injection), please contact one of these authorized specialty distributors and use the appropriate order number:

100 mg/vial
NDC: 83831-0131-01

500 mg/vial
NDC: 83831-0132-01

Institutions/Hospitals	100 mg/vial	500 mg/vial
Cardinal Health Specialty	5962121	5962139
CENCORA - ASD Healthcare	10295451	10295442
McKesson Plasma & Biologics	3005485	3005410
Physician Office	**100 mg/vial**	**500 mg/vial**
Cardinal Health Specialty	5962121	5962139
Oncology Supply	10295426	10295460
McKesson Specialty Health	5019191	5019190

Highlights[1]

- Available as pemetrexed dipotassium
- Free from preservative
- Reconstitute with 5% Dextrose Injection, USP (preservative-free)
- Not made with natural rubber latex
- Unique J-Code: J9292

UNIQUE
J-CODE
J9292

Please see Important Safety Information on pages 3 and 13-19 and full Prescribing Information for AXTLE™.

AVYXASSIST™

Simplifying Patient Access, Providing Comprehensive Support.

AVYXASSIST™ can offer support to qualifying patients in need. The program provides the following services*

- Benefit verification
- Prior authorization requirements
- Appeals process information
- Referrals to 501(c)(3) foundations when applicable
- Free product assistance (uninsured or underinsured), bridge supply (coverage delays)
- Product replacement
- Copay assistance

COPAY ASSISTANCE PROGRAM

Eligible patients may pay as little as **$0** per dose*

TO ENROLL, PLEASE CHOOSE ONE OF THE FOLLOWING OPTIONS

Phone

866-939-8927
Monday through Friday
8 AM to 8 PM ET

CALL NOW

OR

Online

Click on the link below to begin your online enrollment

ENROLL NOW

OR

Fax

Download, print and fax the completed enrollment form to 833-852-3420

DOWNLOAD NOW

*For Eligibility Requirements Please Contact A Patient Access Specialist. Terms And Conditions Apply.

Billing and Coding Information

The information provided is for informational purposes only and represents no statement, promise, or guarantee by AVYXA™ concerning reimbursement, payment, or charges. The information provided is not intended to increase or maximize reimbursement by any payer. Healthcare professionals are responsible for selecting appropriate codes used to file a claim. Codes should be based on the patient s diagnosis and the items and services furnished by the healthcare professional. All codes should be verified between the healthcare professional and the paye . AVYXA™ does not recommend using any particular diagnosis code in any billing situation for AXTLE™ (pemetrexed) for Injection. The below codes are for reference only; coding as submitted is the sole responsibility of the prescribing physician.

NDCs for AXTLE™ FOR INJECTION[1]

Nearly all drugs in the United States are given a unique National Drug Code (NDC), which identifies all currently manufactured drugs and is maintained by the FDA.[2] NDCs are displayed on drug packing in a 10-digit format. Proper NDC billing requires an 11-digit number in a 5-4-2 format, listed below.

NDC	Strength	Vial Size
83831-0131-01	100 mg/vial	Single-dose vial
83831-0132-01	500 mg/vial	Single-dose vial

HCPCS Code[3]

HCPCS Level II codes are used to identify most drugs and biologics that are given in the office

AXTLE™ Unique J-Code	Description
J9292	Injection, pemetrexed (avyxa), not therapeutically equivalent to J9305, 10 mg

J-Code Billing Unit Conversion

Each 10 milligrams of AXTLE™ equals one (1) billing unit. When billing for quantities greater than 10 milligrams, indicate the total amount used as a multiple of billing units on the claim form. Examples:

One (1) Vial (100 mg)	10 Billing Units
One (1) Vial (500 mg)	50 Billing Units

NOTE: There are a few HCPCS codes for pemetrexed but there is only one HCPCS code for **AXTLE™ (J9292),** so please make sure the HCPCS code matches the product purchased and administered.

Please see Important Safety Information on pages 3 and 13-19 and full Prescribing Information for AXTLE™.

CPT Drug Administration Codes[4,5]

CPT codes are used to bill drug administration services provided in the physician's office and other outpatient settings

CPT Code	Description
96413	Chemotherapy administration, intravenous infusion technique; up to 1 hour, single or initial substance/drug.
96417	Chemotherapy administration, intravenous infusion technique; each additional sequential infusion (different substance/drug), up to 1 hour.

AXTLE™ is packaged as a single-dose vial. Medicare will pay for drug waste on single-use items that are medically necessary and appropriately documented in the patient's medical record.

Medicare requires discarded drugs to be reported with the JW modifier on a separate line; if there is no waste, AXTLE™ must be billed on one line with modifier JZ. Medicare requires this; please ascertain if other payers require JZ and JW modifiers [6]

ICD Diagnosis Codes[7,8]

For Drugs with multiple indications, it is best practice to code the most specific ICD-10-CM Code within the indication to justify medical necessity.

International Classification of Disease, 10th Edition, Clinical Modification Codes for AXTLE™	
Indication	**ICD-10-CM Codes**
Non-Small Cell Lung Cancer	C33, C34.00, C34.01, C34.02, C34.10, C34.11, C34.12, C34.2, C34.30, C34.31, C34. 32, C34.80, C34.81, C34.82, C34.90, C34.91, C34.92
Mesothelioma	C45.0

Please see Important Safety Information on pages 3 and 13-19 and full Prescribing Information for AXTLE™.

AXTLE™ Billing and Coding Information: ICD Diagnosis Codes by Indication

ICD-10-CM coding for AXTLE™ varies greatly by payer. Please check with each payer to ascertain the best coding for AXTLE™ according to their policy.

Non-Small Cell Lung Cancer: ICD-10-CM Diagnosis Coding	
ICD-10 Code	**Descriptor**
C33	Malignant neoplasm of trachea
C34.00	Malignant neoplasm of unspecified main bronchu
C34.01	Malignant neoplasm of right main bronchus
C34.02	Malignant neoplasm of left main bronchus
C34.10	Malignant neoplasm of upper lobe, unspecified bronchus or lun
C34.11	Malignant neoplasm of upper lobe, right bronchus or lung
C34.12	Malignant neoplasm of upper lobe, left bronchus or lung
C34.2	Malignant neoplasm of middle lobe, bronchus or lung
C34.30	Malignant neoplasm of lower lobe, unspecified bronchus or lun
C34.31	Malignant neoplasm of lower lobe, right bronchus or lung
C34.32	Malignant neoplasm of lower lobe, left bronchus or lung
C34.80	Malignant neoplasm of overlapping sites of unspecified bronchus and lun
C34.81	Malignant neoplasm of overlapping sites of right bronchus and lung
C34.82	Malignant neoplasm of overlapping sites of left bronchus and lung
C34.90	Malignant neoplasm of unspecified part of unspecified bronchus or lu
C34.91	Malignant neoplasm of unspecified part of right bronchus or lun
C34.92	Malignant neoplasm of unspecified part of left bronchus or lun

Mesothelioma: ICD-10-CM Diagnosis Coding	
ICD-10 Code	**Descriptor**
C45.0	Mesothelioma of pleura

SAMPLE UB-04 / CMS 1450 Claim Form

Form Locator (FL) 42

(Electronic Claim Form =Loop 2400, Segment Type SV201):

List the appropriate revenue code for the drug. Match the descriptor for AXTLE™ for Injection to your revenue code, 0636.

Additionally, enter an appropriate revenue code for the administration service, 0335 for chemotherapy, or others based on the cost center in which the service was performed.

FL 43

(NOT REQUIRED BY MEDICARE):

Enter the description of the procedure for the Revenue Code billed.

If the patient is dualeligible, the N4 indicator first, then the 11-digit NDC code. In the third place, list the quantity and, last, the unit measurement code. Check with other payers for their requirements.

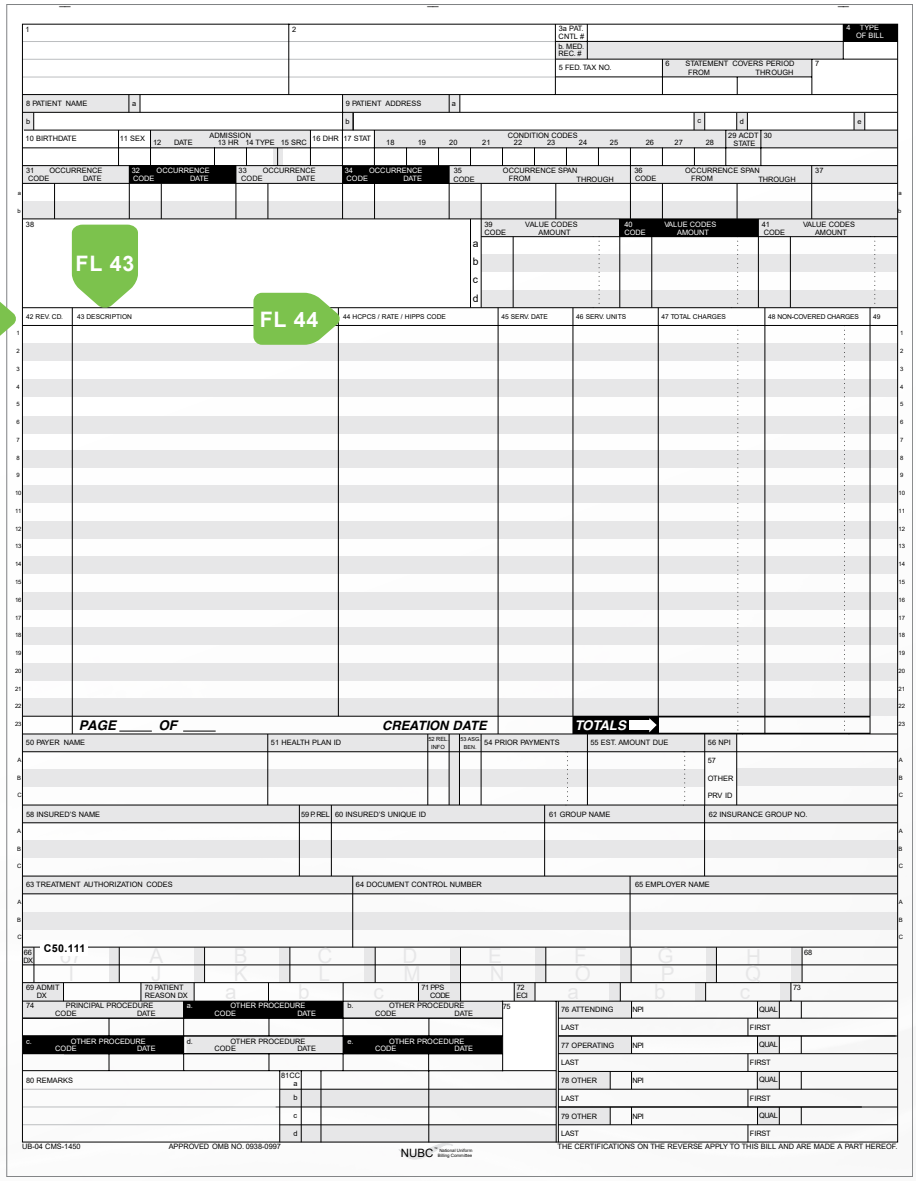
FL 44

(Electronic Claim Form = Loop 2400, SV202-2 (SV202-1=HC/HP):

Enter the appropriate HCPCS code, **J9292,** Injection, pemetrexed **(avyxa), not therapeutically equivalent to J9305, 10 mg.**

AXTLE™ is packaged as a single-dose vial. Medicare requires drug waste be reported with the JW[1] modifier on a separate line. If there is no waste, AXTLE™ must be billed on one line with modifier JZ.[2] Medicare requires this; please ascertain if other payers require JZ and JW modifiers

For administration, enter the appropriate code or codes for the infusion duration. As an example, a 60-minute infusion of chemotherapy requires 96413.[3]



Please see Important Safety Information on pages 3 and 13-19 and full Prescribing Information for AXTLE™.

FL 45

(Electronic Claim Form = Loop 2400, Segment DTP/472/03):

Enter the date of service

FL 46

(Electronic Claim Form = Loop 2400, SV205):

Enter the units for the HCPCS code billed. Enter the number of service units for each item.

For example, 10 units if using one 100 mg/vial, or 50 units if using one 500 mg/vial of AXTLE™ (pemetrexed) for injection.

FL 63

(Electronic Claim Form = Loop 2300,REF/G1/02):

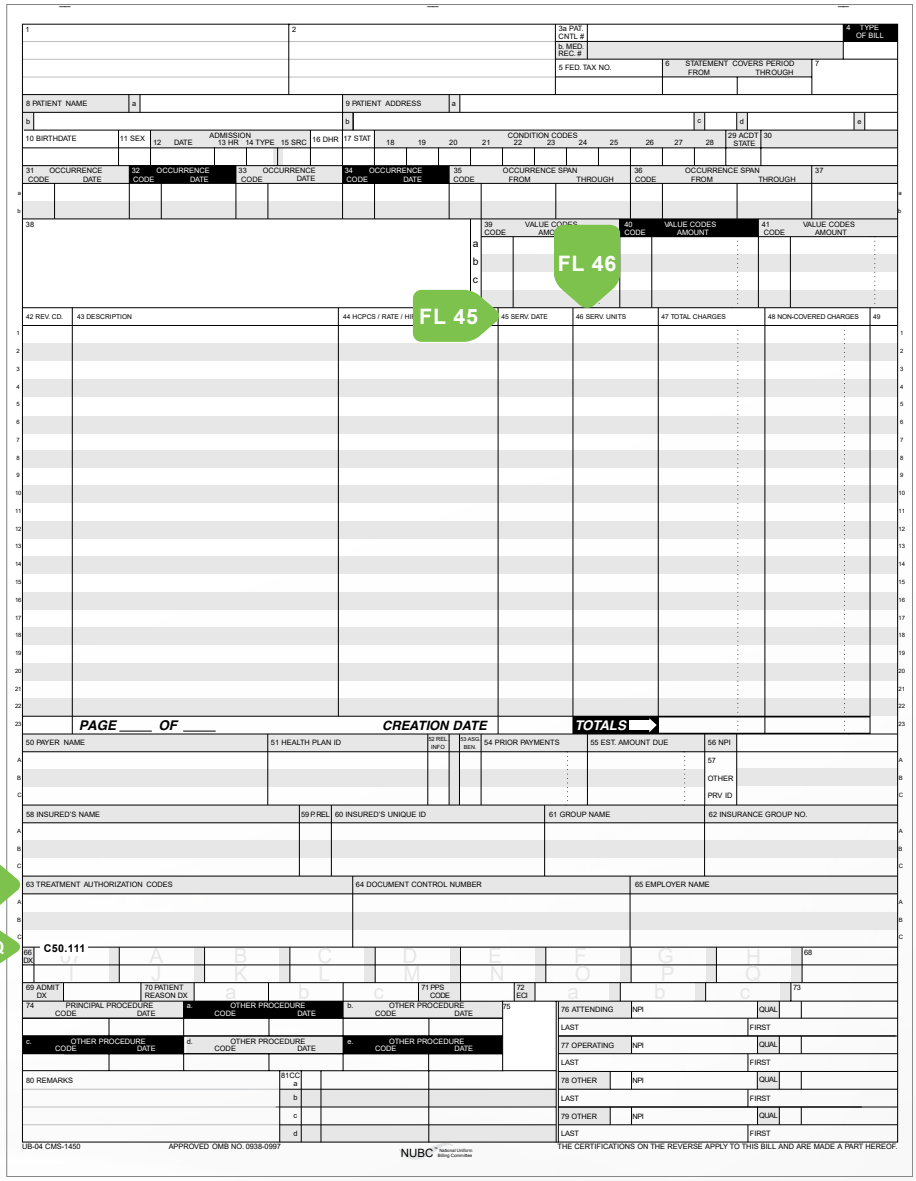
Enter treatment authorization code.

FL 67A-Q

(Electronic Claim Form = Loop 2300, HI01-2 (HI01-1=BK):

Enter a diagnosis code for the drug documented in the medical record. Be as specific as possible.

The code listed here is an example: **C34.01, Malignant neoplasm of right main bronchus.**



[1] Since January 1, 2017, Medicare has required Modifier -JW for waste. Check with other payers as to their requirements for identifying waste.
[2] Effective July 1, 2023, Medicare requires the JZ modifier on all claims for single-dose containers with no discarded amounts.
[3]] CPT Code 96413 Chemotherapy administration, intravenous infusion technique; up to 1 hour, single or initial substance/drug Initial infusion times may vary.
***Electronic Claims Reference:** ASC 837I Version 5010A2 Institutional Health Care Claim to the CMS-1450 Claim Form Crosswalk." Palmettogba.Com. Palmetto GBA, Accessed April 3, 2023. https://www.palmettogba.com/palmetto/providers.nsf/files/EDI_837I_v5010A2_crosswalk.pdf/$FILE/EDI_837I_v5010A2_crosswalk.pdf*

SAMPLE CMS 1500 Claim Form

Box 21

(Electronic Claim Form = Loop 2300, Segment H101-2 through H112=2):

Enter the patient's diagnosis from the patient's medical record. An example code for this drug is **C34.01, Malignant neoplasm of right main bronchus**

Use Box 21 B-L fields for secondary diagnoses.

Box 23

(Electronic Claim Form = Loop 2300, REF02):

Enter prior authorization number if one exists.

Box 24D

(Electronic Claim Form = Loop 2400, Segment SV101):

Enter the appropriate HCPCS code, **J9292**, Injection, pemetrexed (avyxa), not therapeutically equivalent to J9305, 10 mg.

AXTLE™ is packaged as a single-dose vial. Medicare requires drug waste be reported with the -JW[1] modifier on a separate line. If there is no waste, AXTLE™ must be billed on one line with modifier -JZ.[2] Medicar requires this; please ascertain if other payers require JZ and -JW modifiers

For administration, enter the appropriate code or codes for the infusion duration. As an example, a 60-minute infusion of chemotherapy requires 96413.[3]

Box 24E

(Electronic Claim Form = Loop 2400, Segment SV107):

Specify the diagnosis letter that corresponds with the drug and drug administration code(s) in Box 21.

Please see Important Safety Information on pages 3 and 13-19 and full Prescribing Information for AXTLE™.

Box 24G

(Electronic Claim Form = Loop 2400, SV104):

Enter the number of service units for each item.

Box 24A-B

Box 24A-B (Electronic Claim Form: Box 24A (Electronic Claims = Loop 2400, DTP02; Box 24 B (Loop 2300/2400, Segment CLM05-1/SV105)

In the non-shaded area, enter the appropriate date of service and place of service code.
Example: Office = 11

In the shaded area, enter the N4 indicator first, then the 11-digit NDC code. In the third space, list the quantity and, last, the unit measurement code

Box 24A-B

Box 24G

[1] Since January 1, 2017, Medicare has required Modifier -JW for waste. Check with other payers as to their requirements for identifying waste.
[2] Effective July 1, 2023, Medicare requires the JZ modifier on all claims for single-dose containers with no discarded amounts.
[3] CPT Code 96413 Chemotherapy administration, intravenous infusion technique; up to 1 hour, single or initial substance/drug Initial infusion times may vary.
Electronic Claims Reference: *ASC 837I Version 5010A2 Institutional Health Care Claim to the CMS-1450 Claim Form Crosswalk." Palmettogba.Com. Palmetto GBA, Accessed April 3, 2023. https://www.palmettogba.com/palmetto/providers.nsf/files/EDI_837I_v5010A2_crosswalk.pdf/$FILE/EDI_837I_v5010A2_crosswalk.pdf*

THIS INFORMATION IS PROVIDED FOR EDUCATIONAL PURPOSES ONLY AND IS NOT A GUARANTEE OF COVERAGE. IT IS THE SOLE RESPONSIBILITY OF THE HEALTH CARE PROVIDER TO SELECT THE PROPER CODES AND ENSURE THE ACCURACY OF ALL STATEMENTS USED IN SEEKING COVERAGE AND REIMBURSEMENT FOR AN INDIVIDUAL PATIENT.

IMPORTANT SAFETY INFORMATION (CONTINUED)

Renal Failure

AXTLE™ 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. Determine creatinine clearance before each dose and periodically monitor renal function during treatment with AXTLE™. Withhold AXTLE™ in patients with a creatinine clearance of less than 45 mL/minute.

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 AXTLE™. Permanently discontinue AXTLE™ for severe and life-threatening bullous, blistering or exfoliating skin toxicity.

Interstitial Pneumonitis

Serious interstitial pneumonitis, including fatal cases, can occur with AXTLE™ treatment. Withhold AXTLE™ 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 AXTLE™.

Radiation Recall

Radiation recall can occur with AXTLE™ in patients who have received radiation weeks to years previously. Monitor patients for inflammation or blistering in areas of previous radiation treatment. Permanently discontinue AXTLE™ 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 AXTLE™. 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 AXTLE™. 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, AXTLE™ 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 a fetus. Advise females of reproductive potential to use effective contraception during treatment with AXTLE™ and for 6 months after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with AXTLE™ and for 3 months after the last dose.

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IMPORTANT SAFETY INFORMATION (CONTINUED)

ADVERSE REACTIONS

In clinical trials, the most common adverse reactions (incidence ≥20%) of pemetrexed, when administered as a single agent, are fatigue, nausea, and anorexia. The most common adverse reactions (incidence ≥20%) of pemetrexed, when administered in combination with cisplatin are vomiting, neutropenia, anemia, stomatitis/pharyngitis, thrombocytopenia, and constipation.

Non-Squamous NSCLC

Initial Treatment in Combination with Cisplatin (Study JMDB)

The safety of pemetrexed was evaluated in chemotherapy-naïve patients with locally advanced or metastatic NSCLC. Patients received either pemetrexed 500 mg/m^2 intravenously and cisplatin 75 mg/m^2 intravenously (N=839) or gemcitabine 1250 mg/m^2 intravenously and cisplatin 75 mg/m^2 intravenously (N=830).

The following adverse reactions occurred in ≥5% of fully vitamin-supplemented patients (with folic acid and vitamin B_{12}) who received pemetrexed in combination with cisplatin chemotherapy compared to those who received gemcitabine in combination with cisplatin, respectively: anemia (33% [6% Grade 3-4] versus 46% [10% Grade 3-4], respectively), neutropenia (29% [15% Grade 3-4] versus 38% [27% Grade 3-4], respectively), thrombocytopenia (10% [4% Grade 3-4] versus 27% [13% Grade 3-4], respectively), elevated creatinine (10% [1% Grade 3-4] versus 7% [1% Grade 3-4], respectively), fatigue (43% [7% Grade 3-4] versus 45% [5% Grade 3-4], respectively), nausea (56% [7% Grade 3-4] versus 53% [4% Grade 3-4], respectively), vomiting (40% [6% Grade 3-4] versus 36% [6% Grade 3-4], respectively), anorexia (27% [2% Grade 3-4] versus 24% [1% Grade 3-4], respectively), constipation (21% [1% Grade 3-4] versus 20% [0% Grade 3-4], respectively), stomatitis/pharyngitis (14% [1% Grade 3-4] versus 12% [0% Grade 3-4], respectively), diarrhea (12% [1% Grade 3-4] versus 13% [2% Grade 3-4], respectively), dyspepsia/heartburn (5% [0% Grade 3-4] versus 6% [0% Grade 3-4], respectively), sensory neuropathy (9% [0% Grade 3-4] versus 12% [1% Grade 3-4], respectively), taste disturbance (8% [0% Grade 3-4] versus 9% [0% Grade 3-4], respectively), alopecia (12% [0% Grade 3-4] versus 21% [1% Grade 3-4], respectively), and rash/desquamation (7% [0% Grade 3-4] versus 8% [1% Grade 3-4], respectively).

The following additional adverse reactions of pemetrexed were observed with an incidence of 1% to <5%: febrile neutropenia, infection, pyrexia, dehydration, increased AST, increased ALT, renal failure, and conjunctivitis.

The following additional adverse reactions of pemetrexed were observed with an incidence of <1%: arrhythmia, chest pain, increased GGT, and motor neuropathy.

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

The safety of pemetrexed was evaluated 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/ ^{2} (N=438) or matching placebo (N=218) intravenously.

The following adverse reactions occurred in ≥5% of fully vitamin-supplemented patients (with folic acid and vitamin B_{12}) who received pemetrexed compared to placebo, respectively: anemia (15% [3% Grade 3-4] versus 6% [1% Grade 3-4], respectively), neutropenia (6% [3% Grade 3-4] versus 0%, respectively), increased ALT (10% [0% Grade 3-4] versus 4% [0% Grade 3-4], respectively), increased AST (8% [0% Grade 3-4] versus 4% [0% Grade 3-4], respectively), fatigue (25% [5% Grade 3-4] versus 11% [1% Grade 3-4], respectively), nausea (19% [1% Grade 3-4] versus 6% [1% Grade 3-4], respectively), anorexia (19% [2% Grade 3-4] versus 5% [0% Grade 3-4], respectively), vomiting (9% [0% Grade 3-4] versus 1% [0% Grade 3-4], respectively), mucositis/stomatitis (7% [1% Grade 3-4] versus 2% [0% Grade 3-4], respectively), diarrhea (5% [1% Grade 3-4] versus 3% [0% Grade 3-4], respectively), sensory neuropathy (9% [1% Grade 3-4] versus 4% [0% Grade 3-4], respectively), and rash/desquamation (10% [0% Grade 3-4] versus 3% [0% Grade 3-4], respectively).

IMPORTANT SAFETY INFORMATION (CONTINUED)

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 1% to <5% of patients who received pemetrexed: alopecia, pruritis/itching, constipation, edema, fever, thrombocytopenia, ocular surface disease (including conjunctivitis), and increased lacrimation.

The following additional adverse reactions were observed in <1% of patients who received pemetrexed: supraventricular arrhythmia, erythema multiforme, febrile neutropenia, allergic reaction/hypersensitivity, motor neuropathy, and renal failure.

Maintenance Treatment Following First-line Pemetrexed Plus Platinum Chemotherapy

The safety of pemetrexed was evaluated 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 cisplatin as first-line therapy for NSCLC

The following adverse reactions occurred in ≥5% of fully vitamin-supplemented patients (with folic acid and vitamin B_{12}) who received pemetrexed (500 mg/m^2; N=333) intravenously compared to placebo (N=167), respectively: anemia (15% [4.8% Grade 3-4] versus 4.8% [0.6% Grade 3-4], respectively), neutropenia (9% [3.9% Grade 3-4] versus 0.6% [0% Grade 3-4], respectively), fatigue (18% [4.5% Grade 3-4] versus 11% [0.6% Grade 3-4], respectively), nausea (12% [0.3% Grade 3-4] versus 2.4% [0% Grade 3-4], respectively), vomiting (6% [0% Grade 3-4] versus 1.8% [0% Grade 3-4], respectively), mucositis/stomatitis (5% [0.3% Grade 3-4] versus 2.4% [0% Grade 3-4], respectively), and edema (5% [0% Grade 3-4] versus 3.6% [0% Grade 3-4], respectively).

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 patients who received pemetrexed.

At an incidence of 1% to <5%: thrombocytopenia and febrile neutropenia.

At an incidence of <1%: ventricular tachycardia, syncope, pain, gastrointestinal obstruction, depression, renal failure, and pulmonary embolism.

Treatment of Recurrent Disease After Prior Chemotherapy

The safety of pemetrexed was evaluated in patients who had progressed following platinum-based chemotherapy. The following adverse reactions occurred in ≥5% of fully vitamin-supplemented patients (with folic acid and vitamin B_{12}) who received pemetrexed (500 mg/m^2; N=265) intravenously compared to those who received docetaxel (75 mg/m^2; N=276), respectively: anemia (19% [4% Grade 3-4] versus 22% [4% [Grade 3-4], respectively), neutropenia (11% [5% Grade 3-4] versus 45% [40% Grade 3-4], respectively), thrombocytopenia (8% [2% Grade 3-4] versus 1% [0% Grade 3-4], respectively), increased ALT (8% [2% Grade 3-4] versus 1% [0% Grade 3-4], respectively), increased AST (7% [1% Grade 3-4] versus 1% [0% Grade 3-4], respectively), nausea (31% [3% Grade 3-4] versus 17% [2% Grade 3-4], respectively), anorexia (22% [2% Grade 3-4] versus 24% [3% Grade 3-4], respectively), vomiting (16% [2% Grade 3-4] versus 12%

Please see Important Safety Information on pages 3 and 13-19 and full Prescribing Information for AXTLE™.

IMPORTANT SAFETY INFORMATION (CONTINUED)

[1% Grade 3-4], respectively), stomatitis/pharyngitis (15% [1% Grade 3-4] versus 17% [1% Grade 3-4], respectively), diarrhea (13% [0% Grade 3-4] versus 24% [3% Grade 3-4], respectively), constipation (6% [0% Grade 3-4] versus 4% [0% Grade 3-4], respectively), fatigue (34% [5% Grade 3-4] versus 36% [5% Grade 3-4], respectively), fever (8% [0% Grade 3-4] versus 8% [0% Grade 3-4], respectively), rash/desquamation (14% [0% Grade 3-4] versus 6% [0% Grade 3-4], respectively) pruritus (7% [0% Grade 3-4] versus 2% [0% Grade 3-4], respectively), and alopecia (6% [1% Grade 3-4] versus 38% [2% Grade 3-4], respectively).

The following additional adverse reactions were observed in 1% to <5% of patients who received pemetrexed: abdominal pain, allergic reaction/hypersensitivity, febrile neutropenia, infection, erythema multiforme, motor neuropathy, and sensory neuropathy.

The following additional adverse reactions were observed in <1% of patients who received pemetrexed: supraventricular arrhythmias, and renal failure.

Mesothelioma

The safety of pemetrexed was evaluated in patients with MPM who had received no prior chemotherapy for MPM. Among 226 patients who received pemetrexed in combination with cisplatin, 74% (n=168) received full supplementation with folic acid and vitamin B_{12}, 14% (n=32) were never supplemented, and 12% (n=26) were partially supplemented. The following adverse reactions occurred in ≥5% of patients who received pemetrexed (500 mg/m^2) intravenously in combination with cisplatin (75 mg/m^2) intravenously (N=168) compared to those who received cisplatin (75 mg/m^2; N=163), respectively: neutropenia (56% [23% Grade 3-4] versus 13% [3% Grade 3-4], respectively), anemia (26% [4% Grade 3-4] versus 10% [0% Grade 3-4], respectively), thrombocytopenia (23% [5% Grade 3-4] versus 9% [0% Grade 3-4], respectively), elevated creatinine (11% [1% Grade 3-4] versus 10% [1% Grade 3-4], respectively), decreased creatinine clearance (16% [1% Grade 3-4] versus 18% [2% Grade 3-4], respectively), conjunctivitis (5% [0% Grade 3-4] versus 1% [0% Grade 3-4], respectively), nausea (82% [12% Grade 3-4] versus 77% [6% Grade 3-4], respectively), vomiting (57% [11% Grade 3-4] versus 50% [4% Grade 3-4], respectively), stomatitis/pharyngitis (23% [3% Grade 3-4] versus 6% [0% Grade 3-4], respectively), anorexia (20% [1% Grade 3-4] versus 14% [1% Grade 3-4], respectively), diarrhea (17% [4% Grade 3-4] versus 8% [0% Grade 3-4], respectively), constipation (12% [1% Grade 3-4] versus 7% [1% Grade 3-4], respectively), dyspepsia (5% [1% Grade 3-4] versus 1% [0% Grade 3-4], respectively), fatigue (48% [10% Grade 3-4] versus 42% [9% Grade 3-4], respectively), dehydration (7% [4% Grade 3-4] versus 1% [1% Grade 3-4], respectively), sensory neuropathy (10% [0% Grade 3-4] versus 10% [1% Grade 3-4], respectively), taste disturbance (8% [0% Grade 3-4] versus 6% [0% Grade 3-4], respectively), rash (16% [1% Grade 3-4] versus 5% [0% Grade 3-4], respectively), and alopecia (11% [0% Grade 3-4] versus 6% [0% Grade 3-4], respectively).

The following additional adverse reactions were observed in 1% to <5% of patients who received pemetrexed in combination with cisplatin: febrile neutropenia, infection, pyrexia, urticaria, chest pain, increased AST, increased ALT, increased GGT, and renal failure.

The following additional adverse reactions were observed in <1% of patients who received pemetrexed in combination with cisplatin: arrhythmia and motor neuropathy.

Exploratory subgroup analyses demonstrated that NCI CTCAE Grade 3 or 4 adverse reactions were reported in more pemetrexed-treated patient who did not receive vitamin supplementation (never supplemented; N=32) compared to those who received daily folic acid and vitamin B_{12} (fully supplemented; N=168). Selected Grade 3-4 adverse reactions that occurred in patients receiving pemetrexed in combination with cisplatin with or without full vitamin supplementation, respectively, included: neutropenia (23% versus 38%, respectively), thrombocytopenia (5% versus 9%, respectively), vomiting (11% versus 31%, respectively), febrile neutropenia (1% versus 9%, respectively), infection with Grade 3 or 4 neutropenia (0% versus 6%, respectively), and diarrhea (4% versus 9%, respectively).

IMPORTANT SAFETY INFORMATION (CONTINUED)

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%, respectively), chest pain (8% versus 6%, respectively), and thrombosis/embolism (6% versus 3%, respectively).

Additional Experience Across Clinical Trials

Sepsis, with or without neutropenia, including fatal cases occurred in 1% of patients. Severe esophagitis, resulting in hospitalization occurred in <1%.

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.

Immune-mediated hemolytic anemia, colitis, pancreatitis, edema, radiation recall, interstitial pneumonitis, serious and fatal bullous skin conditions, Stevens-Johnson syndrome, and toxic epidermal necrolysis were reported during post-approval use of pemetrexed.

DRUG INTERACTIONS

Effects of Ibuprofen on Pemetrexed

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on findings from animal studies and its mechanism of action, AXTLE™ can cause fetal harm when administered to a pregnant woman. 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. Advise pregnant women of the potential risk to a fetus.

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.

Please see Important Safety Information on pages 3 and 13-19 and full Prescribing Information for AXTLE™.

IMPORTANT SAFETY INFORMATION (CONTINUED)

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).

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 AXTLE™ and for one week after last dose.

Females and Males of Reproductive Potential

Based on animal data, pemetrexed can cause malformations and developmental delays when administered to a pregnant woman.Verify pregnancy status of females of reproductive potential prior to initiating AXTLE™.

Because of the potential for genotoxicity, advise females of reproductive potential to use effective contraception during treatment with AXTLE™ and for 6 months after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with AXTLE™ and for 3 months after the last dose.

AXTLE™ 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 AXTLE™ in pediatric patients have not been established.

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 trial

IMPORTANT SAFETY INFORMATION (CONTINUED)

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

OVERDOSAGE

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

Please see the full Prescribing Information for safety information and dosing guidelines.

To report SUSPECTED ADVERSE REACTIONS, contact Avyxa Pharma, LLC at 1-888-520-0954 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Notes:

References:

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