LifeWise
Health Plan of Washington

# PHARMACY / MEDICAL POLICY – 5.01.617

# Folate Antimetabolites

| | | |
|---|---|---|
| Effective Date: | Mar. 1, 2025 | RELATED MEDICAL POLICIES: |
| Last Revised: | Feb. 11, 2025 | None |
| Replaces: | N/A | |

**Select a hyperlink below to be directed to that section.**

POLICY CRITERIA | DOCUMENTATION REQUIREMENTS | CODING
RELATED INFORMATION | EVIDENCE REVIEW | REFERENCES | HISTORY

∞ Clicking this icon returns you to the hyperlinks menu above.

## Introduction

Folate is a B-vitamin that helps with cell function and tissue growth. It also helps create DNA, the body's genetic material. Folate antimetabolites are drugs that interfere with the enzymes needed to create DNA. These medications can be used to slow the growth of cancers. Folate antimetabolites can also be used to slow the progression of other conditions, including rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, and psoriasis. This policy describes when folate antimetabolites may be considered medically necessary.

**Note:** The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

## Policy Coverage Criteria

| Drug | Medical Necessity |
|---|---|
| **Alimta (pemetrexed) IV, Pemrydi RTU (pemetrexed) IV** | **Alimta (pemetrexed) and Pemrydi RTU (pemetrexed) may be considered medically necessary when one of the following conditions are met:** |

| Drug | Medical Necessity |
|---|---|
| **Managed under medical benefit** | • In combination with Keytruda (pembrolizumab) and platinum chemotherapy (e.g., cisplatin, carboplatin, oxaliplatin), for the initial treatment of individuals with metastatic non-squamous non-small cell lung cancer (NSCLC), with no EGFR or ALK/ROS1 genomic tumor aberrations or while awaiting the results of such confirmed genomic testing<br>• In combination with Keytruda (pembrolizumab) and platinum chemotherapy (e.g., cisplatin, carboplatin, oxaliplatin), for the treatment of individuals with metastatic non-squamous NSCLC with EGFR or ALK/ROS1 genomic mutations who have disease progression on US Food and Drug Administration (FDA) approved therapy for these mutations (i.e., EGFR inhibitors or ALK/ROS1 inhibitors)<br>• In combination with platinum chemotherapy (e.g., cisplatin, carboplatin, oxaliplatin) for the initial chemotherapy treatment of individuals with locally advanced or metastatic, non-squamous NSCLC<br>• As a single agent for the maintenance treatment of individuals with locally advanced or metastatic, non-squamous NSCLC whose disease has not progressed after four cycles of platinum-based (e.g., cisplatin, carboplatin, oxaliplatin) first-line chemotherapy<br>• As a single agent for the treatment of individuals with recurrent, metastatic non-squamous, NSCLC after prior chemotherapy<br>• Initial chemotherapy treatment, in combination with cisplatin, of individuals with malignant pleural mesothelioma whose disease is unresectable or who are otherwise not candidates for curative surgery<br><br>**Note:** Prior use of targeted therapies (e.g., EGFR inhibitors, ALK/ROS1 inhibitors) or immunotherapies (e.g., immune checkpoint inhibitors) are not chemotherapy treatments. |
| • **Axtle (pemetrexed) IV**<br>• **Brand pemetrexed (Avyxa- unbranded) IV**<br>• **Brand pemetrexed (Hospira- unbranded) IV** | **Axtle (pemetrexed), brand pemetrexed (Avyxa-unbranded), brand pemetrexed (Hospira- unbranded), and brand pemetrexed (Novaplus- unbranded) may be considered** |

| Drug | Medical Necessity |
|---|---|
| • **Brand pemetrexed (Novaplus- unbranded) IV** | **medically necessary when one of the following conditions are met:**<br>• In combination with cisplatin for the initial treatment of individuals with locally advanced or metastatic, non-squamous non-small cell lung cancer (NSCLC)<br>• As a single agent for the maintenance treatment of individuals with locally advanced or metastatic NSCLC whose disease has not progressed after four cycles of platinum-based (e.g., cisplatin, carboplatin, oxaliplatin) first-line chemotherapy<br>• As a single agent for the treatment of individuals with recurrent, metastatic non-squamous NSCLC after prior chemotherapy |
| **Folotyn (pralatrexate) IV**<br><br>**Managed under medical benefit** | **Folotyn (pralatrexate) may be considered medically necessary for the treatment of individuals with relapsed or refractory peripheral T-cell lymphoma (PTCL).** |
| **Jylamvo (methotrexate) oral solution**<br><br>**Managed under pharmacy benefit** | **Jylamvo (methotrexate) may be considered medically necessary when the following criteria met:**<br>• Individual has tried generic methotrexate tablets and had an inadequate response after 3-months of treatment<br>**AND**<br>• Not used in combination with another methotrexate product |
| **Otrexup (methotrexate) SC,**<br>**Rasuvo (methotrexate) SC**<br><br>**Managed under medical benefit and pharmacy benefit** | **Otrexup (methotrexate) and Rasuvo (methotrexate) may be considered medically necessary when the following criteria are met:**<br>• Treatment of rheumatoid arthritis (RA)<br>**OR**<br>• Polyarticular juvenile idiopathic arthritis (pJIA) who are intolerant of or had an inadequate response to one prior therapy<br>**OR**<br>• Treatment of psoriasis in adults who are intolerant of or had an inadequate response to two prior therapies<br>**AND**<br>• Individual has tried generic methotrexate tablets and has documentation of one of the following:<br>  ○ Inadequate response after 3-months of treatment |

| Drug | Medical Necessity |
|---|---|
| | **OR**<br>○ Had intolerance to use of generic methotrexate tablets<br>**AND**<br>• Individual has tried the generic injectable methotrexate and has documentation of one of the following:<br>○ Inadequate response after 3-months of treatment<br>**OR**<br>○ Had intolerance to use of generic injectable methotrexate<br>**OR**<br>○ Documented reason for requiring a special injection device such as lack of dexterity or visual acuity challenges<br>**AND**<br>• Not used in combination with another methotrexate product<br>**AND**<br>• The quantity is limited to 4 auto-injectors every 28 days |
| **Brand pemetrexed (Accord- unbranded) IV**<br><br>**Managed under medical benefit** | **Brand pemetrexed (Accord- unbranded) may be considered medically necessary when one of the following conditions are met:**<br>• In combination with pembrolizumab and platinum chemotherapy, for the initial treatment of individuals with metastatic non-small cell lung cancer (NSCLC), with no EGFR or ALK genomic tumor aberrations<br>• In combination with cisplatin for the initial treatment of individuals with locally advanced or metastatic, non-squamous NSCLC<br>• As a single agent for the maintenance treatment of individuals with locally advanced or metastatic, non-squamous non-small cell lung cancer (NSCLC) whose disease has not progressed after four cycles of platinum-based (e.g., cisplatin, carboplatin, oxaliplatin) first-line chemotherapy<br>• As a single agent for the treatment of individuals with recurrent, metastatic non-squamous, non-small cell lung cancer (NSCLC) after prior chemotherapy<br>• Initial treatment, in combination with cisplatin, of individuals with malignant pleural mesothelioma whose disease is unresectable or who are otherwise not candidates for curative surgery |

| Drug | Medical Necessity |
| --- | --- |
| • **Brand pemetrexed (BluePoint Laboratories- unbranded) IV**<br>• **Brand pemetrexed (Sandoz- unbranded) IV**<br>• **Brand pemetrexed (Teva- unbranded) IV**<br><br>**Managed under medical benefit** | **Brand pemetrexed (BluePoint Laboratories- unbranded, brand pemetrexed (Sandoz- unbranded) and brand pemetrexed (Teva- unbranded) may be considered medically necessary when one of the following conditions are met:**<br>• In combination with pembrolizumab and platinum chemotherapy, for the initial treatment of individuals with metastatic non-small cell lung cancer (NSCLC), with no EGFR or ALK genomic tumor aberrations<br>• In combination with cisplatin for the initial treatment of individuals with locally advanced or metastatic, non-squamous NSCLC<br>• As a single agent for the maintenance treatment of individuals with locally advanced or metastatic, non-squamous non-small cell lung cancer (NSCLC) whose disease has not progressed after four cycles of platinum-based (e.g., cisplatin, carboplatin, oxaliplatin) first-line chemotherapy<br>• As a single agent for the treatment of individuals with recurrent, metastatic non-squamous, non-small cell lung cancer (NSCLC) after prior chemotherapy |
| • **Brand pemetrexed ditromethamine IV** | **Brand pemetrexed ditromethamine may be considered medically necessary when one of the following conditions are met:**<br>• In combination with cisplatin for the initial treatment of individuals with locally advanced or metastatic, non-squamous NSCLC<br>• As a single agent for the maintenance treatment of individuals with locally advanced or metastatic, non-squamous non-small cell lung cancer (NSCLC) whose disease has not progressed after four cycles of platinum-based (e.g., cisplatin, carboplatin, oxaliplatin) first-line chemotherapy<br>• As a single agent for the treatment of individuals with recurrent, metastatic non-squamous, non-small cell lung cancer (NSCLC) after prior chemotherapy<br>• Initial treatment, in combination with cisplatin, of individuals with malignant pleural mesothelioma whose disease is unresectable or who are otherwise not candidates for curative surgery |

| Drug | Medical Necessity |
|---|---|
| **Pemfexy (pemetrexed) IV**<br><br>**Managed under medical benefit** | **Pemfexy (pemetrexed) may be considered medically necessary when one of the following conditions are met:**<br>• In combination with Keytruda (pembrolizumab) and platinum chemotherapy (e.g., cisplatin, carboplatin, oxaliplatin), for the initial treatment of individuals with metastatic non-squamous non-small cell lung cancer (NSCLC), with no EGFR or ALK/ROS1 genomic tumor aberrations or while awaiting the results of such confirmed genomic testing<br>• In combination with platinum chemotherapy (e.g., cisplatin, carboplatin, oxaliplatin) for the initial treatment of individuals with locally advanced or metastatic, non-squamous NSCLC<br>• As a single agent for the maintenance treatment of individuals with locally advanced or metastatic, non-squamous NSCLC whose disease has not progressed after four cycles of platinum-based (e.g., cisplatin, carboplatin, oxaliplatin) first-line chemotherapy<br>• As a single agent for the treatment of individuals with recurrent, metastatic non-squamous, NSCLC after prior chemotherapy<br>• Initial treatment, in combination with cisplatin, of individuals with malignant pleural mesothelioma whose disease is unresectable or who are otherwise not candidates for curative |
| **Trexall (methotrexate) oral**<br><br>**Managed under pharmacy benefit** | **Trexall (methotrexate) may be considered medically necessary when:**<br>• Individual has tried generic methotrexate tablets and has documentation of one of the following:<br>○ Inadequate response after 3-months of treatment<br>**OR**<br>○ Had intolerance to use of generic methotrexate tablets<br>**AND**<br>• The quantity is limited to 15 tablets every 28 days |
| **Xatmep (methotrexate) oral solution**<br><br>**Managed under pharmacy benefit** | **Xatmep (methotrexate) may be considered medically necessary for individuals less than 18 years of age when the following criteria are met:**<br>• Treatment of acute lymphoblastic leukemia (**ALL**):<br>○ As a component of a combination chemotherapy maintenance regimen |

| Drug | Medical Necessity |
|---|---|
| | **AND**<br>○ Prescribed by or in consultation with an oncologist or hematologist<br>**OR**<br>• Treatment of polyarticular juvenile idiopathic arthritis (pJIA):<br>○ Intolerant of or had an inadequate response to one prior therapy<br>**AND**<br>○ Prescribed by or in consultation with a rheumatologist<br>**AND**<br>• Individual has tried generic methotrexate tablets and has documentation of one of the following:<br>○ Inadequate response after 3-months of treatment<br>**OR**<br>○ Had intolerance to use of generic methotrexate<br>**OR**<br>○ Documented inability to swallow solid oral dosage forms<br>**AND**<br>• Not used in combination with another methotrexate product<br>**AND**<br>• The quantity is limited to 2 bottles every 28 days |

| Drug | Investigational |
|---|---|
| **As listed** | **The medications listed in this policy are subject to the product's US Food and Drug Administration (FDA) dosage and administration prescribing information.**<br><br>**All other uses of the medications listed in this policy are considered investigational.** |

| Length of Approval | |
|---|---|
| **Approval** | **Criteria** |
| **Initial authorization** | **Non-formulary exception reviews for all drugs listed in the policy may be approved up to 12 months.** |

| Length of Approval | |
|---|---|
| **Approval** | **Criteria** |
| | **All other reviews for oral drugs listed in the policy may be approved up to 3 months.**<br><br>**All other reviews for injectable drugs listed in the policy may be approved up to 6 months.** |
| **Re-authorization criteria** | **Non-formulary exception reviews and all other reviews for all drugs listed in the policy may be approved up to 12 months as long as the drug-specific coverage criteria are met and chart notes demonstrate that the individual continues to show a positive clinical response to therapy.** |

| Documentation Requirements |
|---|
| **The individual's medical records submitted for review for all conditions should document that medical necessity criteria are met. The record should include the following:**<br>• Office visit notes that contain the diagnosis, relevant history, physical evaluation, and medication history |

## Coding

| Code | Description |
|---|---|
| **HCPCS** | |
| J3490 | Unclassified drugs (Use to report Otrexup and Rasuvo,) |
| J8611 | Methotrexate (Jylamvo), oral, 2.5 mg (new code effective 07/01/24) |
| J8612 | Methotrexate (Xatmep), oral, 2.5 mg (new code effective 07/01/24) |
| J9292 | Injection, pemetrexed (avyxa), not therapeutically equivalent to J9305, 10 mg (new code effective 01/01/25) |
| J9294 | Injection, pemetrexed (Hospira) not therapeutically equivalent to J9305, 10 mg |
| J9296 | Injection, pemetrexed (Accord) not therapeutically equivalent to J9305, 10 mg |
| J9297 | Injection, pemetrexed (Sandoz), not therapeutically equivalent to J9305, 10 mg |
| J9304 | Injection, pemetrexed (Pemfexy), 10 mg |

| Code | Description |
|---|---|
| J9305 | Injection, pemetrexed (Alimta), 10 mg |
| J9307 | Injection, pralatrexate (Folotyn), 1 mg |
| J9314 | Injection, pemetrexed (Teva) not therapeutically equivalent to J9305, 10 mg |
| J9322 | Injection, pemetrexed (Bluepoint) not therapeutically equivalent to J9305, 10 mg |
| J9323 | Injection, pemetrexed ditromethamine, 10 mg |
| J9324 | Injection, pemetrexed (Pemrydi RTU), 10 mg |

**Note**: CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).

## Related Information

### Benefit Application

### Medical Benefit

Alimta (pemetrexed), brand pemetrexed, Folotyn (pralatrexate), Pemfexy (pemetrexed), and Pemrydi RTU (pemetrexed) are managed through the medical benefit.

### Pharmacy Benefit

Trexall (methotrexate) is managed through the pharmacy benefit.

### Medical / Pharmacy Benefit

Jylamvo (methotrexate), Otrexup (methotrexate), Rasuvo (methotrexate), and Xatmep (methotrexate) are managed through both the medical benefit and pharmacy benefit.

## Evidence Review

## Background

This medical policy has been developed by appropriately licensed and experienced health care professionals based on a review and consideration of currently available peer-reviewed medical literature, generally accepted standards of medical practice, FDA approval status, evidence-based guidelines, recommendations from leading national health professional organizations, and views of clinicians practicing in relevant clinical areas.

## Summary of Evidence

## Methotrexate

Methotrexate is classified as a folate antimetabolite that functions by impeding DNA synthesis, repair, and cellular replications. It is obtainable in several dosage forms, marketed under different brand names, and prescribed for variety of indications. For example, Otrexup (methotrexate) SC, Rasuvo (methotrexate) SC and RediTrex (methotrexate) SC are indicated for rheumatoid arthritis (RA), polyarticular juvenile idiopathic arthritis (pJIA) and psoriasis. Xatmep (methotrexate) oral solution is indicated for acute lymphoblastic leukemia (ALL) and pJIA. Jylamvo (methotrexate) oral solution is indicated for acute lymphoblastic leukemia (ALL), mycosis fungoides, relapsed or refractory non-Hodgkin lymphoma, rheumatoid arthritis, and severe psoriasis.

Otrexup (methotrexate) SC, Rasuvo (methotrexate) SC and RediTrex (methotrexate) SC was granted approval for the treatment of RA and pJIA based on the clinical trials utilizing the alternative formulations of the medication. In the RA trial, individuals experienced reduction on articular swelling and tenderness as early as three to six weeks. After initiating the treatment. In a six-month, double-blind, placebo-controlled trial involving 127 individuals with pJIA, participants were randomized to receive either methotrexate 10 mg/$m^2$ orally once a week or placebo. Those in the treatment group demonstrated substantial clinical improvement as evaluated by the physician's global assessment or by an individual's composite assessment.

Xatmep (methotrexate) oral solution was granted approved for the treatment of pJIA based on the clinical trials utilizing the alternative formulation of the medication. In a six-month, double-blind, placebo-controlled trial involving 127 individuals with pJIA, participants were randomized to receive either methotrexate 10 mg/$m^2$ orally once a week or placebo. Those in the treatment

group demonstrated substantial clinical improvement as evaluated by the physician's global assessment or by a individual's composite assessment score.

Jylamvo (methotrexate) is an oral solution containing 2mg/ml of methotrexate as the active ingredient. There have been two clinical bioequivalence studies (MTX 001 and MTX 002) done in the Europe, in which the manufacturer compared Jylamvo (methotrexate) with methotrexate "Lederle" 2.5 mg tablets in study MTX001, and with hybrid product Ebetrexat 10mg tablets in study MTX 002. MTX001 study was randomized, single-dose and two-period crossover study with wash-out period of 7 days between two doses of methotrexate, while MTX 002 was randomized, single-dose, open label, laboratory-blind, two-period, two-sequence crossover study to determine the bioequivalence of Jylamvo (methotrexate) with methotrexate "Ledrle" 2.5 mg tablets and hybrid product Ebetrexat 10mg tablets subsequently. Both studies met the bioequivalence criteria with 90% geometric confidence intervals were in the predefined acceptance range of 80.00-125.00.

## Premetrexed

Premetrexed belongs to the drug class known as antifolate. Its mechanism of action involves inhibiting the thymidylate synthase (TS), dihydrofolate reductase (DHFR), glycinamide ribonucleotide formyl transferase (GARFT) and aminoimidazole carboxamide ribonucleotide formyl transferase (AICARFT) enzymes, thereby disturbing the folate metabolism and DNA synthesis. Alimta (premetrexed) IV and Pemfexy (pemetrexed) IV have received FDA approval for multiple indications.

Alimta (premetrexed) was granted approval for the treatment of non-small cell lung cancer (NSCLC) when used in combination with cisplatin.1725 chemo naive individuals with stage IIIb/IV NSCLC were studied in a multi-center, randomized, open-label study where individuals received Alimta in combination with cisplatin versus gemcitabine in combination with cisplatin. The primary efficacy endpoint was the overall survival. The median survival time was 10.3 months in Alimta plus cisplatin group and gemcitabine plus cisplatin group. The overall response rate was 27.1% in the Alimta plus cisplatin group compared to 24.7% in the gemcitabine plus cisplatin group.

Alimta is also indicated for the treatment of NSCLS as a single agent. Individuals with stage III or IV NSCLS after prior chemotherapy were studied in a muti-center, randomized, open label trial. The individuals received either Alimta or docetaxel. The primary endpoint was to compare the overall survival between groups. The mean survival time was 8.3 months in the Alimta treatment

group versus 7.9 months in the docetaxel group. The overall response rate was 8.5% in the Alimta group compared to 8.3% in the docetaxel group.

Alimta in combination with cisplatin is indicated for malignant pleural mesothelioma whose disease is unresectable or who are otherwise not candidates for curative surgery. 448 chemo naïve individuals with malignant pleural mesothelioma (MPM) were studied in a muti-center, randomized, single-blind study, where the individuals received either Alimta plus cisplatin or cisplatin alone. The median overall survival was 12.1 months in the Alimta plus cisplatin group versus 9.3 months in cisplatin alone group.

Pemfexy (pemetrexed) IV in combination with pembrolizumab and platinum chemotherapy is indicated for the initial treatment of metastatic non-squamous non-small cell lung cancer (NSCLC) without EGFR or ALK/ROS1 genomic tumor aberrations. Individuals with metastatic NSCLC without EGFR or ALK genomic tumor aberrations. were studied in a randomized, multicenter, double-blind, active-controlled trial where individuals were randomized (2:1) to receive either pemetrexed plus pembrolizumab plus cisplatin/carboplatin or placebo plus pembrolizumab plus cisplatin/carboplatin. The individuals with the treatment had significant improvement in the overall survival (OS) and the progression free survival (PFS) with p value < 0.0001.

Pemfexy (pemetrexed) IV in combination with cisplatin is also indicated for the initial treatment of NSCLC. 1725 chemo naive individuals with stage IIIb/IV NSCLC were studied in a multi-center, randomized, open-label study where individuals received Pemfexy in combination with cisplatin versus gemcitabine in combination with cisplatin. The primary efficacy endpoint was the overall survival. The median survival time was 10.3 months in Pemfexy plus cisplatin group and gemcitabine plus cisplatin group. The overall response rate was 27.1% in the Pemfexy plus cisplatin group compared to 24.7% in the gemcitabine plus cisplatin group.

Pemfexy is indicated for the maintenance treatment of NSCLC following the first line non-pemetrexed containing platinum-based chemotherapy. Pemfexy was evaluated in a randomized, muti-center, double-blind, placebo-controlled clinical trial, where 663 individuals with stage IIIb/IV NSCLC who did not progress after four cycles of platinum-based chemotherapy were randomized (2:1) receive pemetrexed or placebo. The primary efficacy endpoints were progression-free survival and overall survival. The individuals in the treatment group achieved statistical significance in both overall-survival (OS) and progression-free survival (PFS). The median OS in the treatment group was 13.4 months, while median OS in the placebo group was 10.6 months with p = 0.012. Similarly, the median PFS in the treatment group was 4.0 months compared to 2.0 months in the placebo group with p<0.00001.

Pemfexy in combination with cisplatin was also approved for initial treatment of malignant pleural mesothelioma (MPM) whose disease is unresectable or who are otherwise not candidates for curative surgery. Pemfexy was studied in a multicenter, randomized, single-blind study where individuals with MPM randomized to receive pemetrexed plus cisplatin or cisplatin alone. The treatment group has achieved statistical improvement in the overall survival parameter compared to the placebo. The median OS in the treatment group was 12.1 months, compared to 9.3 months in the cisplatin alone group with long rank p-value of 0.020.

## Pralatrexate

Pralatrexate belongs to the drug class of antifolate analog and inhibits the DNA, RNA, and protein synthesis. Its mechanism of action involves inhibiting the dihydrofolate reductase (DHFR) by competing for the DHFR-folate binding site. FDA has approved Folotyn (pralatrexate) IV for the treatment of relapsed or refractory peripheral T-cell lymphoma (PTCL).

The safety and efficacy of Folotyn was studied in muti-center, single-arm, open-label, international trial where 115 individuals with relapsed or refractory PTCL received Folotyn at 30 $mg/m^2$ once a week by IV push. The primary efficacy endpoint was overall response rate and secondary efficacy endpoint was duration of response. At the end of cycle 1, about 66% of the individuals responded, where median time to first response was 45 days. In this study, there has not been any demonstration of either progression-free survival or overall survival.

## 2021 Update

Reviewed prescribing information for all drugs listed in policy and researched product availability. Identified a new brand methotrexate product called RediTrex (methotrexate) which is a subcutaneous dosage form that has the identical FDA-approved indications as the subcutaneous drugs Otrexup (methotrexate) and Rasuvo (methotrexate). Added RediTrex to the policy for the treatment of rheumatoid arthritis (RA), polyarticular juvenile idiopathic arthritis (pJIA), and psoriasis.

## 2022 Update

Reviewed prescribing information for all drugs listed in policy and researched product availability. Identified a new brand pemetrexed product called Pemfexy (pemetrexed) which is

supplied as a solution in a multi-dose vial versus Alimta (pemetrexed) which comes as a lyophilized powder supplied in single-dose vials. Pemfexy is FDA-approved for the identical indications as Alimta except Pemfexy is NOT approved for use in combination with pembrolizumab and platinum chemotherapy, for the initial treatment of individuals with metastatic non-squamous non-small cell lung cancer (NSCLC), with no EGFR or ALK genomic tumor aberrations. Added coverage criteria for Pemfexy for the treatment of all FDA-approved NSCLC indications and for the treatment of malignant pleural mesothelioma when criteria are met.

## 2023 Update

Reviewed prescribing information for all drugs listed in policy and researched product availability. Updated Pemfexy (pemetrexed) criteria to include the FDA-approved indication of metastatic non-squamous non-small cell lung cancer, with no EGFR or ALK/ROS1 genomic tumor aberrations when used in combination with Keytruda (pembrolizumab) and platinum chemotherapy (e.g., cisplatin, carboplatin, oxaliplatin). Identified a new brand methotrexate product called Jylamvo (methotrexate), which is supplied as an oral solution. Added coverage criteria for Jylamvo to have individuals tried and failed generic methotrexate tablets. In addition to that, added coverage criteria that individuals should not use Jylamvo in combination with other methotrexate products.

## 2024 Update

Reviewed prescribing information for all drugs listed in policy. Added coverage criteria for Pemrydi RTU (pemetrexed). Removed RediTrex (methotrexate) from the policy as it was withdrawn from the market.

## 2025 Update

Reviewed prescribing information for all drugs listed in policy. Clarified that non-formulary exception review authorizations for all drugs listed in this policy may be approved up to 12 months. Clarified that the medications listed in this policy are subject to the product's FDA dosage and administration prescribing information. Updated the coverage criteria for Axtle (pemetrexed), pemetrexed (Avyxa- unbranded), brand pemetrexed (Accord- unbranded), brand pemetrexed (BluePoint Laboratories- unbranded), brand pemetrexed (Sandoz- unbranded),

brand pemetrexed (Teva- unbranded), and brand pemetrexed ditromethamine per the prescribing information.

## References


1. Alimta [package insert]. Indianapolis, IN; Eli Lilly; Revised May 2023.
2. Folotyn [package insert]. Westminster, CO; Allos Therapeutics. Revised August 2024.
3. Otrexup [package insert]. Ewing, NJ; Antares Pharma, Inc. Revised December 2019.
4. Pemetrexed (Teva – unbranded) [package insert]. Parsippany, NJ; Teva Pharmaceuticals; Revised December 2022.
5. Pemfexy [package insert]. Woodcliff Lake, NJ; Eagle Pharmaceuticals, Inc.; Revised December 2022.
6. Rasuvo [package insert]. Chicago, IL; Medac Pharma, Inc. Revised March 2020.
7. Xatmep [package insert]. Greenwood Village, CO; Silvergate Pharmaceuticals, Inc. Revised September 2020.
8. Trexall [package insert]. Parsippany, NJ; Teva Pharmaceuticals USA, Inc. Revised April 2021.
9. Jylamvo [package insert]. Scotch Plains, NJ; Therakind Ltd UK. Revised October 2024.
10. Pemrydi RTU [package insert]. Bridgewater, NJ. Amneal Pharmaceuticals. Revised November 2024.


## History

| Date | Comments |
|---|---|
| 06/01/20 | New policy, approved May 12, 2020. Add to Prescription Drug section. Alimta (pemetrexed) may be considered medically necessary for the treatment of NSCLC and mesothelioma when criteria are met. Coverage criteria for Alimta (pemetrexed) (HCPCS code J9305) becomes effective for dates of service on or after September 4, 2020, following 90-day provider notification. Folotyn (pralatrexate) may be considered medically necessary for the treatment of PTCL when criteria are met. Coverage criteria for Folotyn (pralatrexate) (HCPCS code J9307) becomes effective for dates of service on or after September 4, 2020, following 90-day provider notification. Added coverage criteria for Otrexup (methotrexate) and Rasuvo (methotrexate) for RA, pJIA, and psoriasis, effective June 1, 2020. Added coverage criteria for Trexall (methotrexate) after trial of generic methotrexate, effective June 1, 2020. Added coverage criteria for Xatmep (methotrexate) for ALL and pJIA effective June 1, 2020. |
| 03/01/21 | Interim Review, approved February 18, 2021. Updated Alimta (pemetrexed) criteria for NSCLC expanding coverage from in combination with cisplatin to in combination with platinum chemotherapy. |

| Date | Comments |
|---|---|
| 01/01/22 | Annual Review, approved December 2, 2021. Added RediTrex (methotrexate) for subcutaneous use to policy for the treatment of RA, pJIA, and psoriasis. Added HCPC code J3490 to support Otrexup, Rasuvo, & RediTrex. |
| 05/01/22 | Annual Review, approved April 25, 2022. Added coverage criteria for Pemfexy (pemetrexed) for the treatment of NSCLC and mesothelioma when criteria are met. Added HCPCS code J9304. |
| 07/01/22 | Interim Review, approved June 14, 2022. Added coverage to Alimta (pemetrexed) for use in combination with pembrolizumab and platinum chemotherapy for the treatment of patients with metastatic non-squamous NSCLC with EGFR or ALK/ROS1 genomic mutations who have disease progression on FDA approved therapy for these mutations. Updated Alimta (pemetrexed) criteria to specify use as the initial "chemotherapy" treatment when used in combination with platinum chemotherapy for non-squamous NSCLC and when used in combination with cisplatin for malignant pleural mesothelioma. Added a note to Alimta that prior use of targeted therapies or immunotherapies are not chemotherapy treatments. |
| 01/01/23 | Interim Review, approved December 13, 2022. Updated Alimta (pemetrexed) indication for NSCLC when used in combination with pembrolizumab and platinum chemotherapy for first-line treatment to allow for coverage initiation while awaiting the results of confirmed genomic testing. Added brand pemetrexed (Teva – unbranded) for the treatment of NSCLC after four cycles of platinum-based first-line chemotherapy and for the treatment of metastatic NSCLC after prior chemotherapy. Changed the wording from "patient" to "individual" throughout the policy for standardization. Added new HCPC code J9314. |
| 04/01/23 | Coding update. New HCPCS codes J9294, J9296 and J9297 added. |
| 05/01/23 | Annual Review, approved April 11, 2023. Updated Pemfexy (pemetrexed) criteria to include the FDA-approved indication of metastatic non-squamous non-small cell lung cancer, with no EGFR or ALK/ROS1 genomic tumor aberrations when used in combination with Keytruda (pembrolizumab) and platinum chemotherapy (e.g., cisplatin, carboplatin, oxaliplatin). Identified a new brand methotrexate product called Jylamvo (methotrexate) which is supplied as an oral solution. Added coverage criteria for Jylamvo to have individuals tried and failed generic methotrexate tablets. In addition to that, added coverage criteria that individuals should not use Jylamvo in combination with other methotrexate products. |
| 07/01/23 | Coding update. Added new HCPCS codes J9322, and J9323 |
| 01/01/24 | Coding update. Added new HCPCS code J9255 and J9324. |
| 03/01/24 | Coding update. Corrected code description for HCPCS code J9314. |
| 04/01/24 | Annual Review, approved March 25, 2024. Added coverage criteria for Pemrydi RTU (pemetrexed). Removed RediTrex (methotrexate) from the policy as it was withdrawn from the market. Removed HCPCS code J9255. |
| 07/01/24 | Coding update. Added HCPCS codes J8611 and J8612. |

| Date | Comments |
|---|---|
| 01/01/25 | Coding update. Added new HCPCS code J9292. |
| 03/01/25 | Annual Review, approved February 11, 2025. Clarified that non-formulary exception review authorizations for all drugs listed in this policy may be approved up to 12 months. Clarified that the medications listed in this policy are subject to the product's FDA dosage and administration prescribing information. Updated the coverage criteria for Axtle (pemetrexed), pemetrexed (Avyxa- unbranded), brand pemetrexed (Accord-unbranded), brand pemetrexed (BluePoint Laboratories- unbranded), brand pemetrexed (Sandoz- unbranded), brand pemetrexed (Teva- unbranded), and brand pemetrexed ditromethamine per the prescribing information. |



**Scope**: Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.