


PHARMACY / MEDICAL POLICY – 5.01.617

Folate Antimetabolites

Effective Date:	April 1, 2024	RELATED MEDICAL POLICIES:
Last Revised:	March 25, 2024	None
Replaces:	N/A	

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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
<p>Managed under medical benefit</p>	<ul style="list-style-type: none"> • 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 • 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) • 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 • 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 • As a single agent for the treatment of individuals with recurrent, metastatic non-squamous, NSCLC after prior chemotherapy • 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 <p>Note: Prior use of targeted therapies (e.g., EGFR inhibitors, ALK/ROS1 inhibitors) or immunotherapies (e.g., immune checkpoint inhibitors) are not chemotherapy treatments.</p>
<p>Pemfexy (pemetrexed) IV</p> <p>Managed under medical benefit</p>	<p>Pemfexy (pemetrexed) may be considered medically necessary when one of the following conditions are met:</p> <ul style="list-style-type: none"> • In combination with Keytruda (pembrolizumab) and platinum chemotherapy (e.g., cisplatin, carboplatin, oxaliplatin), for the



Drug	Medical Necessity
	<p>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</p> <ul style="list-style-type: none"> • In combination with platinum chemotherapy (e.g., cisplatin, carboplatin, oxaliplatin) for the initial treatment of individuals with locally advanced or metastatic, non-squamous NSCLC • 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 • As a single agent for the treatment of individuals with recurrent, metastatic non-squamous, NSCLC after prior chemotherapy • Initial treatment, in combination with cisplatin, of individuals with malignant pleural mesothelioma whose disease is unresectable or who are otherwise not candidates for curative
<p>Brand pemetrexed IV</p> <p>Managed under medical benefit</p>	<p>Brand pemetrexed may be considered medically necessary when one of the following conditions are met:</p> <ul style="list-style-type: none"> • 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 • As a single agent for the treatment of individuals with recurrent, metastatic non-squamous, NSCLC after prior chemotherapy
<p>Folotyn (pralatrexate) IV</p> <p>Managed under medical benefit</p>	<p>Folotyn (pralatrexate) may be considered medically necessary for the treatment of individuals with relapsed or refractory peripheral T-cell lymphoma (PTCL).</p>
<p>Otrexup (methotrexate) SC,</p> <p>Rasuvo (methotrexate) SC,</p>	<p>Otrexup (methotrexate) and Rasuvo (methotrexate) may be considered medically necessary when the following criteria are met:</p> <ul style="list-style-type: none"> • Treatment of rheumatoid arthritis (RA) <p>OR</p>



Drug	Medical Necessity
Managed under medical benefit and pharmacy benefit	<ul style="list-style-type: none"> • Polyarticular juvenile idiopathic arthritis (pJIA) who are intolerant of or had an inadequate response to one prior therapy <p>OR</p> <ul style="list-style-type: none"> • Treatment of psoriasis in adults who are intolerant of or had an inadequate response to two prior therapies <p>AND</p> <ul style="list-style-type: none"> • Individual has tried generic methotrexate tablets and has documentation of one of the following: <ul style="list-style-type: none"> ○ Inadequate response after 3-months of treatment <p>OR</p> <ul style="list-style-type: none"> ○ Had intolerance to use of generic methotrexate tablets <p>AND</p> <ul style="list-style-type: none"> • Individual has tried the generic injectable methotrexate and has documentation of one of the following: <ul style="list-style-type: none"> ○ Inadequate response after 3-months of treatment <p>OR</p> <ul style="list-style-type: none"> ○ Had intolerance to use of generic injectable methotrexate <p>OR</p> <ul style="list-style-type: none"> ○ Documented reason for requiring a special injection device such as lack of dexterity or visual acuity challenges <p>AND</p> <ul style="list-style-type: none"> • Not used in combination with another methotrexate product <p>AND</p> <ul style="list-style-type: none"> • The quantity is limited to 4 auto-injectors every 28 days
Trexall (methotrexate) oral Managed under pharmacy benefit	<p>Trexall (methotrexate) may be considered medically necessary when the individual has tried generic methotrexate tablets and has documentation of one of the following:</p> <ul style="list-style-type: none"> • Inadequate response after 3-months of treatment <p>OR</p> <ul style="list-style-type: none"> • Had intolerance to use of generic methotrexate tablets <p>AND</p> <ul style="list-style-type: none"> • The quantity is limited to 15 tablets every 28 days
Xatmep (methotrexate) oral solution	<p>Xatmep (methotrexate) may be considered medically necessary for individuals less than 18 years of age when the following criteria are met:</p> <ul style="list-style-type: none"> • Treatment of acute lymphoblastic leukemia (ALL):



Drug	Medical Necessity
<p>Managed under pharmacy benefit</p>	<ul style="list-style-type: none"> ○ As a component of a combination chemotherapy maintenance regimen <p>AND</p> <ul style="list-style-type: none"> ○ Prescribed by or in consultation with an oncologist or hematologist <p>OR</p> <ul style="list-style-type: none"> • Treatment of polyarticular juvenile idiopathic arthritis (pJIA): <ul style="list-style-type: none"> ○ Intolerant of or had an inadequate response to one prior therapy <p>AND</p> <ul style="list-style-type: none"> ○ Prescribed by or in consultation with a rheumatologist <p>AND</p> <ul style="list-style-type: none"> • Individual has tried generic methotrexate tablets and has documentation of one of the following: <ul style="list-style-type: none"> ○ Inadequate response after 3-months of treatment <p>OR</p> <ul style="list-style-type: none"> ○ Had intolerance to use of generic methotrexate <p>OR</p> <ul style="list-style-type: none"> ○ Documented inability to swallow solid oral dosage forms <p>AND</p> <ul style="list-style-type: none"> • Not used in combination with another methotrexate product <p>AND</p> <ul style="list-style-type: none"> • The quantity is limited to 2 bottles every 28 days
<p>Jylamvo (methotrexate) oral solution</p> <p>Managed under pharmacy benefit</p>	<p>Jylamvo (methotrexate) may be considered medically necessary when following criteria met:</p> <ul style="list-style-type: none"> • Individual has tried generic methotrexate tablets and had an inadequate response after 3-months of treatment <p>AND</p> <ul style="list-style-type: none"> • Not used in combination with another methotrexate product

Drug	Investigational
<p>As listed</p>	<p>All other uses of the medications listed in this policy are considered investigational.</p>



Length of Approval	
Approval	Criteria
Initial authorization	<p>Oral drugs listed in policy may be approved up to 3 months.</p> <p>Injectable drugs listed in policy may be approved up to 6 months.</p>
Re-authorization criteria	Future re-authorization of oral and injectable drugs 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
<p>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:</p> <ul style="list-style-type: none"> 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,)
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
J9305	Injection, pemetrexed (Alimta), 10 mg
J9307	Injection, pralatrexate (Folotyn), 1 mg
J9314	Injection, pemetrexed (Teva) not therapeutically equivalent to J9305, 10mg



Code	Description
J9322	Injection, pemetrexed (Bluepoint) not therapeutically equivalent to j9305, 10 mg (new code effective 7/1/2023)
J9323	Injection, pemetrexed ditromethamine, 10 mg (new code effective 7/1/2023)
J9324	Injection, pemetrexed (Pemrydi RTU), 10 mg (new code effective 1/1/2024)

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Related Information

Benefit Application

Medical Benefit

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

Pharmacy Benefit

Trexall (methotrexate), Xatmep (methotrexate) and Jylamvo (methotrexate) are managed through the pharmacy benefit.

Medical / Pharmacy Benefit

Otrexup (methotrexate) and Rasuvo (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/m² 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/m² 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 multi-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 multi-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 naïve 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, multi-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 Folutyn (pralatrexate) IV for the treatment of relapsed or refractory peripheral T-cell lymphoma (PTCL).

The safety and efficacy of Folutyn was studied in multi-center, single-arm, open-label, international trial where 115 individuals with relapsed or refractory PTCL received Folutyn at 30 mg/m² 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.

References

1. Alimta [package insert]. Indianapolis, IN; Eli Lilly; Revised May 2023.
2. Folutyn [package insert]. Westminster, CO; Allos Therapeutics. Revised June 2023.
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. red
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 November 2023.

10. Pemrydi RTU [package insert]. Bridgewater, NJ. Amneal Pharmaceuticals. Revised June 2023.

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. Folutyn (pralatrexate) may be considered medically necessary for the treatment of PTCL when criteria are met. Coverage criteria for Folutyn (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.
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 –



Date	Comments
	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.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2024 Premera All Rights Reserved.

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.



Discrimination is Against the Law

Premera Blue Cross HMO (Premera HMO) complies with applicable Federal and Washington state civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability, sex, gender identity, or sexual orientation. Premera HMO does not exclude people or treat them differently because of race, color, national origin, age, disability, sex, gender identity, or sexual orientation. Premera HMO provides free aids and services to people with disabilities to communicate effectively with us, such as qualified sign language interpreters and written information in other formats (large print, audio, accessible electronic formats, other formats). Premera HMO provides free language services to people whose primary language is not English, such as qualified interpreters and information written in other languages. If you need these services, contact the Civil Rights Coordinator. If you believe that Premera HMO has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability, sex, gender identity, or sexual orientation, you can file a grievance with: Civil Rights Coordinator — Complaints and Appeals, PO Box 91102, Seattle, WA 98111, Toll free: 855-332-4535, Fax: 425-918-5592, TTY: 711, Email AppealsDepartmentInquiries@Premera.com. You can file a grievance in person or by mail, fax, or email. If you need help filing a grievance, the Civil Rights Coordinator is available to help you. You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at <https://ocrportal.hhs.gov/ocr/portal/lobby.jsf>, or by mail or phone at: U.S. Department of Health and Human Services, 200 Independence Ave SW, Room 509F, HHH Building, Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD). Complaint forms are available at <http://www.hhs.gov/ocr/office/file/index.html>. You can also file a civil rights complaint with the Washington State Office of the Insurance Commissioner, electronically through the Office of the Insurance Commissioner Complaint Portal available at <https://www.insurance.wa.gov/file-complaint-or-check-your-complaint-status>, or by phone at 800-562-6900, 360-586-0241 (TDD). Complaint forms are available at <https://fortress.wa.gov/oic/onlineservices/cc/pub/complaintinformation.aspx>.

Language Assistance

- ATENCIÓN:** si habla español, tiene a su disposición servicios gratuitos de asistencia lingüística. Llame al 844-722-4661 (TTY: 711).
- 注意:** 如果您使用繁體中文，您可以免費獲得語言援助服務。請致電 844-722-4661 (TTY: 711)。
- CHÚ Ý:** Nếu bạn nói Tiếng Việt, có các dịch vụ hỗ trợ ngôn ngữ miễn phí dành cho bạn. Gọi số 844-722-4661 (TTY: 711).
- 주의:** 한국어를 사용하시는 경우, 언어 지원 서비스를 무료로 이용하실 수 있습니다. 844-722-4661 (TTY: 711) 번으로 전화해 주십시오.
- ВНИМАНИЕ:** Если вы говорите на русском языке, то вам доступны бесплатные услуги перевода. Звоните 844-722-4661 (телетайп: 711).
- PAUNAWA:** Kung nagsasalita ka ng Tagalog, maaari kang gumamit ng mga serbisyo ng tulong sa wika nang walang bayad. Tumawag sa 844-722-4661 (TTY: 711).
- УВАГА!** Якщо ви розмовляєте українською мовою, ви можете звернутися до безкоштовної служби мовної підтримки. Телефонуйте за номером 844-722-4661 (телетайп: 711).
- ប្រយ័ត្ន:** បើសិនជាអ្នកនិយាយ ភាសាខ្មែរ, សេវាជំនួយផ្នែកភាសា ដោយមិនគិតល្អឺល្អ គឺអាចមានសំរាប់អ្នក។ ចូរ ទូរស័ព្ទ 844-722-4661 (TTY: 711)។
- 注意事項:** 日本語を話される場合、無料の言語支援をご利用いただけます。844-722-4661 (TTY:711) まで、お電話にてご連絡ください。
- ማስታወሻ:** የሚናገሩት ቋንቋ አማርኛ ከሆነ የትርጉም እርዳታ ድርጅቶች፣ በገጻ ሊያግዝዎት ተዘጋጅተዋል። ወደ ሚከተለው ቁጥር ይደውሉ 844-722-4661 (መስማት ለተሳናቸው: 711)።
- XIYYEEFFANNA:** Afaan dubbattu Oroomiffa, tajaajjila gargaarsa afaanii, kanfaltiidhaan ala, ni argama. Bilbilaa 844-722-4661 (TTY: 711).
- ملحوظة:** إذا كنت تتحدث اذكر اللغة، فإن خدمات المساعدة اللغوية تتوافر لك بالمجان. اتصل برقم 844-722-4661 (رقم هاتف الصم والبكم: 711).
- ਧਿਆਨ ਦਿਓ:** ਜੇ ਤੁਸੀਂ ਪੰਜਾਬੀ ਬੋਲਦੇ ਹੋ, ਤਾਂ ਭਾਸ਼ਾ ਵਿੱਚ ਸਹਾਇਤਾ ਸੇਵਾ ਤੁਹਾਡੇ ਲਈ ਮੁਫਤ ਉਪਲਬਧ ਹੈ। 844-722-4661 (TTY: 711) 'ਤੇ ਕਾਲ ਕਰੋ।
- ACHTUNG:** Wenn Sie Deutsch sprechen, stehen Ihnen kostenlos sprachliche Hilfsdienstleistungen zur Verfügung. Rufnummer: 844-722-4661 (TTY: 711).
- ໂປດອຸບ:** ຖ້າວ່າ ທ່ານວົ້າພາສາ ລາວ, ການບໍລິການຊ່ວຍເຫຼືອດ້ານພາສາ, ໂດຍບໍ່ຄ່າສ່ຽງຄ່າ, ຄວນມີພ້ອມໃຫ້ທ່ານ. ໂທສ 844-722-4661 (TTY: 711).
- ATANSYON:** Si w pale Kreyòl Ayisyen, gen sèvis èd pou lang ki disponib gratis pou ou. Rele 844-722-4661 (TTY: 711).
- ATTENTION:** Si vous parlez français, des services d'aide linguistique vous sont proposés gratuitement. Appelez le 844-722-4661 (ATS : 711).
- UWAGA:** Jeżeli mówisz po polsku, możesz skorzystać z bezpłatnej pomocy językowej. Zadzwoń pod numer 844-722-4661 (TTY: 711).
- ATENÇÃO:** Se fala português, encontram-se disponíveis serviços linguísticos, grátis. Ligue para 844-722-4661 (TTY: 711).
- ATTENZIONE:** In caso la lingua parlata sia l'italiano, sono disponibili servizi di assistenza linguistica gratuiti. Chiamare il numero 844-722-4661 (TTY: 711).
- توجه:** اگر بہ زبان فارسی گفتگو می کنید، تسهیلات زبانی بصورت رایگان برای شما فراهم می باشد. با 844-722-4661 (TTY: 711) تماس بگیرید.