PHARMACY COVERAGE GUIDELINE

JYLAMVO (methotrexate) oral
XATMEP™ (methotrexate) oral
Generic Equivalent (if available)

This Pharmacy Coverage Guideline (PCG):
- Provides information about the reasons, basis, and information sources we use for coverage decisions
- Is not an opinion that a drug (collectively "Service") is clinically appropriate or inappropriate for a patient
- Is not a substitute for a provider's judgment (Provider and patient are responsible for all decisions about appropriateness of care)
- Is subject to all provisions e.g. (benefit coverage, limits, and exclusions) in the member's benefit plan; and
- Is subject to change as new information becomes available.

Scope
- This PCG applies to Commercial and Marketplace plans
- This PCG does not apply to the Federal Employee Program, Medicare Advantage, Medicaid or members of out-of-state Blue Cross and/or Blue Shield Plans

Instructions & Guidance
- To determine whether a member is eligible for the Service, read the entire PCG.
- This PCG is used for FDA approved indications including, but not limited to, a diagnosis and/or treatment with dosing, frequency, and duration.
- Use of a drug outside the FDA approved guidelines, refer to the appropriate Off-Label Use policy.
- The "Criteria" section outlines the factors and information we use to decide if the Service is medically necessary as defined in the Member's benefit plan.
- The "Description" section describes the Service.
- The "Definition" section defines certain words, terms or items within the policy and may include tables and charts.
- The "Resources" section lists the information and materials we considered in developing this PCG
- **We do not accept patient use of samples as evidence of an initial course of treatment, justification for continuation of therapy, or evidence of adequate trial and failure.**
- Information about medications that require prior authorization is available at www.azblue.com/pharmacy. You must fully complete the request form and provide chart notes, lab workup and any other supporting documentation. The prescribing provider must sign the form. Fax the form to BCBSAZ Pharmacy Management at (602) 864-3126 or email it to Pharmacyprecert@azblue.com.

Criteria:

- **Criteria for initial therapy:** Xatmep (methotrexate) oral solution, Jylamvo (methotrexate) oral solution and/or generic equivalent (if available) is considered ***medically necessary*** and will be approved when **ALL** the following criteria are met:

  1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with an Oncologist or Rheumatologist depending upon indication or use

  2. Individual age is **ONE** of the following:
     a. **For Xatmep (methotrexate):** 2.5 years of age or older
     b. **For Jylamvo (methotrexate):** 18 years of age or older

3. Individual has a confirmed diagnosis of **ONE** of the following:
    a. **For Xatmep (methotrexate), ONE** of the following:
        i. Acute lymphoblastic leukemia (ALL) as a component of a combination chemotherapy maintenance regimen
        ii. Other request for a specific oncologic direct treatment use that is found and listed in the National Comprehensive Cancer Network (NCCN) Guidelines with Categories of Evidence and Consensus of 1 and 2A
        iii. Active polyarticular juvenile idiopathic arthritis (pJIA) in an individual who is intolerant of or had an inadequate response to first-line therapy including full dose non-steroidal anti-inflammatory drugs (NSAID)

    b. **For Jylamvo (methotrexate), ONE** of the following:
        i. Acute lymphoblastic leukemia (ALL) as part of a combination chemotherapy maintenance regimen
        ii. Relapsed or refractory non-Hodgkin lymphoma as part of a metronomic combination regimen
        iii. Other request for a specific oncologic direct treatment use that is found and listed in the National Comprehensive Cancer Network (NCCN) Guidelines with Categories of Evidence and Consensus of 1 and 2A
        iv. Mycosis fungoides
        v. Rheumatoid arthritis
        vi. Severe psoriasis

4. Individual has received and completed **ALL** the following **baseline tests** before initiation of treatment and with continued monitoring of the individual as clinically appropriate:
    a. Negative pregnancy test in an individual of childbearing potential before initiation of treatment and with continued monitoring of the individual as clinically appropriate
    b. Liver function tests
    c. Kidney function test (serum creatinine, BUN)

5. **If available:** Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

6. Individual has documented failure, contraindication per FDA label, intolerance, or is not a candidate for **BOTH** of the following:
    a. Oral methotrexate tabs
    b. Methotrexate injection

7. There are **NO** FDA-label contraindications such as:
    a. Pregnancy
    b. Severe hypersensitivity to methotrexate

8. Agent will not be used with live virus vaccines

9. Agent will not be used in an individual with hepatic impairment

10. Agent will not be used with other methotrexate formulations

Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Xatmep (methotrexate) oral solution, Jylamvo (methotrexate) oral solution and/or generic equivalent (if available) is considered ***medically necessary*** and will be approved when **ALL** the following criteria are met **(samples are not considered for continuation of therapy)**:

1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with an Oncologist or Rheumatologist depending upon indication or use

2. Individual's condition has responded while on therapy with response defined as **ONE** of the following:
    a. **For Acute lymphoblastic leukemia**:
        i. No evidence of disease progression
    b. **For Non-Hodgkin lymphoma**:
        i. No evidence of disease progression
    c. **For Mycosis fungoides, ONE** of the following:
        i. No evidence of disease progression defined as worsening of index lesion(s) or development of new cutaneous tumor lesions or development of non-cutaneous manifestations of disease
        ii. Documented evidence of efficacy, disease stability and/or improvement defined as at least a 50% improvement or complete disappearance of the index lesion(s)
    d. **For Rheumatoid arthritis**:
        i. **With first request for continuation**: AT LEAST a 20% improvement in any of the following: ACR, CDAI, DAS28, PAS, PASII, RAPID-3, SDAI
        ii. **With subsequent request for continuation**: Documented evidence of disease stability and/or improvement with no evidence of disease progression
    e. **For Severe psoriasis**:
        i. **With first request for continuation**: AT LEAST a 20% improvement in PASI (see Definitions section)
        ii. **With subsequent request for continuation**: Documented evidence of disease stability and/or improvement with no evidence of disease progression
    f. **For Polyarticular juvenile idiopathic arthritis, TWO** of the following:
        i. Achieved and maintains a 30% improvement in ACR Core Data Set and is without fevers
        ii. Reduced number of joints with active arthritis over baseline
        iii. Reduced number of joints with limited range of motion over baseline
        iv. Reduced pain
        v. Reduced number of acute flares

3. Individual has been adherent with the medication

4. **If available:** Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

5. Individual has not developed any contraindications or other significant adverse drug effects that may exclude continued use as follows:
    a. Contraindications as listed in the criteria for initial therapy section
    b. Significant adverse effect such as:
        i. Bone marrow suppression (pancytopenia, anemia, leukopenia, neutropenia, and thrombocytopenia)
        ii. Dermatologic toxicity such as toxic epidermal necrolysis, Stevens-Johnson syndrome, exfoliative dermatitis, skin necrosis, erythema multiforme
        iii. Development of secondary malignancy such as lymphoproliferative disease
        iv. Gastrointestinal perforation, ulceration, or bleeding
        v. Infection from bacteria, fungal, or viral pathogens
        vi. Kidney toxicity
        vii. Liver toxicity (fibrosis, cirrhosis, liver failure)
        viii. Pulmonary toxicity
        ix. Neurotoxicity
        x. Lymphoproliferative disease

6. Agent will not be used in an individual with hepatic impairment

7. Agent will not be used with other methotrexate formulations

Renewal duration: 12 months

- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

1. **Off-Label Use of Non-Cancer Medications**

2. **Off-Label Use of Cancer Medications**

Description:

Xatmep (methotrexate) oral solution is indicated for the treatment of pediatric patients with acute lymphoblastic leukemia (ALL) as part of a multi-phase, combination chemotherapy maintenance regimen; it is also indicated in the management of pediatric patients with active polyarticular juvenile idiopathic arthritis (pJIA) who have had an insufficient therapeutic response to, or are intolerant of, an adequate trial of first-line therapy including full dose non-steroidal anti-inflammatory agents (NSAIDs).

Jylamvo (methotrexate) oral solution is indicated for the: treatment of adults with acute lymphoblastic leukemia (ALL) as part of a combination chemotherapy maintenance regimen; treatment of adults with mycosis fungoides; treatment of adults with relapsed or refractory non-Hodgkin lymphoma as part of a metronomic combination regimen; treatment of adults with rheumatoid arthritis; and treatment of adults with severe psoriasis.

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Methotrexate, a folate analog, inhibits the enzyme dihydrofolic acid reductase. Dihydrofolate must be reduced to tetrahydrofolate by this enzyme before they can be utilized as carriers of one-carbon groups in the synthesis of purine nucleotides and thymidylate. Methotrexate interferes with DNA synthesis, repair, and cellular replication. Actively proliferating tissues such as malignant cells, bone marrow, fetal cells, buccal and intestinal mucosa, and cells of the urinary bladder are in general more sensitive to this effect of methotrexate. The mechanism of action for methotrexate in pJIA is unknown; it may affect immune function.

Definitions:

U.S. Food and Drug Administration (FDA) MedWatch Forms for FDA Safety Reporting
MedWatch Forms for FDA Safety Reporting | FDA

NCCN recommendation definitions:

Category 1:
Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A:
Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B:
Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3:
Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate

American College of Rheumatology (ACR) Core Data Set

1. Swollen joint count
2. Tender joint count
3. Physician global assessment
4. Acute phase reactant – ESR or CRP
5. Physical function
6. Pain
7. Patient global assessment
8. Radiograph, if study includes more than 1 year

Psoriasis Area and Severity Index (PASI):

	Head	Upper Extremities	Trunk	Lower extremities
1. Redness[1]				
2. Thickness[1]				
3. Scale[1]				
4. Sum of rows 1,2 and 3				
5. Area score[2]				
6. Score of row 4 x row 5 x the area multiplier	row 4 x row 5 x 0.1	row 4 x row 5 x 0.2	Row 4 x row 5 x 0.3	Row 4 x row 5 x 0.4
7. Sum row 6 for each column for PASI score				

Steps in generating PASI score:
(a) Divide body into four areas: head, arms, trunk to groin, and legs to top of buttocks.
(b) Generate an average score for the erythema, thickness, and scale for each of the 4 areas (0 = clear; 1–4 = increasing severity)[1].
(c) Sum scores of erythema, thickness, and scale for each area.
(d) Generate a percentage for skin covered with psoriasis for each area and convert that to a 0–6 scale (0 = 0%; 1 = <10%; 2 = 10–<30%; 3 = 30–<50%; 4 = 50–<70%; 5 = 70–<90%; 6 = 90–100%).
(e) Multiply score of item (c) above times item (d) above for each area and multiply that by 0.1, 0.2, 0.3, and 0.4 for head, arms, trunk, and legs, respectively.
(f) Add these scores to get the PASI score.

[1] Erythema, induration and scale are measured on a 0–4 scale (none, slight, mild, moderate, severe)
[2] Area scoring criteria (score: % involvement)
0: 0 (clear)
1: <10%
2: 10–<30%
3: 30–<50%
4: 50–<70%
5: 70–<90%
6: 90–<100%

Feldman, SR and Krueger, GG. Psoriasis assessment tools in clinical trials. Ann Rheum Dis 2005; 64 (Suppl III): ii65-ii68.

Rheumatoid Arthritis Disease Activity Measurement Instruments:

Instrument	Threshold of Disease Activity
Clinical Disease Activity Index (CDAI)	Range: 0 to 76 Remission: ≤ 2.8 Low activity: >2.8 to ≤ 10 Moderate activity: >10 to ≤ 22 High activity: >22
Disease Activity Score 28 (DAS28)	Range: 0.5 to 9 Remission: < 2.6 Low activity: > 2.6 to ≤ 3.2 Moderate activity: > 3.2 to ≤ 5.1 High activity: > 5.1
Patient Activity Scale (PAS) Patient Activity Scale II (PASII)	Range 0 to 10 Remission: 0 to 0.25 Low activity: >0.25 to 3.7 Moderate activity: > 3.7 to < 8.0 High activity: ≥ 8.0
Routine Assessment of Patient Index Data 3 (RAPID-3)	Range: 0 to 10 Remission: 0 to 1.0 Low activity: > 1.0 to 2.0 Moderate activity: > 2.0 to 4.0 High activity: > 4.0 to 10
Simplified Disease Activity Index (SDAI)	Range: 0 to 90 Remission: ≤ 3.3 Low activity: > 3.3 to ≤ 11.0 Moderate activity: > 11.0 to ≤ 26 High activity: > 26

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American College of Rheumatology 20 Percent Improvement Criteria (ACR20):

At least 20 percent improvement in the following:
1. Swollen joint count
2. Tender joint count
And three of the following five variables:
3. Patient-assessed global disease activity (e.g., by VAS)
4. Evaluator-assessed global disease activity (e.g., by VAS)
5. Patient pain assessment (e.g., by VAS)
6. Functional disability (e.g., by HAQ)
7. Acute phase response (ESR or CRP)
A 50 and 70 percent ACR response (ACR50 and ACR70, respectively) represents respective improvement of at least 50 or 70 percent[1].
 1. *Felson DT, Anderson JJ, Lange ML, et al. Should improvement in rheumatoid arthritis clinical trials be defined as fifty percent or seventy percent improvement in core set measures, rather than twenty percent?. Arthritis Rheum 1998; 41:1564.* 2. *Felson DT, Anderson JJ, Boers M, et al. American College of Rheumatology preliminary definition of improvement in rheumatoid arthritis. Arthritis Rheum 1995; 38:727.*

Resources:

Xatmep (methotrexate) oral solution product information, revised by Azurity Pharmaceuticals, Inc. 09-2020. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed May 08, 2024.

Jylamvo (methotrexate) oral solution product information, revised by Shorla Oncology, Inc. 11-2023. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed May 08, 2024.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Primary Cutaneous Lymphomas Version 2.2024 – Updated May 06, 2024. Available at https://www.nccn.org. Accessed May 08, 2024.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Acute Lymphoblastic Leukemia Version 4.2023 – Updated February 05, 2023. Available at https://www.nccn.org. Accessed May 08, 2024.

Horton TM, McNeer JL. Treatment of acute lymphoblastic leukemia/lymphoma in children and adolescents. In: UpToDate, Newburger P, Rosmarin AG (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through April 2024. Topic last updated November 29, 2022. Accessed May 08, 2024.

Weiss PF. Polyarticular juvenile idiopathic arthritis: Treatment. In: UpToDate, Klein-Gitelman M, TePas E (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through April 2024. Topic last updated November 03, 2023. Accessed May 08, 2024.

Off Label Use of Cancer Medications: A.R.S. §§ 20-826(R) & (S). Subscription contracts; definitions.

Off Label Use of Cancer Medications: A.R.S. §§ 20-1057(V) & (W). Evidence of coverage by health care service organizations; renewability; definitions.