BlueCross BlueShield Arizona

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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/or 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.

Medical Necessity Requirements for JYLAMVO (methotrexate)

Criteria for Initial Therapy:

Prescriber Qualifications
- Prescribed by an Oncologist or Rheumatologist or in consultation with one

Indication
- Acute lymphoblastic leukemia (ALL) in individuals 2 years or older as part of a combination chemotherapy maintenance regimen
- Polyarticular juvenile idiopathic arthritis (pJIA) in individuals 2 years or older

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- Relapsed or refractory non Hodgkin lymphoma in individuals 18 years or older as part of a metronomic combination regimen
- Mycosis fungoides in individuals 18 years or older as a single agent or part of combination chemotherapy
- Rheumatoid arthritis in individuals 18 years or older
- Severe psoriasis in individuals 18 years or older
- Other oncologic direct treatment uses listed in National Comprehensive Cancer Network (NCCN) Guidelines with Categories of Evidence and Consensus of 1 and 2A

Baseline Clinical Evaluation

- Negative pregnancy test for individuals of childbearing potential
- Liver function tests
- Kidney function tests (serum creatinine, blood urea nitrogen)
- Complete blood count

Alternative Therapies

- Failure, contraindication, intolerance to **BOTH** of the following:
  - Oral methotrexate tablets
  - Methotrexate injection

Brand Specific Criteria

- Have failure, contraindication or intolerance with **THREE** generic equivalents (if available) for at least three months each. **Note**: Any failure, contraindication, or intolerance to the generic drugs should be reported to the FDA (see Definitions section)

Safety

- No concomitant use with live virus vaccines
- No hepatic impairment
- No use with other methotrexate formulations
- No FDA labeled contraindications such as pregnancy or severe hypersensitivity to methotrexate
- There is concurrent use of folic acid when used in non neoplastic diseases (rheumatoid arthritis, psoriasis, polyarticular juvenile idiopathic arthritis)

Documentation Requirements

- A completed request form must be submitted including:
  - Chart notes
  - Lab results (pregnancy test, liver and kidney function tests)
  - Supporting clinical documentation

Initial Therapy Criteria Approval Duration

- 6 months OR end of plan year

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Criteria for Continuation of Therapy (renewal therapy):

Note: Manufacturer assistance (e.g., coupons, samples, etc.) are not considered for continuation of therapy

Prescriber Qualification

- Continues to be seen by a physician specializing in or in consultation with an Oncologist or Rheumatologist

Clinical Response

- **Acute lymphoblastic leukemia:** No evidence of disease progression
- **Non Hodgkin lymphoma:** No evidence of disease progression
- **Mycosis fungoides, ONE** of the following:
  - No worsening of index lesions or development of new cutaneous/non cutaneous manifestations
  - At least 50 percent improvement or complete disappearance of index lesions
- **Rheumatoid arthritis:**
  - First renewal: At least 20 percent improvement in ACR, CDAI, DAS28, PAS, PASII, RAPID 3, SDAI
  - Subsequent renewals: Documented stability or improvement with no progression
- **Severe psoriasis:**
  - First renewal: At least 20 percent improvement in Psoriasis Area and Severity Index (PASI)
  - Subsequent renewals: Documented stability or improvement with no progression
- **Polyarticular juvenile idiopathic arthritis**, **TWO** of the following:
  - 30 percent improvement in ACR Core Data Set and no fevers
  - Reduced joints with active arthritis
  - Reduced joints with limited range of motion
  - Reduced pain
  - Reduced number of acute flares

Adherence

- Adherence to the prescribed therapy regimen has been documented

Brand Specific Criteria

- Have failure, contraindication or intolerance with **THREE** generic equivalents (if available) for at least three months each. **Note:** Any failure, contraindication, or intolerance to the generic drugs should be reported to the FDA (see Definitions section)

Safety

- No concomitant use with live virus vaccines
- No hepatic impairment
- No use with other methotrexate formulations
- No FDA labeled contraindications such as pregnancy or severe hypersensitivity to methotrexate
- There is concurrent use of folic acid when used in non neoplastic diseases (rheumatoid arthritis, psoriasis, polyarticular juvenile idiopathic arthritis)

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- No development of significant adverse effects including:
  - Bone marrow suppression (pancytopenia, anemia, leukopenia, neutropenia, and thrombocytopenia)
  - Dermatologic toxicity (toxic epidermal necrolysis, Stevens Johnson syndrome, exfoliative dermatitis, skin necrosis, erythema multiforme)
  - Secondary malignancy such as lymphoproliferative disease
  - Gastrointestinal perforation or bleeding
  - Serious infection (bacterial, fungal, viral)
  - Kidney toxicity
  - Hepatotoxicity (fibrosis, cirrhosis, liver failure)
  - Pulmonary toxicity (acute or chronic interstitial pneumonitis)
  - Neurotoxicity
  - Lymphoproliferative disease

Documentation Requirements
- Chart notes
- Supporting clinical documentation with evidence of improvement
- Lab values confirming safe use

Continuation Therapy Criteria Approval Duration
- 12 months OR end of plan year

Medical Necessity Requirements for XATMEP (methotrexate)

Criteria for Initial Therapy:

Prescriber Qualifications
- Prescribed by an Oncologist or Rheumatologist or in consultation with one

Indication
- Acute lymphoblastic leukemia (ALL) as part of a combination chemotherapy maintenance regimen
- Active polyarticular juvenile idiopathic arthritis (pJIA) who are intolerant of or had inadequate response to first line therapy including full dose non steroidal anti inflammatory drugs (NSAIDs)
- Other oncologic direct treatment uses listed in National Comprehensive Cancer Network (NCCN) Guidelines with Categories of Evidence and Consensus of 1 and 2A

Age Requirement
- 2.5 years of age or older

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Baseline Clinical Evaluation

- Negative pregnancy test for individuals of childbearing potential
- Liver function tests
- Kidney function tests (serum creatinine, blood urea nitrogen)
- Complete blood count

Alternative Therapies

- Failure, contraindication, intolerance to **BOTH** of the following:
  - Oral methotrexate tablets
  - Methotrexate injection

Brand Specific Criteria

- Have failure, contraindication or intolerance with **THREE** generic equivalents (if available) for at least three months each. **Note:** Any failure, contraindication, or intolerance to the generic drugs should be reported to the FDA (see Definitions section)

Safety

- No concomitant use with live virus vaccines
- No hepatic impairment
- No use with other methotrexate formulations
- No FDA labeled contraindications such as pregnancy or severe hypersensitivity to methotrexate
- There is concurrent use of folic acid when used in non neoplastic diseases (rheumatoid arthritis, psoriasis, polyarticular juvenile idiopathic arthritis)

Documentation Requirements

- A completed request form must be submitted including:
  - Chart notes
  - Lab results (pregnancy test, liver and kidney function tests)
  - Supporting clinical documentation

Initial Therapy Criteria Approval Duration

- 6 months OR end of plan year

Criteria for Continuation of Therapy (renewal therapy):

Note: Manufacturer assistance (e.g., coupons, samples, etc.) are not considered for continuation of therapy

Prescriber Qualification

- Continues to be seen by a physician specializing in or in consultation with an Oncologist or Rheumatologist

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Clinical Response

- **Acute lymphoblastic leukemia:** No evidence of disease progression
- **Polyarticular juvenile idiopathic arthritis, TWO** of the following:
  - 30 percent improvement in ACR Core Data Set and no fevers
  - Reduced joints with active arthritis
  - Reduced joints with limited range of motion
  - Reduced pain
  - Reduced number of acute flares

Adherence

- Adherence to the prescribed therapy regimen has been documented

Brand Specific Criteria

- Have failure, contraindication or intolerance with **THREE** generic equivalents (if available) for at least three months each. **Note:** Any failure, contraindication, or intolerance to the generic drugs should be reported to the FDA (see Definitions section)

Safety

- No concomitant use with live virus vaccines
- No hepatic impairment
- No use with other methotrexate formulations
- No FDA labeled contraindications such as pregnancy or severe hypersensitivity to methotrexate
- There is concurrent use of folic acid when used in non neoplastic diseases (rheumatoid arthritis, psoriasis, polyarticular juvenile idiopathic arthritis)
- No development of significant adverse effects including:
  - Bone marrow suppression (pancytopenia, anemia, leukopenia, neutropenia, and thrombocytopenia)
  - Dermatologic toxicity (toxic epidermal necrolysis, Stevens Johnson syndrome, exfoliative dermatitis, skin necrosis, erythema multiforme)
  - Secondary malignancy such as lymphoproliferative disease
  - Gastrointestinal perforation or bleeding
  - Serious infection (bacterial, fungal, viral)
  - Kidney toxicity
  - Hepatotoxicity (fibrosis, cirrhosis, liver failure)
  - Pulmonary (acute or chronic interstitial pneumonitis)
  - Neurotoxicity
  - Lymphoproliferative disease

Documentation Requirements

- Chart notes
- Supporting clinical documentation with evidence of improvement

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- Lab values confirming safe use

Continuation Therapy Criteria Approval Duration

- 12 months OR end of plan year

Criteria for Off-Label Use Requests:

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:

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.

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).

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.

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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.

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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

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].
© 2024 UpToDate, Inc. 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.*

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Resources:

Xatmep (methotrexate) oral solution product information, revised by Azurity Pharmaceuticals, Inc. 09-2020. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed January 29, 2026.

Jylamvo (methotrexate) oral solution product information, revised by Shorla Oncology, Inc. 10-2025. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed January 29, 2026.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Cutaneous Lymphomas Version 2.2026 – Updated February 13, 2026. Available at https://www.nccn.org. Accessed March 16, 2026.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Acute Lymphoblastic Leukemia Version 2.2025 – Updated June 27, 2025. Available at https://www.nccn.org. Accessed March 16, 2026.

Weiss PF. Polyarticular juvenile idiopathic arthritis: Treatment and prognosis. In: UpToDate, Klein-Gitelman M, Case SM (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through February 2026. Topic last updated March 03, 2026. Accessed March 16, 2026.

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.

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