BlueCross BlueShield of Arizona
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PHARMACY COVERAGE GUIDELINES	
SECTION: DRUGS	
ORIGINAL EFFECTIVE DATE:	**09/09/14**
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ARCHIVE DATE:	

OTREXUP™ (methotrexate) subcutaneous injection

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Pharmacy Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Pharmacy Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as "Description" defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as "Criteria" defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Pharmacy Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Pharmacy Coverage Guideline, the terms "experimental" and "investigational" are considered to be interchangeable.

This Pharmacy Coverage Guideline does not apply to FEP or other states' Blues Plans.

Information about medications that require precertification is available at www.azblue.com/pharmacy.

Some large (100+) benefit plan groups may customize certain benefits, including adding or deleting precertification requirements.

All applicable benefit plan provisions apply, e.g., waiting periods, limitations, exclusions, waivers and benefit maximums.

Precertification for medication(s) or product(s) indicated in this guideline requires completion of the request form in its entirety with the chart notes as documentation. All requested data must be provided. Once completed the form must be signed by the prescribing provider and faxed back to BCBSAZ Pharmacy Management at (602) 864-3126 or emailed to Pharmacyprecert@azblue.com. **Incomplete forms or forms without the chart notes will be returned.**

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Criteria:

- **Criteria for initial therapy:** Otrexup (methotrexate) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met :

1. A confirmed diagnosis is **ONE** of the following:
   - An individual 18 years of age or older with **either:**
     - Severe active Rheumatoid Arthritis (RA)
     - Symptomatic control of severe, recalcitrant, disabling psoriasis
   - An individual 2 years of age or older with severe active polyarticular juvenile idiopathic arthritis (pJIA)

2. Individual has failed, or is intolerant to, or has a contraindication such that the individual is unable to use **ALL** the following preferred step therapy agents:
   - Preferred step therapy agents include:
     - Oral methotrexate using FDA-recommended doses for the condition
     - Methotrexate injection not associated with an auto-injection device using FDA-recommended doses for the condition
     - Rasuvo (methotrexate) auto-injection using FDA-recommended doses for the condition

3. **ALL** of the following baseline tests have been completed before initiation of treatment with continued monitoring as clinically appropriate:
   - Pregnancy test in a woman of child bearing age
   - Complete blood count
   - Kidney function tests
   - Liver function tests
   - Serum albumin
   - Chest x-ray
   - Pulmonary function tests, in selected patients

4. There are **NO** contraindications:
   - Contraindications include:
     - Pregnancy
     - Nursing an infant or child
     - Alcoholism, alcoholic liver disease or chronic liver disease
     - Immunodeficiency syndrome either overt or laboratory evidence of immune deficiency
     - Pre-existing blood dyscrasia such as bone marrow hypoplasia, leukopenia, thrombocytopenia, or significant anemia
     - Known hypersensitivity to methotrexate

5. Will not be used simultaneously with another methotrexate preparation

Initial approval duration: 6 months

OTREXUP™ (methotrexate) subcutaneous injection (cont.)

- **Criteria for continuation of coverage (renewal request):** Otrexup (methotrexate) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Individual's condition responded while on therapy
    - Response is defined as:
        - For RA:
            - At least a 20% improvement in any of the following: CDAI, DAS28, PAS, PASII, RAPID-3, SDAI (see Definition section)
        - For pJIA:
            - At least a 30% improvement in JIA Core Set (see Definition section)
        - For psoriasis:
            - At least a 20% improvement in PASI (see Definition section)

2. Individual has been adherent with the medication

3. Individual has not developed any contraindications or other significant level 4 adverse drug effects that may exclude continued use
    - Contraindications as listed in the criteria for initial therapy section
    - Significant adverse effect such as:
        - Myelosuppression
        - Liver toxicity
        - Interstitial lung disease
        - Kidney dysfunction
        - Severe gastrointestinal toxicity
        - Severe skin reactions

4. There are no significant interacting drugs

5. Will not be used simultaneously with another methotrexate preparation

Renewal duration: 12 months

Description:

Otrexup (methotrexate) is a single-dose auto-injector containing the prescription medicine methotrexate (MTX). MTX is used for the management of individuals with severe, active rheumatoid arthritis (RA) and polyarticular juvenile idiopathic arthritis (pJIA) who are intolerant of or had an inadequate response to first-line therapy and for symptomatic control of severe, recalcitrant, disabling psoriasis in adults who are not adequately responsive to other forms of therapy. The precise mechanism of action of MTX in the treatment of RA, psoriasis, and pJIA is unknown, but it is speculated that it may produce its effects through immunosuppression and/or anti-inflammatory actions.

MTX is a folate analog which inhibits the enzymes dihydrofolate reductase and thymidylate synthetase. Dihydrofolate reductase is responsible for the reduction of folic acid to tetrahydrofolate. Tetrahydrofolate is involved in the synthesis of purine nucleotides and thymidyate. Thymidylate synthetase generates thymidine

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monophosphate that is subsequently phosphorylated to its triphosphate form for use in DNA synthesis and repair. The inhibition of these enzymes ultimately results in the interference with DNA synthesis, repair, and cellular reproduction. In general, actively proliferating tissues, such as neoplasms, bone marrow, fetal cells, oral and intestinal mucosal cells, and cells of the urinary bladder are more sensitive to the effects of MTX.

MTX tablets have been on the market since 1953 and as an injection that may be given intramuscular (IM), intravenous (IV), subcutaneous (Sub-Q), intra-arterial (IA), and intrathecal (IT) since 1959. It is used in a variety of neoplastic diseases and inflammatory conditions. Otrexup contains MTX in a fixed volume prefilled syringe with an auto-injection device, available in 7.5 mg, 10 mg, 12.5 mg, 15 mg, 17.5 mg, 20 mg, 22.5 mg and 25 mg strengths for Sub-Q administration only. Otrexup is not indicated for the treatment of any neoplastic disease. Other MTX formulations should be used if the required dose does not match an available strengths of Otrexup. Other MTX formulations should be used for individuals requiring oral, IM, IV, IA, or IT dose of MTX.

Definitions:

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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JIA Core Set 30%

At least 30 percent improvement in at least 3 of the 6 core set variables with no more than 1 remaining variable worsening by > 30%
1. Physician's global assessment of overall disease activity measured on a visual analog scale (VAS)
2. Parent or patient global assessment of overall well-being measured on VAS
3. Functional ability
4. Number of joints with active arthritis
5. Number of joints with limited range of motion
6. Erythrocyte sedimentation rate (ESR)
Giannini, EH, Ruperto, N, Ravelli A, et al. Preliminary Definition of Improvement in Juvenile Arthritis. Arthritis & Rheumatism 1997

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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Resources:

Otrexup (methotrexate) product information accessed 01-16-19 at DailyMed: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=9ab8ce16-f7de-41d4-a4c8-1c742621b6d5

Otrexup package insert, revised by the manufacturer on 11-2014, reviewed on 12-12-2015

Otrexup package insert, revised by the manufacturer on 03-2016, reviewed on 08-09-2016, 12-20-2017

Rasuvo package insert, revised by the manufacturer on 11-2014, reviewed on 12-12-2015

Otrexup package insert reference ID 3389733, revised by manufacturer on 10/2013, FDA Center for Drug Evaluation and Research labeling application number 204824Orig1s000

BCBSAZ Medical Coverage Guidelines for Methotrexate Subcutaneous Auto-Injection, O854

UpToDate: Assessment of rheumatoid arthritis activity in clinical trials and clinical practice. Current through Nov 2017. https://www-uptodate-com.mwu.idm.oclc.org/contents/assessment-of-rheumatoid-arthritis-activity-in-clinical-trials-and-clinical-practice?source=related_link

UpToDate: Clinical manifestations of rheumatoid arthritis. Current through Nov 2017. https://www-uptodate-com.mwu.idm.oclc.org/contents/clinical-manifestations-of-rheumatoid-arthritis?search=rheumatoid%20arthritis&source=search_result&selectedTitle=4~150&usage_type=default&display_rank=4#H281164264

UpToDate: Classification of juvenile arthritis. Current through Nov 2017. https://www-uptodate-com.mwu.idm.oclc.org/contents/classification-of-juvenile-arthritis?search=polyarticular%20juvenile%20idiopathic%20arthritis&source=search_result&selectedTitle=3~32&usage_type=default&display_rank=3

UpToDate: Polyarticular juvenile idiopathic arthritis: Clinical manifestations, diagnosis, and complications. Current through Nov 2017. https://www-uptodate-com.mwu.idm.oclc.org/contents/polyarticular-juvenile-idiopathic-arthritis-clinical-manifestations-diagnosis-and-complications?search=polyarticular%20juvenile%20idiopathic%20arthritis&source=search_result&selectedTitle=1~32&usage_type=default&display_rank=1

UpToDate: Epidemiology, clinical manifestations, and diagnosis of psoriasis. Current through Nov 2017. https://www-uptodate-com.mwu.idm.oclc.org/contents/epidemiology-clinical-manifestations-and-diagnosis-of-psoriasis?search=psoriasis&source=search_result&selectedTitle=2~150&usage_type=default&display_rank=2

UpToDate: Treatment of psoriasis in adults. Current through Nov 2017. https://www-uptodate-com.mwu.idm.oclc.org/contents/treatment-of-psoriasis-in-adults?source=see_link

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Fax completed prior authorization request form to 602-864-3126 or email to pharmacyprecert@azblue.com.
Call 866-325-1794 to check the status of a request.
All requested data must be provided. **Incomplete forms or forms without the chart notes will be returned.**
Pharmacy Coverage Guidelines are available at www.azblue.com/pharmacy.

Pharmacy Prior Authorization Request Form

Do not copy for future use. Forms are updated frequently.
REQUIRED: Office notes, labs, and medical testing relevant to the request that show medical justification are required.

Member Information			
Member Name (first & last):	Date of Birth:	Gender:	BCBSAZ ID#:
Address:	City:	State:	Zip Code:
Prescribing Provider Information			
Provider Name (first & last):	Specialty:	NPI#:	DEA#:
Office Address:	City:	State:	Zip Code:
Office Contact:	Office Phone:	Office Fax:	
Dispensing Pharmacy Information			
Pharmacy Name:	Pharmacy Phone:	Pharmacy Fax:	
Requested Medication Information			
Medication Name:	Strength:	Dosage Form:	
Directions for Use:	Quantity: / Refills:	Duration of Therapy/Use:	

☐ Check if requesting **brand** only ☐ Check if requesting **generic**

☐ Check if requesting continuation of therapy (prior authorization approved by BCBSAZ expired)

Turn-Around Time For Review

☐ Standard ☐ Urgent. Sign here: _____ ☐ Exigent (requires prescriber to include a written statement)

Clinical Information

1. **What is the diagnosis? Please specify below.**

   ICD-10 Code: _____ **Diagnosis Description:** _____

2. ☐ Yes ☐ No **Was this medication started on a recent hospital discharge or emergency room visit?**

3. ☐ Yes ☐ No **There is absence of ALL contraindications.**

4. **What medication(s) has the individual tried and failed for this diagnosis? Please specify below.**
Important note: Samples provided by the provider are not accepted as continuation of therapy or as an adequate trial and failure.

Medication Name, Strength, Frequency	Dates started and stopped or Approximate Duration	Describe response, reason for failure, or allergy

5. **Are there any supporting labs or test results? Please specify below.**

Date	Test	Value

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Pharmacy Prior Authorization Request Form

6. Is there any additional information the prescribing provider feels is important to this review? Please specify below.
For example, explain the negative impact on medical condition, safety issue, reason formulary agent is not suitable to a specific medical condition, expected adverse clinical outcome from use of formulary agent, or reason different dosage form or dose is needed.

Signature affirms that information given on this form is true and accurate and reflects office notes

Prescribing Provider's Signature: Date:

Please note: Some medications may require completion of a drug-specific request form.

Incomplete forms or forms without the chart notes will be returned.

Office notes, labs, and medical testing relevant to the request that show medical justification are required.