BlueCross BlueShield of Arizona
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PHARMACY COVERAGE GUIDELINES	**ORIGINAL EFFECTIVE DATE: 9/9/14**
SECTION: DRUGS	**LAST REVIEW DATE: 1/18/18**
	LAST CRITERIA REVISION DATE: 1/18/18
	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.**

OTREXUP™ (methotrexate) subcutaneous injection (cont.)

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 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.

Otrexup (methotrexate)

Medication class:
Antineoplastic Agent, Antimetabolite (Antifolate); Antirheumatic, Disease Modifying; Immunosuppressant Agent

FDA-approved indication(s):
- Management of adults with severe, active rheumatoid arthritis (RA) and active polyarticular juvenile idiopathic arthritis (pJIA), who are intolerant of or had an inadequate response to first-line therapy, including non-steroidal anti-inflammatory drugs (NSAIDs)
- Symptomatic control of severe, recalcitrant, disabling psoriasis in adults who are not adequately responsive to other forms of therapies

Limitations of use:
- Otrexup is not indicated for the treatment of neoplastic diseases

Recommended Dose:
- Use another formulation of methotrexate for patients requiring oral, intramuscular, intravenous, intra-arterial, or intrathecal dosing, doses less than 7.5 mg per week, doses above 25 mg per week, high-dose regimens, or dose adjustments between the available doses

OTREXUP™ (methotrexate) subcutaneous injection (cont.)

- RA: 7.5 mg SQ once weekly
- pJIA: 10 mg/m^2 SQ once weekly
- Psoriasis: 10-25 mg SQ once weekly

Maximum dosage

- RA: not stated
- pJIA: too few data to assess risk for toxicities for doses above 20 mg/m^2/week but doses up to 30 mg/m^2/week have been given
- Psoriasis: 30 mg/week should not be exceeded, but labeling states to use other MTX formulations if the required dose does not match an available strength of Otrexup

Available Dosage Forms:

- 7.5 mg, 10 mg, 12.5 mg, 15 mg. 17.5 mg. 20 mg, 22.5 mg, and 25 mg single-dose auto-injectors in a carton of 1 injector or 4 injectors

Warnings, Precautions, and other Clinical Information:

- Baseline assessments should include CBC with differential and platelet count, hepatic enzymes, renal function tests, and chest x-ray
- Exclude pregnancy before treatment
- Avoid pregnancy if either partner is receiving Otrexup
- Contraception should be used by both males and females of child bearing potential while on Otrexup
- Methotrexate can cause toxicity to multiple organs including gastrointestinal, hemorrhagic, hepatic, infectious, neurologic, pulmonary, renal, and skin; reactions can be fatal
- Diarrhea, ulcerative stomatitis, hemorrhagic enteritis and intestinal perforation may occur
- Anemia, aplastic anemia, pancytopenia, leukopenia, neutropenia, and/or thrombocytopenia may occur
- Acute (elevated transaminases) and chronic (fibrosis and cirrhosis) hepatotoxicity may occur, Otrexup should be used with caution in the presence of pre-existing liver damage or impaired hepatic function
- Liver tests should be done before starting therapy
- For psoriasis, liver test should be done before therapy to assess for fibrosis or cirrhosis, the labeling recommends liver biopsy in the following: pre-therapy or after 2-4 months of use; total cumulative dose of 1.5 g; and after each additional 1-1.5 g and that Otrexup should be discontinued for moderate fibrosis or any cirrhosis
- For RA, the labeling recommends a liver biopsy for patients with persistent liver test abnormalities, patients with chronic hepatitis B or C, history of excessive alcohol consumption, or if there is a decrease in serum albumin below the normal range and that Otrexup should be discontinued in any patient who has persistently abnormal liver tests and refuses a liver biopsy or in a patient whose biopsy shows moderate to severe changes
- Lung toxicity, including acute or chronic interstitial pneumonitis, may occur at any time, even with low doses; it is not always fully reversible
- Precipitation of methotrexate and its metabolite in renal tubules may occur, especially with dehydration and acidic urine
- Use of live virus vaccine is not recommended
- NSAIDs should not be used with high-dose methotrexate as they reduce tubular excretion of methotrexate
- Use caution if high-dose methotrexate is used with PPI as elevated methotrexate levels may occur
- Use of a penicillin with methotrexate may increase hematologic and gastrointestinal toxicity of methotrexate
- Folic acid or its derivatives may decrease the response to methotrexate

OTREXUP™ (methotrexate) subcutaneous injection (cont.)

- Otrexup is not indicated for the treatment of any cancer, mycosis fungoides, prevention of graft versus host disease, ectopic pregnancy, systemic lupus erythematosus, or Crohn's disease

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:
     - Severe active Rheumatoid Arthritis
     - Active polyarticular juvenile idiopathic arthritis (pJIA)
     - Symptomatic control of severe, recalcitrant, disabling psoriasis

  2. Individual has failure, contraindication or intolerance to **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. 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
       - Pre-existing blood dyscrasia such as bone marrow hypoplasia, leukopenia, thrombocytopenia, or significant anemia
       - Known hypersensitivity to methotrexate

  Initial approval duration: 12 months

- **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 and pJIA:
         - Joint swelling and tenderness have been reduced
       - For psoriasis:
         - PASI score of 75%

  2. Individual has been adherent with the medication

OTREXUP™ (methotrexate) subcutaneous injection (cont.)

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
            - Signs and symptoms may include: fever, chills, infection, unexplained bleeding or bruising, or unexplained weakness or shortness of breath
        - Liver toxicity
            - Signs and symptoms may include: right sided abdominal pain, bruising, yellow skin or eyes, dark brown urine, severe nausea or vomiting, fatigue, light colored pale stools, itching, confusion
        - Interstitial lung disease
            - Signs and symptoms may include: chest pain, palpitations, tachycardia, shortness of breath at rest dyspnea on exertion, dry cough, fatigue, weakness
        - Kidney dysfunction
            - Signs and symptoms may include: decreased urine output, abdominal discomfort, muscle cramps or spasms, muscle tetany, change in mentation, weakness, fatigue, nausea

4. There are no significant interacting drugs

Renewal duration: 12 months

Resources:

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

OTREXUP™ (methotrexate) subcutaneous injection (cont.)

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.