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.

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Description:

Otrexup™ is a single-dose auto-injectors 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 several, 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 thymidate. 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
OTREXUP™ (methotrexate) subcutaneous injection (cont.)

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, 20 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 strength of Otrexup. Other MTX formulations should be used for individuals requiring oral, IM, IV, IA, or IT dose of MTX.

Definitions:

Drug related events:

Ineffective / failure
Use of a drug employing optimal doses (FDA-recommended doses) for optimal duration; where the condition being treated has not improved or worsened

A request for branded agent due to generic drug failure or ineffectiveness will be assessed for potential approval with documentation of use of optimal dose / duration of the generic product and meeting other criteria within the coverage guideline. When the drug in question is a combination product, there must be documentation of failure / ineffectiveness of concurrent use (each ingredient used at the same time) of individual generic components. When the drug in question is a low dose formulation, there must be documentation of failure / ineffectiveness of low dose generic formulation.

Adverse Drug Event: Allergic reaction / Hypersensitivity / Intolerance
Use of a drug produced a significant reaction where continued use of the drug places the individual at risk for either lack of improvement or worsening of the condition being treated or at risk for harm and the concern is documented in medical record. A significant adverse drug event is when an individual's outcome is death, life-threatening, hospitalization (initial or prolonged), disability resulting in a significant, persistent, or permanent change, impairment, damage or disruption in the individuals' body function/structure, physical activities or quality of life, or requires intervention to prevent permanent impairment or damage.

Allergic reaction / hypersensitivity – may or may not involve the active ingredient. When the active ingredient is involved, use of same or a chemically similar agent places the individual at risk for harm when the same or chemically similar agent is used. The subsequent reaction may be the same as the original reaction or a more exaggerated response may be seen, potentially placing the individual at even greater risk for harm.

If the reaction occurred from the active/main generic ingredient; request for branded agent with same active ingredient will not be considered unless it is proven (documented) that active ingredient did not cause reaction and the request meets other criteria within the coverage guideline.
OTREXUP™ (methotrexate) subcutaneous injection (cont.)

Intolerance – these events represent circumstance(s) where use of a drug produced a significant reaction and continued use may result in non-adherence to proposed therapy and this concern is documented in medical record.

Contraindication
Use of a drug that is not recommended by the manufacturer or FDA labelling.

Use of any drug in the face of a contraindication is outside of the FDA and manufacturer’s labelled recommendation and is considered investigational or experimental.

Non-adherence
Individual does not follow prescribed regimen that places the individual at risk for lack of improvement or worsening of the condition being treated and this concern is documented in medical record.

Precertification:

Precertification (Prior Authorization) is required for members with a Blue Cross Blue Shield of Arizona (BCBSAZ) pharmacy benefit for medication(s) or product(s) indicated in this guideline.

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.

Criteria:

See “Resources” section for FDA-approved dosage.

- Precertification for Otrexup requires completion of the specific request form in its entirety. 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 will be returned.

- FDA-approved product labeling (indication, age, dosage, testing, contraindications, exclusions, etc.) of Otrexup is considered medically necessary with documentation of ALL of the following:

  1. Failure of oral methotrexate employing optimal doses (FDA-recommended doses) for optimal duration.
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2. Failure of methotrexate injection (various) not associated with an auto-injection device employing optimal doses (FDA-recommended doses) for optimal duration

3. Failure of Rasuvo (methotrexate) auto-injection employing optimal doses (FDA-recommended doses) for optimal duration

4. Requested dose matches an available strength of Otrexup

5. Diagnosis is ONE of the following:
   - Individual 18 years of age or older with severe active rheumatoid arthritis (RA) who has had an insufficient response to or is intolerant of an adequate trial of first-line therapy including full dose non-steroidal anti-inflammatory drugs (NSAIDS)
   - Individual 2-18 years of age with active polyarticular juvenile idiopathic arthritis (pJIA), who has had an insufficient therapeutic response to or is intolerant of an adequate trial of first-line therapy including full dose non-steroidal anti-inflammatory drugs (NSAIDs)
   - Individual 18 years of age or older for the symptomatic control of severe, recalcitrant, disabling psoriasis that is not adequately responsive to other forms of therapy, but only when the diagnosis has been established, as by biopsy and/or after dermatologic consultation

6. Absence of ALL of the following contraindications:
   - Pregnancy or likelihood of becoming pregnant in a woman of child bearing age
   - Both men and women of child bearing age using inadequate contraception
   - Nursing an infant or child
   - Alcoholism or liver disease (acute or chronic)
   - Immunodeficiency syndrome
   - Pre-existing blood dyscrasia such as bone marrow hypoplasia, leukopenia, thrombocytopenia, or significant anemia
   - Hypersensitivity to Methotrexate

➢ Otrexup for all other indications not previously listed or if above criteria not met is considered experimental or investigational based upon:

1. Lack of final approval from the Food and Drug Administration, and
2. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes, and
3. Insufficient evidence to support improvement of the net health outcome, and
4. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives, and
5. Insufficient evidence to support improvement outside the investigational setting.

These indications include, but are not limited to:
   - Treatment of neoplastic diseases
   - Osteosarcoma
   - Acute lymphoid leukemia
   - Lung cancer
   - Gestational trophoblastic tumors
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- Meningeal leukemia
- Breast cancer
- Head and neck cancer
- Mycosis fungoides
- Non-Hodgkin’s lymphoma
- Testicular carcinoma
- Bladder cancer
- Gastrointestinal cancer
- Soft tissue sarcoma
- Prevention of graft versus host disease
- Ectopic pregnancy
- Systemic lupus erythematosus
- Crohn’s disease

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

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

FDA-approved indication and dosage:

<table>
<thead>
<tr>
<th>Indication</th>
<th>Recommended Dose</th>
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<tbody>
<tr>
<td>Otrexup is a folate analog metabolic inhibitor indicated for the:</td>
<td>• Otrexup is for once weekly subcutaneous use only. Administer Otrexup in the</td>
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<tr>
<td>• Management of patients with severe, active rheumatoid arthritis (RA)</td>
<td>abdomen or thigh.</td>
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<td>and polyarticular juvenile idiopathic arthritis (pJIA), who are</td>
<td>• Use another formulation of methotrexate for patients requiring oral,</td>
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<tr>
<td>intolerant of or had an inadequate response to first-line therapy</td>
<td>intramuscular, intravenous, intra-arterial, or intrathecal dosing, doses less</td>
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<tr>
<td>• Symptomatic control of severe, recalcitrant, disabling psoriasis in</td>
<td>than 7.5 mg per week, doses above 25 mg per week, high-dose regimens, or dose</td>
</tr>
<tr>
<td>adults who are not adequately responsive to other forms of therapy</td>
<td>adjustments of less than 5 mg increments</td>
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<tr>
<td>Limitation of Use</td>
<td>• Starting doses of methotrexate:</td>
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<tr>
<td>Otrexup is not indicated for the treatment of neoplastic diseases</td>
<td>– RA: 7.5 mg once weekly</td>
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<td></td>
<td>– pJIA: 10 mg/m2 once weekly</td>
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<td></td>
<td>– Psoriasis: 10 to 25 mg once weekly of an oral, intramuscular,</td>
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<td>subcutaneous, or intravenous formulation</td>
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<td>• Adjust dose gradually to achieve an optimal response</td>
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