Clinical Policy: Methotrexate (Otrexup, Rasuvo, Reditrex, Xatmep)

Reference Number: ERX.SPA.348
Effective Date: 12.01.19
Last Review Date: 11.21
Line of Business: Commercial, Medicaid

Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description
Methotrexate injection (Otrexup™, Rasuvo®, Reditrex™) and oral solution (Xatmep®) are folate analog metabolic inhibitors.

FDA Approved Indication(s)
Otrexup, Rasuvo, and Reditrex are indicated for:

- Management of selected adults with severe, active rheumatoid arthritis (RA), or children 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)
- In adults for the symptomatic control of severe, recalcitrant, disabling psoriasis (PsO) 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

Limitation(s) of use: Otrexup, Rasuvo, and Reditrex are not indicated for the treatment of neoplastic diseases.

Xatmep is indicated for:

- Treatment of pediatric patients with acute lymphoblastic leukemia (ALL) as part of a multi-phase, combination chemotherapy maintenance regimen
- Management of pediatric patients with active polyarticular juvenile idiopathic arthritis (pJIA) who have had an insufficient therepeutic response to, or are intolerant of, an adequate trial of first-line therapy including full dose NSAIDs

Policy/Criteria
Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

Health plan approved formularies should be reviewed for all coverage determinations. Requirements to use preferred alternative agents apply only when such requirements align with the health plan approved formulary.

It is the policy of health plans affiliated with Envolve Pharmacy Solutions™ that Otrexup, Rasuvo, Reditrex, and Xatmep are **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Polyarticular Juvenile Idiopathic Arthritis (must meet all)**:**

1. Diagnosis of pJIA;
2. Prescribed by or in consultation with a rheumatologist;
3. Member meets one of the following (a or b):
   a. For Otrexup, Rasuvo, or Reditrex: Age ≥ 2 years;
   b. For Xatmep: Age ≤ 18 years;
4. For Otrexup, Rasuvo, or Reditrex: Failure of generic methotrexate injection, unless contraindicated or clinically significant adverse effects are experienced;
5. For Xatmep: Documentation supports inability to swallow pills;
   Dose does not exceed the following (a or b):
   a. Otrexup, Ravuso, or Reditrex: 20 mg per week;

b. Xatmep: 30 mg/m^2 per week.

Approval duration: 6 months

B. Rheumatoid Arthritis or Psoriasis (must meet all)**:**
1. Diagnosis of RA or PsO;
2. Request is for Otrexup, Rasuvo, or Reditrex;
3. Prescribed by or in consultation with one of the following specialists (a or b):
   a. RA: Rheumatologist;
   b. PsO: Rheumatologist or a dermatologist;
4. Age ≥ 2 years;
5. Failure of generic methotrexate injection, unless contraindicated or clinically significant adverse effects are experienced;
6. Dose does not exceed the following (a or b):
   a. RA: 20 mg per week;
   b. PsO: 30 mg per week.

Approval duration: 6 months

C. Acute Lymphoblastic Leukemia (must meet all):
1. Diagnosis of ALL;
2. Request is for Xatmep;
3. Prescribed by or in consultation with an oncologist or hematologist;
4. Age < 18 years;
5. Documentation supports inability to swallow pills;
6. Request meets one of the following (a or b):*
   a. Dose does not exceed 30 mg/m^2 per week;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

**Prescribed regimen must be FDA-approved or recommended by NCCN*

Approval duration:
Commercial – Length of Benefit
Medicaid – 6 months

D. Other diagnoses/indications
1. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

II. Continued Therapy

A. All Indications in Section I (must meet all)**:**
1. Member meets one of the following (a or b):
   a. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;
   b. Documentation supports that member is currently receiving Xatmep for ALL and has received this medication for at least 30 days
2. Member is responding positively to therapy;
3. If request is for a dose increase, new dose does not exceed the following (a or b):
   a. Otrexup, Ravuso, or Reditrex:
      i. RA, pJIA: 20 mg per week;
      ii. Psoriasis: 30 mg per week;
   b. Xatmep:
      i. pJIA: 30 mg/m^2 per week;
      ii. ALL: Request meets one of the following (1 or 2):*
         1) New dose does not exceed 20 mg/m^2 per week;
         2) New dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

**Prescribed regimen must be FDA-approved or recommended by NCCN.*

Approval duration:

Commercial –
- **Xatmep:** Length of Benefit
- **Otrexup, Rasuvo, and Reditrex:** 12 months

Medicaid – 12 months

B. Other diagnoses/indications (must meet 1 or 2)**:**
1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions and documentation supports positive response to therapy.
   Approval duration: Duration of request or 6 months (whichever is less); or
2. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off-label use policy – ERX.PA.01 or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

ALL: acute lymphoblastic leukemia
FDA: Food and Drug Administration
NSAID: non-steroidal anti-inflammatory drug
PJIA: polyarticular juvenile idiopathic arthritis
PsO: psoriasis
RA: rheumatoid arthritis

Appendix B: Therapeutic Alternatives
This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
methotrexate injection	**RA** 7.5 mg SC once weekly **PJIA** 10 mg/m^2 SC once weekly **PsO** 10-25 mg SC once weekly	RA, pJIA: 20 mg/week; PsO: 30 mg/week
methotrexate tablets	**ALL, PJIA** 10 – 30 mg/m^2 once weekly	30 mg/m^2/week

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.

Appendix C: Contraindications/Boxed Warnings
- Contraindication(s):
  - Otrexup, Rasuvo, Reditrex: pregnancy; alcoholism or liver disease; immunodeficiency syndromes; pre-existing blood dyscrasias; hypersensitivity
  - Xatmep: pregnancy in patients with PJIA; severe hypersensitivity to methotrexate
- Boxed warning(s): severe toxic reactions, including embryo-fetal toxicity and death

Appendix D: General Information
- Otrexup, Rasuvo, and Reditrex are not indicated for the treatment of neoplastic diseases.

V. Dosage and Administration

Drug Name	Indication	Dosing Regimen	Maximum Dose
Methotrexate injection	RA	7.5 mg SC once weekly	20 mg/week
	PJIA	10 mg/m^2 SC once weekly	20 mg/week

Drug Name	Indication	Dosing Regimen	Maximum Dose
(Otrexup, Rasuvo, Reditrex)	PsO	10-25 mg SC once weekly	30 mg/week
Methotrexate oral solution (Xatmep)	ALL	20 mg/m^2 PO once weekly	20 mg/m^2/week
	PJIA	10 mg/m^2 PO once weekly	30 mg/m^2/week

VI. Product Availability

Drug Name	Availability
Methotrexate injection (Otrexup)	Auto-injector: 10 mg/0.4 mL, 12.5 mg/0.4 mL, 15 mg/0.4 mL, 17.5 mg/0.4 mL, 20 mg/0.4 mL, 22.5 mg/0.4 mL, 25 mg/0.4 mL
Methotrexate injection (Rasuvo)	Auto-injector: 7.5 mg/0.15 mL, 10 mg/0.2 mL, 12.5 mg/0.25 mL, 15 mg/0.3 mL, 17.5 mg/0.35 mL, 20 mg/0.4 mL, 22.5 mg/0.45 mL, 25 mg/0.5 mL, 27 mg/0.55 mL, 30 mg/0.6 mL
Methotrexate injection (Reditrex)	Single-dose pre-filled injection: 7.5 mg/0.3 mL, 10 mg/0.4 mL, 12.5 mg/0.5 mL, 15 mg/0.6 mL, 17.5 mg/0.7 mL, 20 mg/0.8 mL, 22.5 mg/0.9 mL, 25 mg/mL
Methotrexate oral solution (Xatmep)	2.5 mg/mL in a 60 mL or 120 mL bottle

VII. References

1. Otrexup Prescribing Information. Ewing, NJ: Antares Pharma, Inc. December 2019. Available at: www.otrexup.com. Accessed July 30, 2021.
2. Rasuvo Prescribing Information. Chicago, IL: Medac Pharma, Inc. March 2020. Availale at: http://cdn.rasuvo.com/assets/pdf/Prescribing-Information-current.pdf. Accessed July 30, 2021.
3. Reditrex Prescribing Information. Nashville, TN: Cumberland Pharmaceuticals, Inc.; November 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/210737s000lbl.pdf. Accessed July 30, 2021.
4. Xatmep Prescribing Information. Greenwood Village, CO: Silvergate Pharmaceuticals, Inc.; September 2020. Available at: www.xatmep.com. Accessed July 30, 2021.
5. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2021. Available at: http://www.clinicalpharmacology-ip.com/.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created.	12.01.19	11.19
RT4: added Reditrex to policy.	03.17.20	
4Q 2020 annual review: no significant changes; references reviewed and updated.	08.03.20	11.20
4Q 2021 annual review: added Xatmep; references reviewed and updated.	07.30.21	11.21

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members.