RXADVANCE
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Clinical Policy Title:	methotrexate
Policy Number:	RxA.304
Drug(s) Applied:	Otrexup™, Rasuvo®, Xatmep®
Original Policy Date:	02/07/2020
Last Review Date:	12/07/2020
Line of Business Policy Applies to:	All lines of business

Background

Methotrexate injection (Otrexup™, Rasuvo®) and oral solution (Xatmep®) are folate analog metabolic inhibitors. Otrexup™ and Rasuvo® 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™ and Rasuvo® 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 multiphase, combination chemotherapy maintenance regimen
- 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 NSAIDs

Dosing Information

Drug Name	Indication	Dosing Regimen	Maximum Dose
methotrexate injection (Otrexup™, Rasuvo®)	RA	7.5 mg SC once weekly	20 mg/week
methotrexate injection (Otrexup™, Rasuvo®)	PJIA	10 mg/m^2 SC once weekly	20 mg/week
methotrexate injection (Otrexup™, Rasuvo®)	PsO	10-25 mg SC once weekly	30 mg/week
methotrexate oral solution	ALL	20 mg/m^2 PO once	20 mg/m^2/week

(Xatmep®)		weekly	
methotrexate oral solution (Xatmep®)	PJIA	10 mg/m^2 PO once weekly	30 mg/m^2/week

Dosage Forms

- 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, 30 mg per 0.6 mL
- methotrexate oral solution (Xatmep®): 2.5 mg/mL in a 60 mL or 120 mL bottle

Clinical Policy

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

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™ or Rasuvo®: age ≥ 2 years;
   b. For Xatmep®: age ≤ 18 years;
4. For Otrexup™ or Rasuvo®: failure of generic methotrexate injection, unless contraindicated or clinically significant adverse effects are experienced;
5. For Xatmep®: documentation supports inability to swallow pills;
6. Dose does not exceed the following (a or b):
   a. Otrexup™ or Ravuso®: 20 mg per week;
   b. Xatmep®: 30 mg/m^2 per week.

Approval duration
Commercial: 6 months
Medicaid: 6 months
HIM: 6 months for Otrexup™ and Rasuvo®

B. Rheumatoid Arthritis or Psoriasis (must meet all):

1. Diagnosis of RA or PsO;
2. Request is for Otrexup™ or Rasuvo®;
3. For RA: prescribed by or in consultation with a rheumatologist;
4. For PsO: by or in consultation with a rheumatologist or a dermatologist;
5. Age ≥ 2 years;
6. Failure of generic methotrexate injection, unless contraindicated or clinically significant adverse effects are experienced;
7. Dose does not exceed the following (a or b):
   a. RA: 20 mg per week;
   b. Psoriasis: 30 mg per week.

Approval duration

Commercial: 6 months
Medicaid: 6 months
HIM: 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 20 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: 6 months
Medicaid: 6 months
HIM: 6 months

II. Continued Therapy Approval

A. All Indications in Section I (must meet all):
1. Member meets one of the following (a or b):
   a. Currently receiving medication that has been authorized by RxAdvance or member has previously met initial approval criteria listed in this policy;
   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™ or Ravuso®:
      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):*
         a) Dose does not exceed 20 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: Otrexup™ and Rasuvo®: 6 months; Xatmep®: 12 months
Medicaid: 12 months
HIM: 12 months for Otrexup™ and Rasuvo®

III. Appendices

APPENDIX A: Abbreviation Key
ALL: acute lymphoblastic leukemia
FDA: Food and Drug Administration

NSAID: non-steroidal anti-inflammatory
PJIA: polyarticular juvenile idiopathic arthritis
PsO: psoriasis
RA: rheumatoid arthritis

APPENDIX B: Therapeutic Alternatives

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®: Pregnancy; nursing mothers; alcoholism or liver disease; immunodeficiency syndromes; pre-existing blood dyscrasias; hypersensitivity
  - Xatmep®: Pregnancy; severe hypersensitivity to methotrexate

- Boxed warning(s):
  - Otrexup™, Rasuvo®: Fetal death and/or congenital anomalies; reduced elimination when impaired renal function; bone marrow suppression, aplastic anemia, gastrointestinal toxicity; hepatotoxicity, fibrosis and cirrhosis; methotrexate-induced lung disease; diarrhea and ulcerative stomatitis; malignant lymphomas; tumor lysis syndrome; severe, occasionally fatal, skin reactions; opportunistic infections; soft tissue necrosis and osteonecrosis when used with radiotherapy.
  - Xatmep®: Bone marrow suppression; serious infections; renal toxicity; gastrointestinal toxicity; hepatic toxicity; pulmonary toxicity; hypersensitivity and dermatologic reactions; embryo-fetal toxicity, including fetal death.

APPENDIX D: General Information

- Otrexup™ and Rasuvo® are not indicated for the treatment of neoplastic diseases.
- Xatmep® suppresses hematopoiesis and can cause severe and life-threatening pancytopenia, anemia, leukopenia, neutropenia, and thrombocytopenia.

References

1. Otrexup™ Prescribing Information. Ewing, NJ: Antares Pharma, Inc. December 2019. Available at: www.Otrexup.com. Accessed September 03 2020.
2. Rasuvo® Prescribing Information. Chicago, IL: Medexus Pharma, Inc. March 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/205776s004lbl.pdf . Accessed September 03, 2020.

3. Xatmep® Prescribing Information. Wilmington, MA: Azurity Pharmaceuticals, Inc.. March 2020. Available at: https://xatmep.com/Xatmep-Prescribing-Info.pdf . Accessed September 03, 2020.
4. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2018. Available at: http://www.clinicalpharmacology-ip.com/. Accessed September 03, 2020.
5. National Comprehensive Cancer Network. Acute lymphoblastic leukemia Version 2.2020. Available at: https://www.nccn.org/professionals/physician_gls/pdf/ped_all.pdf . Accessed September 08, 2020

Review/Revision History	Review/Revision Date	P&T Approval Date
Policy established.	01/2020	02/07/2020
Policy was reviewed 1. Policy was updated for formatting. 2. 'Line of business policy applies' to was updated to All lines of business 3. Continued Therapy criteria II.A.1 was rephrased to "Currently receiving medication that has been authorized by RxAdvance..." 4. Appendix D updated. 5. Reference was reviewed and updated.	09/08/2020	12/07/2020