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

Reference Number: CP.PHAR.134
Effective Date: 12.01.18
Last Review Date: 11.23

Coding Implications
Revision Log

Line of Business: Commercial, HIM, Medicaid

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®, Jylamvo®) 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 therapeutic response to, or are intolerant of, an adequate trial of first-line therapy including full dose NSAIDs

Jylamvo is indicated for:

- Treatment of adults with acute lymphoblastic leukemia (ALL) as part of a combination chemotherapy maintenance regimen
- Treatment of adults with mycosis fungoides (MF)
- Treatment of adults with relapsed or refractory non-Hodgkin lymphoma (NHL) as part of a metronomic combination regimen
- Treatment of adults with rheumatoid arthritis
- Treatment of adults with severe psoriasis

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.

It is the policy of health plans affiliated with Centene Corporation® that Otrexup, Rasuvo, Xatmep, Reditrex, and Jylamvo 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. Request is for Otrexup, Rasuvo, Reditrex, or Xatmep;
3. Prescribed by or in consultation with a rheumatologist;
4. Member meets one of the following (a or b):
   a. For Otrexup, Rasuvo, or Reditrex: Age ≥ 2 years;
   b. For Xatmep: Age ≤ 18 years;
5. For Otrexup, Rasuvo, or Reditrex: Failure of generic methotrexate injection, unless contraindicated or clinically significant adverse effects are experienced;
6. For Xatmep: Documentation supports inability to swallow pills;
7. 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:
Medicaid/HIM – 6 months
Commercial – *Otrexup, Rasuvo, and Reditrex*: 6 months or to the member's renewal date, whichever is longer; *Xatmep*: 12 months or duration of request, whichever is less

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

1. Diagnosis of RA or PsO;
2. Request is for Otrexup, Rasuvo, Reditrex, or Jylamvo;
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. Member meets one of the following (a or b):
   a. For Otrexup, Rasuvo, or Reditrex: Age ≥ 2 years;
   b. For Jylamvo: Age ≥ 18 years;
5. For Oxtrexup, Rasuvo, and Reditrex: Failure of generic methotrexate injection, unless contraindicated or clinically significant adverse effects are experienced;
6. For Jylamvo: Documentation supports inability to swallow pills;
7. Dose does not exceed 30 mg per week.

Approval duration:
Medicaid/HIM – 6 months
Commercial – *Oxtrexup, Rasuvo, and Reditrex*: 6 months or to the member's renewal date, whichever is longer; *Jylamvo*: 12 months or duration of request, whichever is less

C. Acute Lymphoblastic Leukemia (must meet all):

1. Diagnosis of ALL;
2. Request is for Xatmep or Jylamvo;
3. Prescribed by or in consultation with an oncologist or hematologist;
4. Member meets on of the following (a or b):

a. Xatmep: Age < 18 years;
b. Jylamvo: 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:
Medicaid/HIM – 6 months
Commercial – 12 months or duration of request, whichever is less

D. Mycosis Fungoides (must meet all)**:**

1. Diagnosis of MF;
2. Request is for Jylamvo;
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, b, or c):*
   a. Dose does not exceed 75 mg per week when administered as a single agent;
   b. Dose does not exceed 10 mg/m^2 twice weekly as part of a combination chemotherapy regimen;
   c. 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:
Medicaid/HIM – 6 months
Commercial – 12 months or duration of request, whichever is less

E. Non-Hodgkin Lymphoma (must meet all)**:**

1. Diagnosis of relapsed or refractory NHL;
2. Request is for Jylamvo;
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 10 mg 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:
Medicaid/HIM – 6 months
Commercial – 12 months or duration of request, whichever is less

F. Other diagnoses/indications (must meet 1 or 2)**:**
1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

II. Continued Therapy

A. All Indications in Section I (must meet all)**:**
1. Member meets one of the following (a, b, or c):
   a. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
   b. Member is currently receiving medication and is enrolled in a state and product with continuity of care regulations (*refer to state specific addendums for CC.PHARM.03A and CC.PHARM.03B);*
   c. 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, b, or c):
   a. Otrexup, Ravuso, or Reditrex (i or ii):
      i. pJIA: 20 mg per week;
      ii. RA, psoriasis: 30 mg per week;
   b. Xatmep (i or ii):
      i. pJIA: 30 mg/m^2 per week;
      ii. ALL: Request meets one of the following (1 or 2):*
         1) Dose does not exceed 20 mg/m^2 per week;
         2) 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*
   c. Jylamvo (i, ii, iii, or iv):
      i. RA, psoriasis: 30 mg per week;
      ii. ALL: Request meets one of the following (1 or 2):*
         1) Dose does not exceed 20 mg/m^2 per week;
         2) 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*

iii. MF: Request meets one of the following (1, 2, or 3):*
1) Dose does not exceed 75 mg per week when administered as a single agent;
2) Dose does not exceed 10 mg/m^2 twice weekly as part of a combination chemotherapy regimen;
3) 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*

iv. NHL: Request meets one of the following (1 or 2):*
1) Dose does not exceed 10 mg per week;
2) 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:
Medicaid/HIM – 12 months
Commercial – *Otrexup, Rasuvo, and Reditrex*: 6 months or to the member's renewal date, whichever is longer; *Xatmep and Jylamvo*: 12 months or duration of request, whichever is less

B. Other diagnoses/indications (must meet 1 or 2)**:**
1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

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 – CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid, or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation Key

ALL: acute lymphoblastic leukemia	MF: mycosis fungoides
FDA: Food and Drug Administration	NHL: non-Hodgkin lymphoma

NSAID: non-steroidal anti-inflammatory drug
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	pJIA: 20 mg/week; RA, PsO: 30 mg/week
methotrexate tablets	**ALL, PJIA** 10 – 30 mg/m^2 PO once weekly **MF** 25 mg – 75 mg PO once weekly or 10 mg/m^2 PO twice weekly **NHL** 2.5 mg PO two to four times weekly	ALL: 20 mg/m^2/week; MF: 75 mg/ week or 20 mg/m^2 /week; NHL: 10 mg/ week; pJIA: 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
  - Jylamvo: pregnant patients with non-neoplastic diseases; 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.
- Jylamvo is not approved for use in pediatric patients.

V. Dosage and Administration

Drug Name	Indication	Dosing Regimen	Maximum Dose
Methotrexate injection (Otrexup,	RA	7.5 mg SC once weekly	30 mg/week
	PJIA	10 mg/m^2 SC once weekly	20 mg/week
	PsO	10-25 mg SC once weekly	30 mg/week

Drug Name	Indication	Dosing Regimen	Maximum Dose
Rasuvo, Reditrex)			
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
Methotrexate oral solution (Jylamvo)	RA	7.5 – 20 mg PO once weekly	30 mg/ week
	PsO	10 – 25 mg PO once weekly	30 mg/ week
	ALL	20 mg/m^2 PO once weekly	20 mg/m^2/week
	NHL	2.5 mg PO two to four times weekly	10 mg/week
	MF	25 – 75 mg PO once weekly or 10 mg/m^2 PO twice weekly	75 mg/ week or 20 mg/m^2/week

VI. Product Availability

Drug	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, 27.5 mg/0.55 mL, 30 mg/0.6 mL
Methotrexate injection (Reditrex)	Single-dose pre-filled injection: 15 mg/0.6 mL, 20 mg/0.8 mL, 25 mg/mL
Methotrexate oral solution (Xatmep)	2.5 mg/mL in a 60 mL or 120 mL bottle
Methotrexate oral solution (Jylamvo)	2 mg/mLin a 60 mL bottle

VII. References

1. Otrexup Prescribing Information. Ewing, NJ: Antares Pharma, Inc. December 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/204824s010lbl.pdf. Accessed August 11, 2023.
2. Rasuvo Prescribing Information. Chicago, IL: Medac Pharma, Inc. March 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/205776s004lbl.pdf. Accessed August 11, 2023.
3. Xatmep Prescribing Information. Wilmington, MA: Azurity Pharmaceuticals; September 2020. Available at: https://xatmep.com/wp-content/uploads/2021/11/Xatmep-Prescribing-Info.pdf. Accessed August 11, 2023.
4. Reditrex Prescribing Information. Nashville, TN: Cumberland Pharmaceuticals, Inc.; March 2023. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/210737s002lbl.pdf. Accessed August 11, 2023.

5. Jylamvo Prescibing Information. Scotch Plains, NJ: Lukare Medical, LLC.; November 2022. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/212479s000lbl.pdf. Accessed August 14, 2023.
6. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2023. Available at: https://www.clinicalkey.com/pharmacology/. Accessed August 14, 2023.
7. Methotrexate; methotrexate sodium. National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at: http://www.nccn.org/professionals/drug_compendium. Accessed August 14, 2023.

Coding Implications
Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

HCPCS Codes	Description
J8610	Methotrexate, 2.5 mg
J8611	Methotrexate (jylamvo), oral, 2.5 mg
J8612	Methotrexate (xatmep), oral, 2.5 mg
J9255	Injection, methotrexate (accord) not therapeutically equivalent to J9250 or J9260, 50 mg
J9260	Injection, methotrexate sodium, 50 mg

Reviews, Revisions, and Approvals	Date	P&T Approval Date
4Q 2019 annual review: no significant changes; added HIM NF language for Xatmep; references reviewed and updated.	08.22.19	11.19
RT4: added Reditrex to policy; revised HIM-medical benefit to HIM line of business.	03.17.20	
4Q 2020 annual review: no significant changes; references reviewed and updated.	08.03.20	11.20
4Q 2021 annual review: no significant changes; references for HIM line of business off-label use revised from HIM.PHAR.21 to HIM.PA.154; references reviewed and updated.	07.30.21	11.21
Revised approval duration for Commercial line of business from length of benefit to 12 months or duration of request, whichever is less	09.27.21	02.22
4Q 2022 annual review: no significant changes; references reviewed and updated. Template changes applied to other diagnoses/indications and continued therapy section.	07.21.22	11.22
RT4: added new dosage formulation Jylamvo and criteria for MF and NHL indications; updated RA maximum dosing to 30 mg/week.	12.10.22	02.23
4Q 2023 annual review: removed Reditrex dosage strengths per label update; references reviewed and updated. Added HCPCS code [J9255].	08.14.23	11.23

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Removed HCPCS code [J9250]; revised HCPCS code [J9260] to refer to methotrexate sodium, 50 mg.	02.20.24	
Added HCPCS codes [J8611, J8612].	06.03.24	

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. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions, and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment, or medical care. It is not intended to dictate to providers how to practice medicine. 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. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.