

STEP THERAPY POLICY

- POLICY:** Methotrexate Injection Step Therapy Policy
- Methotrexate sodium (solution for injection, various manufacturers)
 - Otrexup™ (methotrexate subcutaneous injection autoinjector– Antares Pharma)
 - Rasuvo® (methotrexate subcutaneous injection autoinjector – Medac Pharma)
 - Reditrex™ (methotrexate subcutaneous injection prefilled syringe – Cumberland pharmaceuticals)

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OVERVIEW

Methotrexate has been widely studied and is commonly used for **treatment of inflammatory conditions**, including rheumatoid arthritis, juvenile idiopathic arthritis, and plaque psoriasis.¹ The mechanism of action is unknown; however, methotrexate may affect immune function. Methotrexate does interfere with DNA synthesis, repair, and cellular replication; actively proliferating tissues such as malignant cells, bone marrow, fetal cells, buccal and intestinal mucosa, and cells of the urinary bladder are generally more sensitive to this effect of methotrexate. It has been demonstrated that the bioavailability of injectable methotrexate is greater and less variable when compared with oral methotrexate.² Therefore, studies have demonstrated that injectable methotrexate dosage forms have provided superior efficacy compared with the same dosage of oral methotrexate. Moreover, studies have shown improved tolerance, particularly gastrointestinal tolerance, with injectable methotrexate compared with oral tablets.³ The toxicity profile, especially gastrointestinal distress, is a dose-limited adverse event and is often a primary reason for discontinuation of oral methotrexate.^{3,4}

All of the injectable methotrexate products require proper patient training in sterile injection technique and require a patient to have the manual dexterity to self-inject.⁵ For inflammatory conditions, the dose of methotrexate is initiated low and adjusted gradually to achieve optimal response and/or tolerability, generally to a maximum of 25 to 30 mg/week.^{1,6,7} Flexibility to decrease or increase methotrexate dosing, including in 2.5-mg increments, may be needed in clinical practice. Generic injectable methotrexate is available as a 25 mg/mL injection solution (single-dose and multi-dose vials) and provides flexibility in dose adjustments.⁵ Otrexup, Rasuvo, and Reditrex are available as preservative-free, single-dose injections for subcutaneous use.^{6,7} A formulation other than Otrexup, Rasuvo, or Reditrex should be used for patients who require a route of administration other than subcutaneous, for doses that are not available in the respective product, and for dose adjustments in < 2.5 mg increments.

POLICY STATEMENT

This program has been developed to encourage the use of a Step 1 Product prior to the use of a Step 2 Product. If the Step Therapy rule is not met for a Step 2 Product at the point of service, coverage will be determined by the Step Therapy criteria below. All approvals are provided for 1 year in duration. Note: Unless administered by a healthcare provider, all of the injectable methotrexate products, including Rasuvo, Otrexup, and Reditrex, require proper patient training in sterile injection technique and require a patient or caregiver to have the manual dexterity to inject.

Automation: A patient with a history of one Step 1 Product within the 130-day look-back period is excluded from Step Therapy.

Step 1: Generic methotrexate injection (single- or multi-dose vials)

Step 2: Otrexup, Rasuvo, Reditrex

CRITERIA

1. If the patient has tried one Step 1 Product, approve a Step 2 Product.
2. If, according to the prescriber, the patient and/or caregiver is/are unable to administer generic methotrexate injection (single-dose or multi-dose vial NOT including Otrexup, Rasuvo, or Reditrex), approve a Step 2 Product.
3. No other exceptions are recommended.

REFERENCES

1. Methotrexate injection [prescribing information]. Rockford, IL: Mylan; September 2014.
2. Braun J, Kästner P, Flaxenberg P, et al. Comparison of the clinical efficacy and safety of subcutaneous versus oral methotrexate in patients with active rheumatoid arthritis: results of a six-month, multicenter, randomized, double-blind, controlled, phase IV trial. *Arthritis Rheum*. 2008;58(1):73-81.
3. Wegrzyn J, Adeleine P, Miossec P. Better efficacy of methotrexate given by intramuscular injection than orally in patients with rheumatoid arthritis. *Ann Rheum Dis*. 2004;63(10):1232-1234.
4. Abolmaali SS, Tamaddon AM, Dinarvand R. A review of therapeutic challenges and achievements of methotrexate delivery systems for treatment of cancer and rheumatoid arthritis. *Cancer Chemother Pharmacol*. 2013;71(5):1115-1130.
5. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2020. Available at: <http://www.clinicalpharmacology-ip.com/Default.aspx>. Accessed on November 17, 2020. Search term: methotrexate.
6. Otrexup™ injection [prescribing information]. Ewing, NJ: Antares Pharma, Inc.; December 2019.
7. Rasuvo® injection [prescribing information]. Chicago, IL: Medac Pharma, Inc.; March 2020.
8. Reditrex™ injection [prescribing information]. Nashville, TN: Cumberland Pharmaceuticals; November 2019.