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Methotrexate Injectable Step Therapy Program Summary

FDA APPROVED INDICATIONS AND DOSAGE[1,2,7]

Agent(s)	Indication(s)	Dosage
Otrexup® (methotrexate) Subcutaneous injection	Management of patients 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 Symptomatic control of severe, recalcitrant, disabling psoriasis in adults who are not adequately responsive to other forms of therapy <u>Limitation of Use:</u> Not indicated for the treatment of neoplastic diseases	Starting doses: • RA: 7.5 mg once weekly • pJIA: 10 mg/m^2 once weekly • Psoriasis: 10-25 mg once weekly of an oral, intramuscular, subcutaneous, or intravenous formulation Adjust dose gradually to achieve optimal response
Rasuvo® (methotrexate) Subcutaneous injection	Management of patients 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 Symptomatic control of severe, recalcitrant, disabling psoriasis in adults who are not adequately responsive to other forms of therapy <u>Limitation of Use:</u> Not indicated for the treatment of neoplastic diseases	Starting doses: • RA: 7.5 mg once weekly of an oral or subcutaneous formulation • pJIA: 10 mg/m^2 once weekly • Psoriasis: 10-25 mg once weekly of an oral, intramuscular, subcutaneous, or intravenous formulation Adjust dose gradually to achieve optimal response
RediTrex® (methotrexate) Subcutaneous injection	Management of patients 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 Symptomatic control of severe, recalcitrant, disabling psoriasis in adults who are not adequately responsive to other forms of therapy <u>Limitation of Use:</u> Not indicated for the treatment of neoplastic diseases	Starting doses: • RA: 7.5 mg once weekly • pJIA: 10 mg/m^2 once weekly • Psoriasis: 10-25 mg once weekly of an oral, intramuscular, subcutaneous, or intravenous formulation Adjust dose gradually to achieve optimal response

CLINICAL RATIONALE

Methotrexate

Methotrexate (MTX) is commonly used for the treatment of patients with rheumatoid arthritis (RA), polyarticular juvenile idiopathic arthritis (pJIA), psoriasis, and other forms of autoimmune disease.[3] MTX inhibits folate metabolism and adenosine-receptor-mediated effects, thus diminishing inflammatory synovial cell turnover, decreasing exudation in the joint spaces, and impairing the response to histamine and other vasoactive substances.[5]

MTX can be given by oral or parenteral [i.e., intravenous (IV), intramuscular (IM), subcutaneous (SC)] routes. The existence of different routes of MTX has led to the conduction of pharmacokinetic studies designed to compare and highlight any significant differences in the drug's therapeutic impact.[3-5] Oral MTX has been a mainstay in the field of rheumatology and dermatology for decades, due to its efficacy, easy intake, and low cost. However, some patients may require higher doses of oral MTX within the therapeutic range that can be poorly tolerated. There is considerable interpatient variability of clinical and safety outcomes with low-dose MTX, which can be due to differences in patients' individual pharmacogenomic profile. Several studies support better bioavailability, higher efficacy, better tolerability (e.g., lower frequency of gastrointestinal toxicities), and better compliance of parenteral MTX as compared to oral MTX.[3-5] This does not mean that all patients should be treated with parenteral MTX; rather suggests that patients with an inadequate response and/or intolerance to oral MTX may benefit from parenteral MTX.

The pharmacokinetics of MTX received via oral, intramuscular (IM), and subcutaneous (SC) routes of administration was studied in patients with rheumatoid arthritis. The authors showed that mean bioavailability was significantly lower with MTX oral than with MTX parenteral, and that there was no significant difference between the IM and SC routes of administration.[4] In a separate study comparing IM and SC injections, values for the observed peak concentration, the time to the observed peak concentration, and the area under the time versus concentration curve for IM injections were not significantly different from these values for SC injections. These results suggest that IM and SC are interchangeable routes of administration.[5] In recent years, the use of subcutaneous injections gained in importance with the development of prefilled syringes containing MTX. Compared to injection by nursing staff, self-injection can increase patients' treatment adherence and reduce costs for society and patients by decreasing frequency of healthcare professionals' visits and transport. However, reduced manual dexterity, dependence on others, injection site reactions, and injection pain can impair compliance to MTX injections in patients with RA. Manual injections require grip and dexterity. This could be difficult in case of functional limitations due to joint pain and impaired mobility commonly encountered in RA patients. Prefilled auto-injector (AI) technology is a valuable response to such limitations. AIs automatically insert the needle and deliver a controlled and fixed dose of drug. Minimizing the pain at injection site, they are easy to learn and use and RA patients express a high level of satisfaction.[6]

Safety

Otrexup, Rasuvo and RediTrex carry a black box warning for the following:[1,2,7]

- Serious toxic reactions and death have been reported with the use of methotrexate. Patients should be closely monitored for bone marrow, liver, lung, skin, and kidney toxicities.
- Methotrexate has been reported to cause fetal death and/or congenital anomalies and is contraindicated in pregnancy.
- Unexpectedly severe (sometimes fatal) bone marrow suppression, aplastic anemia, and gastrointestinal toxicity have been reported with concomitant administration of methotrexate (usually in high dosage) along with some nonsteroidal anti-inflammatory drugs (NSAIDs).

- Hepatotoxicity, fibrosis, and cirrhosis may occur after prolonged use.
- Methotrexate may cause interstitial pneumonitis at any time during therapy and has been reported at low doses. Pulmonary symptoms (especially a dry, nonproductive cough) may require interruption of treatment and careful investigation.
- Diarrhea, ulcerative stomatitis, hemorrhagic enteritis, and death from intestinal perforation may occur.
- Severe, occasionally fatal, skin reactions have been reported.
- Potentially fatal opportunistic infections may occur.

The following are the current contraindications listed for Otrexup, Rasuvo, and Reditrex:
Otrexup and Rasuvo:

- Pregnancy
- Nursing mothers
- Alcoholism or liver disease
- Immunodeficiency syndromes
- Preexisting blood dyscrasias
- Hypersensitivity to methotrexate

RediTrex:

- Pregnancy
- Alcoholism or liver disease
- Immunodeficiency syndromes
- Preexisting blood dyscrasias
- Hypersensitivity to methotrexate

References

1. Otrexup prescribing information. Antares Pharma, Inc. December 2019.
2. Rasuvo prescribing information. Medac Pharma Inc. March 2018.
3. Vena GA, Cassano N, Iannone F. Update on Subcutaneous Methotrexate for Inflammatory Arthritis and Psoriasis. *Ther Clin Risk Manag*. 2018;14:105-116. Available at: www.ncbi.nlm.nih.gov/pmc/articles/PMC5767093/. Accessed on October 10, 2019.
4. Bianchi G, Caporali R, Todoerti M, Mattana P. Methotrexate and Rheumatoid Arthritis: Current Evidence Regarding Subcutaneous Versus Oral Routes of Administration. *Adv Ther.* 2016;33:369-378. Available at: www.ncbi.nlm.nih.gov/pmc/articles/PMC4833794/. Accessed on October 10, 2019.
5. Brooks PJ, Spruill WJ, Parish RC, Birchmore DA. Pharmacokinetics of Methotrexate Administered by Intramuscular and Subcutaneous Injections in Patients with Rheumatoid Arthritis. *Arthritis Rheum.* 1990;33(1):91-94. Available at: onlinelibrary.wiley.com/doi/epdf/10.1002/art.1780330112. Accessed on October 10, 2019.
6. Saraux A, Hudry C, Zinovieva E, et al. Use of Auto-Injector for Methotrexate Subcutaneous Self-Injections: High Satisfaction Level and Good Compliance in SELF-I Study, a Randomized, Open-Label, Parallel Group Study. *Rheumatol Ther.* 2019;6(1):47-60. Available at: www.ncbi.nlm.nih.gov/pmc/articles/PMC6393262/. Accessed on October 11, 2019.
7. RediTrex prescribing information. Cumberland Pharmaceuticals Inc. November 2019.

Methotrexate Injectable Step Therapy (Through Preferred Agents)

TARGET AGENT(S)

Preferred Agent(s)

Otrexup® (methotrexate auto-injector)

RediTrex® (methotrexate prefilled syringe)

Nonpreferred Agent(s)

Rasuvo® (methotrexate auto-injector)

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL

Otrexup, RediTrex will be approved when ONE of the following is met:

1. The requested agent is eligible for continuation of therapy AND ONE of the following:
    a. Information has been provided that indicates the patient is currently being treated with the requested agent within the past 90 days
    OR
    b. The prescriber states the patient is currently being treated with the requested agent within the past 90 days AND is at risk if therapy is changed

Agents Eligible for Continuation of Therapy
Otrexup
RediTrex

OR

2. The patient's medication history includes use of a generic methotrexate injectable within the past 90 days
OR
3. The patient has an intolerance or hypersensitivity to a generic methotrexate injectable agent
OR
4. The patient has an FDA labeled contraindication to ALL generic methotrexate injectable agents
OR
5. The prescriber has provided information that the patient has a physical or a mental disability that would prevent the patient from using ALL generic methotrexate injectable agents

Length of Approval: 12 months

Rasuvo will be approved when ONE of the following is met:

1. The requested agent is eligible for continuation of therapy AND ONE of the following:
    a. Information has been provided that indicates the patient is currently being treated with the requested agent within the past 90 days
    OR
    b. The prescriber states the patient is currently being treated with the requested agent within the past 90 days AND is at risk if therapy is changed

Agents Eligible for Continuation of Therapy
Rasuvo

OR

2. The patient's medication history includes use of a generic methotrexate injectable, Otrexup, AND RediTrex within the past 270 days
   OR
3. The patient has an intolerance or hypersensitivity to a generic methotrexate injectable agent, Otrexup, AND RediTrex
   OR
4. The patient has an FDA labeled contraindication to ALL generic methotrexate injectable agents, Otrexup, AND RediTrex
   OR
5. The prescriber has provided information that the patient has a physical or a mental disability that would prevent the patient from using ALL generic methotrexate injectable agents, Otrexup, AND RediTrex

Length of Approval: 12 months

