Methotrexate Injectable Step Therapy Program Summary

This program applies to FlexRx Closed, FlexRx Open, FocusRx, GenRx Closed, GenRx Open, Health Insurance Marketplace, and KeyRx formularies.

This is a FlexRx Standard and GenRx Standard program.

The BCBS MN Step Therapy Supplement also applies to this program for all Commercial/HIM lines of business

POLICY REVIEW CYCLE

Effective Date	Date of Origin
06-01-2024	07-01-2019

FDA APPROVED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Otrexup® (methotrexate) Subcutaneous injection	Management of selected adults with severe, active rheumatoid arthritis (RA) (ACR criteria), or children with polyarticular juvenile idiopathic arthritis (pJIA), who have had an insufficient therapeutic response to, or are intolerant of, an inadequate trial of first-line therapy including full dose non-steroidal anti-inflammatory agents (NSAIDs). Indicated in adults for the symptomatic control of severe, recalcitrant, disabling psoriasis 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 of Use: not indicated for the treatment of neoplastic diseases.		1
Rasuvo® (methotrexate) Subcutaneous injection	Management of selected adults with severe, active rheumatoid arthritis (RA) (ACR criteria), or children with polyarticular juvenile idiopathic arthritis (pJIA), who have had an insufficient therapeutic response to, or are intolerant of, an inadequate trial of first-line therapy including full dose non-steroidal anti-inflammatory agents (NSAIDs). Indicated in adults for the symptomatic control of severe, recalcitrant, disabling psoriasis 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 of Use: not indicated for the treatment of neoplastic diseases.		2
RediTrex® (methotrexate) Subcutaneous injection	Management of selected adults with severe, active rheumatoid arthritis (RA) (ACR criteria), or children with polyarticular juvenile idiopathic arthritis (pJIA), who have had an insufficient therapeutic response to, or are intolerant of, an inadequate trial of first-line therapy including full dose non-steroidal anti-inflammatory agents (NSAIDs). Indicated in adults for the symptomatic control of severe, recalcitrant, disabling psoriasis 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 of Use: not indicated for the treatment of neoplastic diseases.		7

See package insert for FDA prescribing information: https://dailymed.nlm.nih.gov/dailymed/index.cfm

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) Methotrexate inhibits dihydrofolic acid reductase. Dihydrofolates must be reduced to tetrahydrofolates by this enzyme before they can be utilized as carriers of one-carbon groups in the synthesis of purine nucleotides and thymidylate. Therefore, methotrexate interferes 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 in general more sensitive to this effect of methotrexate.(1,2,7) MTX can be given by oral or parenteral [i.e., intravenous (IV), intramuscular (IM), subcutaneous (SC)] route of administraton (ROA). The existence of different ROAs of MTX has led to the conduction of pharmacokinetic studies designed to compare and highlight any significant differences in the drug's therapeutic impact. 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 at various dosages in oral, intramuscular (IM), and subcutaneous (SC) formulations were studied in patients with RA. The authors showed that mean bioavailability was significantly lower with oral MTX than with parenteral MTX, and that there was no significant difference between the IM and SC ROAs. Overall, SC MTX is characterized by higher bioavailability, greater clinical efficacy, and a better tolerability profile than oral MTX, thus suggesting that the choice of the ROA route of administration is a fundamental parameter for optimizing treatment.(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 ROAs.(5) In recent years, the use of SC 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 have a boxed 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 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. Otrexup, Rasuvo, and RediTrex have the following contraindications:(1,2,7) • Pregnancy • Alcoholism or liver disease • Immunodeficiency syndromes • Preexisting blood dyscrasias • Hypersensitivity to methotrexate

REFERENCES

Number	Reference
1	Otrexup prescribing information. Antares Pharma, Inc. December 2019.
2	Rasuvo prescribing information. Medac Pharma Inc. March 2020.
3	Vena, G. A., Cassano, N., & Iannone, F. (2018). Update on subcutaneous methotrexate for inflammatory arthritis and psoriasis. Therapeutics and Clinical Risk Management, 14, 105–116. https://doi.org/10.2147/tcrm.s154745
4	Bianchi, G., Caporali, R., Todoerti, M., & Mattana, P. (2016). Methotrexate and rheumatoid arthritis: Current evidence regarding subcutaneous versus oral routes of administration. Advances in Therapy, 33(3), 369–378. https://doi.org/10.1007/s12325-016-0295-8
5	Brooks, P. J., Spruill, W. J., Parish, R. C., & Birchmore, D. A. (1990). Pharmacokinetics of Methotrexate Administered by Intramuscular and Subcutaneous Injections in Patients with Rheumatoid Arthritis. Arthritis & Rheumatology, 33(1), 91–94. https://doi.org/10.1002/art.1780330112
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. www.ncbi.nlm.nih.gov/pmc/articles/PMC6393262/
7	RediTrex prescribing information. Cumberland Pharmaceuticals Inc. March 2023.

POLICY AGENT SUMMARY STEP THERAPY

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Targeted MSC	Available MSC	Final Age Limit	Preferred Status
Otrexup ; Rasuvo	methotrexate soln pf auto-injector	10 MG/0.2ML ; 10 MG/0.4ML ; 12.5 MG/0.25ML ; 12.5 MG/0.4ML ; 15 MG/0.3ML ; 15 MG/0.4ML ; 17.5 MG/0.35ML ;	M ; N ; O	N		

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Targeted MSC	Available MSC	Final Age Limit	Preferred Status
		17.5 MG/0.4ML ; 20 MG/0.4ML ; 22.5 MG/0.45ML ; 22.5 MG/0.4ML ; 25 MG/0.4ML ; 25 MG/0.5ML ; 30 MG/0.6ML ; 7.5 MG/0.15ML				
Reditrex	methotrexate soln prefilled syringe	10 MG/0.4ML ; 12.5 MG/0.5ML ; 15 MG/0.6ML ; 17.5 MG/0.7ML ; 20 MG/0.8ML ; 22.5 MG/0.9ML ; 25 MG/ML ; 7.5 MG/0.3ML	M ; N ; O	N		

CLIENT SUMMARY – STEP THERAPY

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Otrexup ; Rasuvo	methotrexate soln pf auto-injector	10 MG/0.2ML ; 10 MG/0.4ML ; 12.5 MG/0.25ML ; 12.5 MG/0.4ML ; 15 MG/0.3ML ; 15 MG/0.4ML ; 17.5 MG/0.35ML ; 17.5 MG/0.4ML ; 20 MG/0.4ML ; 22.5 MG/0.45ML ; 22.5 MG/0.4ML ; 25 MG/0.4ML ; 25 MG/0.5ML ; 30 MG/0.6ML ; 7.5 MG/0.15ML	FlexRx Closed ; FlexRx Open ; FocusRx ; GenRx Closed ; GenRx Open ; Health Insurance Marketplace/BasicRx ; KeyRx
Reditrex	methotrexate soln prefilled syringe	10 MG/0.4ML ; 12.5 MG/0.5ML ; 15 MG/0.6ML ; 17.5 MG/0.7ML ; 20 MG/0.8ML ; 22.5 MG/0.9ML ; 25 MG/ML ; 7.5 MG/0.3ML	FlexRx Closed ; FlexRx Open ; FocusRx ; GenRx Closed ; GenRx Open ; Health Insurance Marketplace/BasicRx ; KeyRx

STEP THERAPY CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	TARGET AGENT(S) **Otrexup®** (methotrexate auto-injector) **Rasuvo®** (methotrexate auto-injector) **RediTrex®** (methotrexate prefilled syringe) **Target Agent(s)** will be approved when ONE of the following is met: 1. The patient is currently being treated with the requested agent as indicated by ALL of the following: A. A statement by the prescriber that the patient is currently taking the requested agent **AND** B. A statement by the prescriber that the patient is currently receiving a positive therapeutic outcome on requested agent **AND** C. The prescriber states that a change in therapy is expected to be ineffective or cause harm **OR** 2. The patient has a medication history of use of a generic methotrexate injectable agent as indicated by ONE of the following: A. Evidence of a paid claim(s) **OR** B. The prescriber has stated that the patient has tried a generic methotrexate injectable agent AND it was discontinued due to lack of effectiveness or an adverse event **OR** 3. The patient has an intolerance or hypersensitivity to a generic methotrexate injectable agent **OR**

Module	Clinical Criteria for Approval
	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 **OR** 6. The prescriber has provided documentation that ALL generic methotrexate injectable agents cannot be used due to a documented medical condition or comorbid condition that is likely to cause an adverse reaction, decrease ability of the patient to achieve or maintain reasonable functional ability in performing daily activities or cause physical or mental harm **Length of Approval:** 12 months