

Methotrexate Injectable Step Therapy Program Summary

POLICY REVIEW CYCLE

Effective Date
04-01-2024

Date of Origin

FDA APPROVED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Otrexup® (methotrexate) Subcutaneous injection	<p>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).</p> <p>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.</p> <p>Limitation of Use: not indicated for the treatment of neoplastic diseases.</p>		1
Rasuvo® (methotrexate) Subcutaneous injection	<p>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).</p> <p>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.</p> <p>Limitation of Use: not indicated for the treatment of neoplastic diseases.</p>		2
RediTrex® methotrexate) Subcutaneous injection	<p>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).</p> <p>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.</p> <p>Limitation of Use: not indicated for the treatment of neoplastic diseases.</p>		7

CLINICAL RATIONALE

Methotrexate	<p>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)</p> <p>MTX can be given by oral or parenteral [i.e., intravenous (IV), intramuscular (IM), subcutaneous (SC)] route of administration (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.</p> <p>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)</p>
Safety	<p>Otrexup, Rasuvo, and RediTrex have a boxed warning for the following:(1,2,7)</p> <ul style="list-style-type: none"> • 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

	<p>administration of methotrexate (usually in high dosage) along with some NSAIDs.</p> <ul style="list-style-type: none"> • 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. <p>Otrexup, Rasuvo, and RediTrex have the following contraindications:(1,2,7)</p> <ul style="list-style-type: none"> • Pregnancy • Alcoholism or liver disease • Immunodeficiency syndromes • Preexisting blood dyscrasias • Hypersensitivity to methotrexate
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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. <i>Therapeutics and Clinical Risk Management</i> , 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. <i>Advances in Therapy</i> , 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. <i>Arthritis & Rheumatology</i> , 33(1), 91–94. https://doi.org/10.1002/art.1780330112
6	Saroux 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. <i>Rheumatol Ther</i> . 2019;6(1):47-60. Available at: 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
Step Therapy (Through Preferred Agents) - Otrexup, RediTrex						
Otrexup	methotrexate soln pf auto-injector	20 MG/0.4ML	M ; N ; O	N		
Otrexup	Methotrexate Soln PF Auto-Injector 10 MG/0.4ML	10 MG/0.4ML	M ; N ; O	N		
Otrexup	Methotrexate Soln PF Auto-Injector 12.5 MG/0.4ML	12.5 MG/0.4ML	M ; N ; O	N		

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Targeted MSC	Available MSC	Final Age Limit	Preferred Status
Otrexup	Methotrexate Soln PF Auto-Injector 15 MG/0.4ML	15 MG/0.4ML	M ; N ; O	N		
Otrexup	Methotrexate Soln PF Auto-Injector 17.5 MG/0.4ML	17.5 MG/0.4ML	M ; N ; O	N		
Otrexup	Methotrexate Soln PF Auto-Injector 22.5 MG/0.4ML	22.5 MG/0.4ML	M ; N ; O	N		
Otrexup	Methotrexate Soln PF Auto-Injector 25 MG/0.4ML	25 MG/0.4ML	M ; N ; O	N		
Rasuvo	methotrexate soln pf auto-injector	20 MG/0.4ML	M ; N ; O	N		
Rasuvo	Methotrexate Soln PF Auto-Injector 10 MG/0.2ML	10 MG/0.2ML	M ; N ; O	N		
Rasuvo	Methotrexate Soln PF Auto-Injector 12.5 MG/0.25ML	12.5 MG/0.25ML	M ; N ; O	N		
Rasuvo	Methotrexate Soln PF Auto-Injector 15 MG/0.3ML	15 MG/0.3ML	M ; N ; O	N		
Rasuvo	Methotrexate Soln PF Auto-Injector 17.5 MG/0.35ML	17.5 MG/0.35ML	M ; N ; O	N		
Rasuvo	Methotrexate Soln PF Auto-Injector 22.5 MG/0.45ML	22.5 MG/0.45ML	M ; N ; O	N		
Rasuvo	Methotrexate Soln PF Auto-Injector 25 MG/0.5ML	25 MG/0.5ML	M ; N ; O	N		
Rasuvo	Methotrexate Soln PF Auto-Injector 30 MG/0.6ML	30 MG/0.6ML	M ; N ; O	N		
Rasuvo	Methotrexate Soln PF Auto-Injector 7.5 MG/0.15ML	7.5 MG/0.15ML	M ; N ; O	N		
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	methotrexate soln pf auto-injector	20 MG/0.4ML	Commercial ; HIM ; ResultsRx
Otrexup	Methotrexate Soln PF Auto-Injector 10 MG/0.4ML	10 MG/0.4ML	Commercial ; HIM ; ResultsRx
Otrexup	Methotrexate Soln PF Auto-Injector 12.5 MG/0.4ML	12.5 MG/0.4ML	Commercial ; HIM ; ResultsRx
Otrexup	Methotrexate Soln PF Auto-Injector 15 MG/0.4ML	15 MG/0.4ML	Commercial ; HIM ; ResultsRx
Otrexup	Methotrexate Soln PF Auto-Injector 17.5 MG/0.4ML	17.5 MG/0.4ML	Commercial ; HIM ; ResultsRx
Otrexup	Methotrexate Soln PF Auto-Injector 22.5 MG/0.4ML	22.5 MG/0.4ML	Commercial ; HIM ; ResultsRx
Otrexup	Methotrexate Soln PF Auto-Injector 25 MG/0.4ML	25 MG/0.4ML	Commercial ; HIM ; ResultsRx
Rasuvo	methotrexate soln pf auto-injector	20 MG/0.4ML	Commercial ; HIM ; ResultsRx
Rasuvo	Methotrexate Soln PF Auto-Injector 10 MG/0.2ML	10 MG/0.2ML	Commercial ; HIM ; ResultsRx
Rasuvo	Methotrexate Soln PF Auto-Injector 12.5 MG/0.25ML	12.5 MG/0.25ML	Commercial ; HIM ; ResultsRx
Rasuvo	Methotrexate Soln PF Auto-Injector 15 MG/0.3ML	15 MG/0.3ML	Commercial ; HIM ; ResultsRx
Rasuvo	Methotrexate Soln PF Auto-Injector 17.5 MG/0.35ML	17.5 MG/0.35ML	Commercial ; HIM ; ResultsRx

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Rasuvo	Methotrexate Soln PF Auto-Injector 22.5 MG/0.45ML	22.5 MG/0.45ML	Commercial ; HIM ; ResultsRx
Rasuvo	Methotrexate Soln PF Auto-Injector 25 MG/0.5ML	25 MG/0.5ML	Commercial ; HIM ; ResultsRx
Rasuvo	Methotrexate Soln PF Auto-Injector 30 MG/0.6ML	30 MG/0.6ML	Commercial ; HIM ; ResultsRx
Rasuvo	Methotrexate Soln PF Auto-Injector 7.5 MG/0.15ML	7.5 MG/0.15ML	Commercial ; HIM ; ResultsRx
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	Commercial ; HIM ; ResultsRx

STEP THERAPY CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval		
ST (preferred agents)	<p>TARGET AGENT(S)</p> <p>Preferred Agent(s)</p> <p>Otrexup (methotrexate auto-injector) RediTrex (methotrexate prefilled syringe)</p> <p>Non-preferred Agent(s)</p> <p>Rasuvo (methotrexate auto-injector)</p> <p>Otrexup, RediTrex will be approved when ONE of the following is met:</p> <p>1. The requested agent is eligible for continuation of therapy AND ONE of the following:</p> <table><tr><td>Agents Eligible for Continuation of Therapy</td></tr><tr><td>Otrexup Reditrex</td></tr></table> <p>A. Information has been provided that indicates the patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days OR</p> <p>B. The prescriber states the patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days AND is at risk if therapy is changed OR</p> <p>2. The patient has a medication history of use in the past 90 days with ONE generic injectable methotrexate agent OR</p> <p>3. The patient has an intolerance or hypersensitivity to ONE generic injectable methotrexate agent OR</p> <p>4. The patient has an FDA labeled contraindication to ALL generic injectable methotrexate agents OR</p> <p>5. There is information that the patient has a physical or a mental disability that would prevent the patient from using ALL generic injectable methotrexate agents</p> <p>Length of Approval: 12 months</p> <p>Rasuvo will be approved when ONE of the following is met:</p>	Agents Eligible for Continuation of Therapy	Otrexup Reditrex
Agents Eligible for Continuation of Therapy			
Otrexup Reditrex			

Module	Clinical Criteria for Approval		
	<p>1. The requested agent is eligible for continuation of therapy AND ONE of the following:</p> <table><tr><th>Agents Eligible for Continuation of Therapy</th></tr><tr><td>Rasuvo</td></tr></table> <p>A. Information has been provided that indicates the patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days OR</p> <p>B. The prescriber states the patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days AND is at risk if therapy is changed OR</p> <p>2. The patient has a medication history of use in the past 270 days of generic injectable methotrexate agent, Otrexup, AND Reditrex OR</p> <p>3. The patient has an intolerance or hypersensitivity to generic injectable methotrexate agent, Otrexup, AND Reditrex OR</p> <p>4. The patient has an FDA labeled contraindication to ALL generic injectable methotrexate agents, Otrexup, AND RediTrex OR</p> <p>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 injectable methotrexate agents, Otrexup, AND RediTrex</p> <p>Length of Approval: 12 months</p>	Agents Eligible for Continuation of Therapy	Rasuvo
Agents Eligible for Continuation of Therapy			
Rasuvo			