Otrexup (methotrexate)

STRENGTH	DOSAGE FORM	ROUTE	GPID
10, 15, 20, 25mg per 0.4mL	auto injector	subcutaneous	35427, 35428, 35437, 35438

MANUFACTURER

Antares Pharma, Inc.

INDICATION(S)

Otrexup is a folate analog metabolic inhibitor indicated for the:
• 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

Limitation of Use: Otrexup is not indicated for the treatment of neoplastic diseases.

DRUG CLASS

INFLAMMATORY DISEASE; ANTI-ARTHRITIC, FOLATE ANTAGONIST AGENTS

PLACE IN THERAPY

Otrexup is the first FDA-approved methotrexate for once-weekly subcutaneous self-administration in a single-dose, disposable autoinjector. Methotrexate (MTX) has been used for the treatment of rheumatoid arthritis (RA) and psoriasis since 1951 and is currently available as a tablet and as solution for injection which may be given by the intramuscular (IM), intravenous (IV), intra-arterial (IA), or intrathecal (IT) route; however, the MTX package insert mentions that it can be administered subcutaneously for better absorption and fewer gastrointestinal side effects in children. In the dosage range used to treat RA and psoriasis, oral MTX has variable absorption. As the dose of MTX is increased from a starting dose of 7.5 mg to the typical maintenance weekly doses employed in RA, bioavailability may decrease by a mean of 13.5 percent. At a 17.5 to 20 mg weekly dose of MTX, a 13.5 percent difference is equivalent to one full 2.5 mg MTX tablet. At higher doses, decreased bioavailability may be even more pronounced. This was illustrated in a pharmacokinetic analysis of 15 patients taking more than 25 mg/week of MTX (mean of 30 mg/week); the ratio of oral to subcutaneous absorption was decreased by approximately one-third. Thus, patients may appear to respond better to parenteral therapy, when the actual explanation is that more drug is reaching the circulation. For patients in whom doses of at least 15 mg once weekly are ineffective or poorly tolerated, a trial of subcutaneous methotrexate administration is an alternative to switching to another DMARD or to adding a TNF inhibitor. An alternative approach to switching to parenteral MTX is splitting the oral dose, giving it every 12 hours on the same day each week. In this manner, a dose of oral MTX which would have decreased bioavailability could be split into two lesser doses, each with improved bioavailability.

The American College of Rheumatology RA treatment guidelines recommend DMARDs (i.e. methotrexate, hydroxychloroquine, leflunomide, minocycline and sulfasalazine) as first line

pharmacological treatment. Failure with a DMARD is followed by a trial of one or more TNF inhibitors (Humira, Cimzia, Enbrel, Simponi, and Remicade) followed by a non-TNF biologic such as Orencia (T-cell costimulation modulator), Ritxuan (B-cell CD20 antagonist) and Actemra (IL-6 receptor antagonist).

EFFICACY

In relative bioavailability studies in rheumatoid arthritis patients, systemic exposure of methotrexate was found to be similar between Otrexup and intramuscular or subcutaneous administration of methotrexate injection at the same doses, however systemic exposure of methotrexate was higher with Otrexup as compared to oral administration of methotrexate at the same dose. Bioavailability following oral dosing showed a plateau effect at doses of 15 mg and greater. The systemic exposure of methotrexate from Otrexup at doses of 10, 15, 20, and 25 mg was higher than that of oral methotrexate by 17, 13, 31, and 36%, respectively. Methotrexate systemic absorption from Otrexup was similar when administered into the abdomen or thigh.

Clinical trials in patients with rheumatoid arthritis and polyarticular juvenile idiopathic arthritis were performed using other formulations of methotrexate.

In patients with rheumatoid arthritis, effects of methotrexate on articular swelling and tenderness can be seen as early as 3 to 6 weeks. Most studies of methotrexate in patients with rheumatoid arthritis are relatively short term (3 to 6 months). Limited data from long-term studies indicate that an initial clinical improvement is maintained for at least two years with continued therapy.

In a 6-month double-blind, placebo-controlled trial of 127 pediatric patients with pJIA (mean age, 10.1 years; age range, 2.5 to 18 years; mean duration of disease, 5.1 years) on background nonsteroidal anti-inflammatory drugs and/or prednisone, methotrexate given weekly at an oral dose of 10 mg/m^2 provided significant clinical improvement compared to placebo as measured by either the physician's global assessment, or by a patient composite (25% reduction in the articular-severity score plus improvement in parent and physician global assessments of disease activity). Over two-thirds of the patients in this trial had polyarticular-course JIA, and the numerically greatest response was seen in this subgroup treated with 10 mg/m^2/wk methotrexate. The overwhelming majority of the remaining patients had systemic-course JIA. All patients were unresponsive to NSAIDs; approximately one-third were using low dose corticosteroids. Weekly methotrexate at a dose of 5 mg/m^2 was not significantly more effective than placebo in this trial.

SAFETY

As with other formulations of methotrexate, Otrexup has a lengthy black box warning that discusses its contraindications in further detail.

Otrexup has a number of contraindications including:

- Alcoholism or Liver Disease
- Immunodeficiency Syndromes
- Preexisting Blood Dyscrasias (i.e. bone marrow hypoplasia, leukopenia, thrombocytopenia, or significant anemia)
- Pregnancy and lactation (Pregnancy Category X)

Furthermore, the black box warning discusses other warnings and precautions such as methotrexate-induced lung disease, hemorrhagic enteritis and death from intestinal perforation, malignant lymphomas, severe (occasionally fatal) skin reactions, potentially fatal opportunistic infections, tumor lysis syndrome, and the risk of soft tissue necrosis and osteonecrosis when given concomitantly with radiotherapy.

Common adverse reactions include nausea, abdominal pain, dyspepsia, stomatitis/mouth sores, rash, nasopharyngitis, diarrhea, liver function test abnormalities, vomiting, headache, bronchitis, thrombocytopenia, alopecia, leucopenia, pancytopenia, dizziness, photosensitivity, and "burning of skin lesions".

DOSAGE

Otrexup should be administered subcutaneously in the abdomen or the thigh as a single-dose auto-injector for once-weekly use only. Otrexup is only available in doses between 10 to 25 mg in 5 mg increments. Use another formulation of methotrexate in patients who require less than 10 mg per week, doses more than 25 mg per week, or dose adjustments of less than 5 mg increments.

Recommended starting dose of methotrexate are as follows:

- Adult RA: single doses of 7.5 mg weekly
- pJIA: 10 mg/m^2 once weekly
- Psoriasis: 10 to 25 mg once weekly

For patients switching from oral methotrexate to Otrexup, consider any differences in bioavailability between oral and subcutaneously administered methotrexate. Adjust dose gradually to achieve an optimal response. Limited experience shows a significant increase in the incidence and severity of serious toxic reactions, especially bone marrow suppression, at doses greater than 20 mg per week in adults. Although there is experience with doses up to 30mg/m^2/week in children, there is little published data to assess how doses over 20 mg/m^2/week might affect the risk of serious toxicity in children.

For psoriasis, 30 mg per week should not ordinarily be exceeded. Once optimal clinical response has been achieved, the dosage should be reduced to the lowest possible amount of drug and to the longest possible rest period.

COST

Drug	Cost/unit	Cost per 30 Days
Otrexup (methotrexate) 10, 15, 20, 25mg per 0.4mL	AWP=$164.40	$658
methotrexate 2.5mg tablet	MAC=$2.59	$83-124*
methotrexate solution for injection (preservative-free) 25mg/mL, 50mg/2mL, 100mg/4mL, 200mg/8mL, 250mg/10mL, 1g/40mL	MAC=$1.86/mL	$8-12*

*Cost is based on the following: Adult RA 20mg/week and psoriasis 30mg per week.

FORMULARY PLACEMENT RECOMMENDATIONS

Based on this initial assessment of available clinical and financial information, consider NOT ADDING Otrexup to the formulary pending complete review by the appropriate oversight committee for the plan.

REFERENCES

- Otrexup [Prescribing Information]. Ewing, NJ: Antares Pharma, Inc; October 2013.
- Methotrexate [Prescribing Information]. Sellersville, PA Teva Pharmaceuticals USA; April 2012.
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- American College of Rheumatology Committee to Reevaluate Improvement Criteria. A proposed revision to the ACR20: the hybrid measure of American College of Rheumatology response. Arthritis Rheum 2007;57:193-202.