

**MTF Formulary Management for Anti-Rheumatic Drugs; Injectable Methotrexate Subclass**  
 Defense Health Agency Pharmacy Operations Division

**Bottom Line**

- MTF utilization of oral methotrexate is significantly higher than the injectable methotrexate products.
- Generic methotrexate 50 mg/2 mL vials are the most commonly dispensed injectable methotrexate formulation in the MHS.
- Subcutaneous (SC) methotrexate dosed conventionally using the vials is significantly more effective than the oral route at the same dose. Both oral and SC methotrexate have similar tolerability profiles.
- Two new SC auto-injector formulations of MTX, Otrexup and Rasuvo, are now available.
- Aside from the patient convenience factor, Otrexup and Rasuvo methotrexate auto-injectors offer no additional clinical advantages than the generic injectable MTX 50 mg/2 mL vials. They were designated as nonformulary. Manual prior authorization is now required in new users see below).

**Uniform Formulary Decision:** The Director, DHA, approved the recommendations from the November 2015 DoD P&T Committee meeting on January 29, 2016, with an implementation date of May 4, 2016.

Injectable MTX Uniform Formulary (UF) drugs		Injectable MTX Nonformulary (NF) drugs
BCF drugs — MTFs <u>must</u> have on formulary	MTFs <u>may</u> have on formulary*	MTFs <u>must not</u> have on formulary
None*	<ul style="list-style-type: none"> <li>• Injectable MTX – generic 50 mg/2 mL vials</li> </ul>	<ul style="list-style-type: none"> <li>• Injectable MTX (Otrexup auto-injector)**</li> <li>• Injectable MTX (Rasuvo auto-injector)**</li> </ul>
* Note that generic methotrexate 2.5 mg tablets are BCF as part of the Anti-Rheumatics Drug Class **Prior Authorization applies (see below)		

**Clinical Summary**

**Methotrexate Low Dose Oral and Injectable Vial Formulations**

- Methotrexate absorption via the oral route is variable, especially at doses greater than 15 mg. Subcutaneously injected methotrexate is completely absorbed.
- Anecdotal observations report that some gastrointestinal (GI) toxicities may be avoided by administering methotrexate by the subcutaneous (SC) route, rather than orally.
- A 2008 randomized controlled trial comparing the efficacy and safety of oral and SC methotrexate reported SC administration was significantly more effective than oral administration at the same dose, with no difference in tolerability profiles.

**Methotrexate Low Dose Injectable Vials vs. Auto-Injector Formulations Methotrexate (Otrexup and Rasuvo)**

- There are no head-to-head trials or systematic reviews comparing the different types of injectable methotrexate formulations.
- The two new MTX auto-injectors, Otrexup and Rasuvo, were FDA-approved through 505(b)(2) applications by demonstrating bioequivalence to the generic injectable methotrexate vial formulation.
- There are no clinical trials that demonstrate Otrexup or Rasuvo auto-injectors provide greater benefit to patients over oral or conventionally injected methotrexate using vials. There is no comparative effectiveness, safety, or tolerability data.

- The auto-injectors have the same black box warnings, contraindications, and precautions as oral methotrexate.
- The most common adverse events (occurring at an incidence  $\geq 5\%$ ) include nausea, abdominal pain, dyspepsia, stomatitis/mouth sores, rash, nasopharyngitis, diarrhea, liver function test abnormalities, vomiting, headache, and diarrhea.
- While offering patient convenience, the auto-injector formulations of Otrexup and Rasuvo offer no additional clinical advantages over generic methotrexate vials. The benefit of the new products may be limited to a select group of patients with limited vision, decreased finger dexterity, or impaired cognition.

### Prior Authorization (PA) Criteria and Quantity Limits

- All new users of Otrexup and Rasuvo are required to undergo the manual PA.
- Otrexup or Rasuvo will be approved if the following:
  - The patient has experienced intolerance or significant adverse effects from generic injectable methotrexate vials. OR
  - The patient has decreased finger dexterity, limited vision, or impaired cognition resulting in the inability to utilize generic injectable MTX.
- Quantity Limits for Otrexup and Rasuvo are set at 12 auto-injectors/90 days at the MTFs.

### References

- The Cochrane Library 2014, Issue 6.
- Arthritis Rheum. 2008 Jan;58(1):73-81.
- DoD P&T Committee minutes: <http://www.health.mil/PandT>
- Current/future drug classes under review by the DoD P&T Committee: <http://www.health.mil/About-MHS/Other-MHS-Organizations/DoD-Pharmacy-and-Therapeutics-Committee>
- TRICARE Formulary Search Tool: <http://www.health.mil/formulary>
- Prior Authorization/Medical Necessity forms: See Formulary Search Tool above.
- Formulary Management Documents (including this one) available at: <http://www.health.mil/DoDPTResources>
- Point of contact for additional information: [dha.jbsa.pharmacy.list.poduf@mail.mil](mailto:dha.jbsa.pharmacy.list.poduf@mail.mil)

Injectable Methotrexate Price Comparison at MTF	
Drug	MTF cost/month (Nov 2015)
<b>Basic Core Formulary</b>	
No Injectable MTX products are designated as BCF	
MTX generic 2.5 tablets (Anti-Rheumatics Drug Class)	<b>\$ Most Cost-Effective</b>
<b>Uniform Formulary</b>	
MTX injectable – generic 50 mg/2 mL vials	<b>\$ Most Cost-Effective</b>
MTX injectable (Otrexup)	<b>\$\$\$\$ Least Cost-Effective</b>
MTX injectable (Rasuvo)	<b>\$\$\$\$ Least Cost-Effective</b>
Legend:	
<b>\$</b>	= “Most Cost-Effective” represents Rx with the <u>lowest cost</u> and best clinical efficacy
<b>\$\$</b>	= “Less Cost-Effective” represents <u>higher cost</u> Rx with similar clinical efficacy
<b>\$\$\$</b>	= “Less Cost-Effective” represents <u>next higher cost</u> Rx with similar clinical efficacy
<b>\$\$\$\$</b>	= “Least Cost-Effective” represents Rx with the <u>highest cost</u> with similar clinical efficacy