HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use OTREXUP™ safely and effectively. See full prescribing information for OTREXUP.

OTREXUP (methotrexate) injection, for subcutaneous use
Initial U.S. Approval: 1953

WARNING: SEVERE TOXIC REACTIONS, INCLUDING EMBRYO-FETAL TOXICITY AND DEATH
See full prescribing information for complete boxed warning.
• 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 (5.1).
• Methotrexate has been reported to cause fetal death and/or congenital anomalies and is contraindicated in pregnancy (4, 5.2).
• 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) (5.1).
• Hepatotoxicity, fibrosis, and cirrhosis may occur after prolonged use (5.1).
• 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 (5.1).
• Diarrhea, ulcerative stomatitis, hemorrhagic enteritis, and death from intestinal perforation may occur (5.1).
• Severe, occasionally fatal, skin reactions have been reported (5.1).
• Potentially fatal opportunistic infections may occur (5.1).

----------RECENT MAJOR CHANGES----------
Dosage and Administration (2) 11/2014

----------INDICATIONS AND USAGE----------
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 (1.1)
- Symptomatic control of severe, recalcitrant, disabling psoriasis in adults who are not adequately responsive to other forms of therapy (1.2)

Limitation of Use
Otrexup is not indicated for the treatment of neoplastic diseases (1.3).

----------DOSAGE AND ADMINISTRATION----------
- Otrexup is for once weekly subcutaneous use only. Administer Otrexup in the abdomen or thigh. (2.1)
- Use another formulation of methotrexate for patients requiring oral, intramuscular, intravenous, intra-arterial, or intrathecal dosing, doses less than 7.5 mg per week, doses above 25 mg per week, high-dose regimens, or dose adjustments of less than 5 mg increments (2.1)
- Starting doses of methotrexate:
  - RA: 7.5 mg once weekly (2.2)
  - pJIA: 10 mg/m^2 once weekly (2.2)
  - Psoriasis: 10 to 25 mg once weekly of an oral, intramuscular, subcutaneous, or intravenous formulation (2.3)
- Adjust dose gradually to achieve an optimal response (2.2, 2.3)

----------DOSAGE FORMS AND STRENGTHS----------
Injection: Single-dose auto-injector delivering 0.4 mL of methotrexate in the following dosage strengths: 7.5 mg, 10 mg, 15 mg, 20mg, and 25 mg (3).

----------CONTRAINDICATIONS----------
- Pregnancy (4)
- Nursing mothers (4)
- Alcoholism or liver disease (4)
- Immunodeficiency syndromes (4)
- Preexisting blood dyscrasias (4)
- Hypersensitivity to methotrexate (4)

----------WARNINGS AND PRECAUTIONS----------
- Organ system toxicity: Potential for serious toxicity. Only for use by physicians experienced in antimetabolite therapy (5.1).
- Embryo-fetal toxicity: Exclude pregnancy before treatment. Avoid pregnancy if either partner is receiving Otrexup. Advise males to avoid pregnancy for a minimum of three months after therapy and females to avoid pregnancy for at least one ovulatory cycle after therapy (5.2).
- Effects on reproduction: May cause impairment of fertility, oligospermia and menstrual dysfunction (5.3)
- Laboratory tests: Monitor complete blood counts, renal function and liver function tests (5.4).
- Risks from improper dosing: Mistaken daily use has led to fatal toxicity (5.5)
- Patients with impaired renal function, ascites, or pleural effusions: Elimination is reduced (5.6).
- Dizziness and fatigue: May impair ability to drive or operate machinery (5.7)

----------ADVERSE REACTIONS----------
Common adverse reactions are: 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" (6).

To report SUSPECTED ADVERSE REACTIONS, contact Antares at 1-855-Otrexup (1-855-687-3987) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Aspirin, NSAIDs, and steroids: concomitant use may elevate and prolong serum methotrexate levels and cause increased toxicity (7.1)
- Proton pump inhibitors: concomitant use may elevate and prolong serum methotrexate levels and cause increased toxicity (7.2)

----------USE IN SPECIFIC POPULATIONS----------
- Pediatric use: Safety and efficacy of methotrexate, including Otrexup, have not been established in pediatric patients with psoriasis. Safety and efficacy of Otrexup have not been established in pediatric patients with malignancy (8.4)
- Geriatric use: Use caution in dose selection (8.5)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 11/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

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FULL PRESCRIBING INFORMATION

WARNING: SEVERE TOXIC REACTIONS, INCLUDING EMBRYO-FETAL TOXICITY AND DEATH

Otrexup should be used only by physicians whose knowledge and experience include the use of antimetabolite therapy. Because of the possibility of serious toxic reactions (which can be fatal), Otrexup should be used only in patients with psoriasis or rheumatoid arthritis with severe, recalcitrant, disabling disease which is not adequately responsive to other forms of therapy. Deaths have been reported with the use of methotrexate in the treatment of malignancy, psoriasis, and rheumatoid arthritis. Patients should be closely monitored for bone marrow, liver, lung, skin, and kidney toxicities. Patients should be informed by their physician of the risks involved and be under a physician's care throughout therapy *[see Warnings and Precautions (5.1)]*.

1. Methotrexate has been reported to cause fetal death and/or congenital anomalies.

Therefore, Otrexup is not recommended for females of childbearing potential unless there is clear medical evidence that the benefits can be expected to outweigh the considered risks *[see Warnings and Precautions (5.2)]*. Otrexup is contraindicated in pregnant women *[see Contraindications (4)]*.

2. Methotrexate elimination is reduced in patients with impaired renal functions, ascites, or pleural effusions. Such patients require especially careful monitoring for toxicity, and require dose reduction or, in some cases, discontinuation of Otrexup administration *[see Warnings and Precautions (5.6)]*.

3. 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) *[see Warnings and Precautions (5.1) and Drug Interactions (7.1)]*.

4. Methotrexate causes hepatotoxicity, fibrosis and cirrhosis, but generally only after prolonged use. Acutely, liver enzyme elevations are frequently seen. These are usually transient and asymptomatic, and also do not appear predictive of subsequent hepatic disease. Liver biopsy after sustained use often shows histologic changes, and fibrosis and cirrhosis have been reported; these latter lesions may not be preceded by symptoms or abnormal liver function tests in the psoriasis population. For this reason, periodic liver biopsies are usually recommended for psoriatic patients who are under long-term treatment. Persistent abnormalities in liver function tests may precede appearance of fibrosis or cirrhosis in the rheumatoid arthritis population *[see Warnings and Precautions (5.1)]*.

5. Methotrexate-induced lung disease, including acute or chronic interstitial pneumonitis, is a potentially dangerous lesion, which may occur acutely at any time during therapy and has been reported at low doses. It is not always fully reversible and fatalities have been reported. Pulmonary symptoms (especially a dry, nonproductive cough) may require interruption of treatment and careful investigation *[see Warnings and Precautions (5.1)]*.

6. Diarrhea and ulcerative stomatitis require interruption of therapy: otherwise, hemorrhagic enteritis and death from intestinal perforation may occur *[see Warnings and Precautions (5.1)]*.

7. Malignant lymphomas, which may regress following withdrawal of methotrexate, may occur in patients receiving low-dose methotrexate and, thus, may not require cytotoxic treatment. Discontinue Otrexup first and, if the lymphoma does not regress, appropriate treatment should be instituted *[see Warnings and Precautions (5.8)]*.

8. Like other cytotoxic drugs, methotrexate may induce "tumor lysis syndrome" in patients with rapidly growing tumors *[see Warnings and Precautions (5.9)]*.

9. Severe, occasionally fatal, skin reactions have been reported following single or multiple doses of methotrexate. Reactions have occurred within days of oral, intramuscular, intravenous, or intrathecal methotrexate administration. Recovery has been reported with discontinuation of therapy *[see Warnings and Precautions (5.1)]*.

10. Potentially fatal opportunistic infections, especially *Pneumocystis jiroveci* pneumonia, may occur with methotrexate therapy *[see Warnings and Precautions (5.1)]*.

11. Methotrexate given concomitantly with radiotherapy may increase the risk of soft tissue necrosis and osteonecrosis *[see Warnings and Precautions (5.10)]*.

1 INDICATIONS AND USAGE

1.1 Rheumatoid Arthritis including Polyarticular Juvenile Idiopathic Arthritis

Otrexup is indicated in the management of selected adults with severe, active rheumatoid arthritis (RA) (ACR criteria), or children with active polyarticular juvenile idiopathic arthritis (pJIA), who have had an insufficient therapeutic response to, or are intolerant of, an adequate trial of first-line therapy including full dose non-steroidal anti-inflammatory agents (NSAIDs).

1.2 Psoriasis

Otrexup is 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. It is important to ensure that a psoriasis "flare" is not due to an undiagnosed concomitant disease affecting immune responses.

1.3 Limitation of Use

Otrexup is not indicated for the treatment of neoplastic diseases.

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosing Information

Otrexup is a single-dose auto-injector for once-weekly subcutaneous use only *[see Warnings and Precautions (5.5)]*. Administer Otrexup in the abdomen or the thigh. Otrexup is available in the following dosage strengths: 7.5, 10, 15, 20 and 25 mg. Use another formulation of methotrexate for alternative dosing in patients who require oral, intramuscular, intravenous, intra-arterial, or intrathecal dosing, doses less than 7.5 mg per week, doses more than 25 mg per week, high-dose regimens, or dose adjustments between the available doses.

2.2 Rheumatoid Arthritis including Polyarticular Juvenile Idiopathic Arthritis

Recommended starting dose of methotrexate:

Adult RA: 7.5 mg once weekly.

pJIA: 10 mg/m^2 once weekly.

For patients switching from oral methotrexate to Otrexup, consider any differences in bioavailability between oral and subcutaneously administered methotrexate *[see Clinical Pharmacology (12.3)]*.

Dosages may be adjusted 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/wk in adults. Although there is experience with doses up to 30 mg/m^2/wk in children, there are too few published data to assess how doses over 20 mg/m^2/wk might affect the risk of serious toxicity in children. Experience does suggest, however, that children receiving 20 to 30 mg/m^2/wk (0.65 to 1.0 mg/kg/wk) may have better absorption and fewer gastrointestinal side effects if methotrexate is administered either intramuscularly or subcutaneously.

Therapeutic response usually begins within 3 to 6 weeks and the patient may continue to improve for another 12 weeks or more.

The optimal duration of therapy is unknown. Limited data available from long-term studies in adults indicate that the initial clinical improvement is maintained for at least two years with continued therapy. When methotrexate is discontinued, the arthritis usually worsens within 3 to 6 weeks.

The patient should be fully informed of the risks involved and should be under constant supervision of the physician. Assessment of hematologic, hepatic, renal, and pulmonary function should be made by history,

physical examination, and laboratory tests before beginning, periodically during, and before reinstituting Otrexup therapy *[see Warnings and Precautions (5.4)]*. Females of childbearing potential should not be started on Otrexup until pregnancy is excluded *[see Contraindications (4) and Warnings and Precautions (5.2)]*

All schedules should be continually tailored to the individual patient. An initial test dose may be given prior to the regular dosing schedule to detect any extreme sensitivity to adverse effects.

Maximal myelosuppression usually occurs in seven to ten days.

2.3 Psoriasis

Recommended starting dose of methotrexate:

Psoriasis: single weekly oral, intramuscular, subcutaneous, or intravenous doses of 10-25 mg.

For patients switching from oral methotrexate to Otrexup, consider any differences in bioavailability between oral and subcutaneously administered methotrexate *[see Clinical Pharmacology (12.3)]*.

Dosage may be gradually adjusted to achieve optimal clinical response; 30 mg/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. The use of Otrexup may permit the return to conventional topical therapy, which should be encouraged.

2.4 Administration and Handling

Otrexup is an auto-injector intended for subcutaneous use under the guidance and supervision of a physician.

Patients may self-inject with Otrexup if a physician determines that it is appropriate, if they have received proper training in how to prepare and administer the correct dose, and if they receive medical follow-up, as necessary. A trainer device is available for training purposes.

Visually inspect Otrexup for particulate matter and discoloration prior to administration. Do not use Otrexup if the seal is broken.

Handle and dispose of Otrexup consistent with recommendations for handling and disposal of cytotoxic drugs[1].

3 DOSAGE FORMS AND STRENGTHS

Otrexup is an injection available as an autoinjector that administers a single 0.4 mL dose of methotrexate solution in the following dosage strengths:

- 7.5 mg/0.4 mL methotrexate
- 10 mg/0.4 mL methotrexate
- 15 mg/0.4 mL methotrexate
- 20 mg/0.4 mL methotrexate
- 25 mg/0.4 mL methotrexate

4 CONTRAINDICATIONS

Otrexup is contraindicated in the following:

• Pregnancy

Otrexup can cause fetal death or teratogenic effects when administered to a pregnant woman.

Otrexup is contraindicated in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus *[see Warnings and Precautions (5.2) and Use in Specific Populations (8.1)]*.

•Nursing Mothers

Because of the potential for serious adverse reactions from methotrexate in breast fed infants, Otrexup is contraindicated in nursing mothers *[see Use in Specific Populations (8.3)]*.

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