***תאריך: ינואר 2022***

**רופא/ה, רוקח/ת נכבד/ה**

**חברת טבע מודיעה על העדכונים הבאים בעלון לרופא של התכשיר:**

# Abitrexate Teva, Solution for Injection

## אביטרקסט טבע, תמיסה להזרקה

**Contains: Methotrexate 25 mg/ml**

## עדכונים בעלון לרופא

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**<u>התוויה כפי שאושרה בתעודת הרישום:</u>**

**Antineoplastic chemotherapy:**
Treatment of gestational choriocarcinoma, chorioadenoma destruens and hydatidiform mole. Palliation of acute lymphocytic leukemia. Abitrexate Teva is also indicated in the treatment and prophylaxis of meningeal leukemia. Greatest effect has been observed in palliation of acute lymphoblastic (stem-cell) leukemias in children. In combination with other anticancer agents, Abitrexate Teva may be used for the induction of remission, but is most commonly used in the maintenance of induced remissions.

Abitrexate Teva may be used alone, or in combination with other antineoplastic drugs, in the management of breast cancer, epidermoid cancers of the head and neck, lung cancer (particularly squamous cell and small cell types), bladder cancer and osteogenic cancer. Abitrexate Teva is effective in the treatment of the advanced stages (III and IV, Peter's Staging system) of lymphosarcoma, particularly in children, and in advanced cases of mycosis fungoides.

**Psoriasis:**
Because of the high risk attending its use, Abitrexate Teva is indicated only in the symptomatic control of severe recalcitrant, disabling psoriasis which is not adequately responsive to other forms of therapy, and only when the diagnosis has been established, as by biopsy and/or after dermatological consultation.

**Rheumatoid Arthritis:**
Abitrexate can be used in the treatment of selected adults with severe rheumatoid arthritis, only when the
diagnosis has been well established according to rheumatological standards, with inadequate response to other forms of antirheumatic therapy, including full dose NSAIDs and usually a trial of at least one or more disease-modifying antirheumatic drugs.

**ברצוננו להודיע שהעלון לרופא עודכן, בפירוט שלהלן כלולים העדכונים העיקריים בלבד (תוספות מסומנות באדום והסרות מידע כטקסט מחוק):**

## CONTRAINDICATIONS

Abitrexate Teva is contraindicated:

- In patients with psoriasis or rheumatoid arthritis with alcoholism, alcoholic liver disease or other chronic liver disease.
- In patients with psoriasis or rheumatoid arthritis who have overt or laboratory evidence of immunodeficiency syndromes.
- In patients with psoriasis or rheumatoid arthritis who have pre-existing blood dyscrasias, such as bone marrow hypoplasia, leucopenia, thrombocytopenia or significant anemia.
- With nitrous oxide anesthesia (see *WARNINGS AND PRECAUTIONS: Renal and DRUG INTERACTIONS: Drug-Drug Interactions*).

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## WARNINGS AND PRECAUTIONS

### General

[…]

Bone marrow and mucosal toxicity depend on dose and duration of exposure of high levels (>$2x10^{-8}$ mol/L (0.02 micromolar)) of methotrexate. Since the critical time factor has been defined for these organs as being 42 hours in humans, this has the following implications:

- when high doses of methotrexate are employed (>$1g/m^2$), drug levels in serum should be monitored
- when drug levels exceeding $2x10^{-8}$ mol/L (0.02 micromolar) for >42 hours may forecast significant toxicity
- when toxicity can be minimized by appropriate administration of Leucovorin Calcium
- when high-dose methotrexate (HDMTX) is employed, it is imperative to alkalinise the urine in order to prevent crystallisation of methotrexate and its 7-hydroxy metabolite in the urine, which may lead to acute renal failure.

### Hematologic

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In psoriasis and rheumatoid arthritis, methotrexate should be stopped immediately if there is a significant drop in blood counts. In the treatment of neoplastic diseases, methotrexate should be continued only if the potential benefit warrants the risk of severe myelosuppression. Patients with profound granulocytopenia and fever should be evaluated immediately and usually require parenteral broad-spectrum antibiotic therapy.

### Hepatic/Biliary/Pancreatic

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Methotrexate is not recommended for patients with active or chronic hepatitis B or C infection.

In psoriasis, liver damage and function tests, including serum albumin and prothrombin time, should be performed several times prior to dosing, but are often normal in the face of developing fibrosis or cirrhosis. These lesions may be detectable only by biopsy. The usual recommendation is to obtain a liver biopsy: 1) before the start of therapy or shortly after initiation of therapy (4-8 weeks); 2) after a

total cumulative dose of 1.5 grams; and 3) after each additional 1.0 to 1.5 grams. Moderate fibrosis or any cirrhosis normally leads to discontinuation of the drug; mild fibrosis normally suggests a repeat biopsy in 6 months. Milder histologic findings such as fatty change and low-grade portal inflammation are relatively common pre-therapy. Although these mild changes are usually not a reason to avoid or discontinue methotrexate therapy, the drug should be used with caution.

Clinical experience with liver disease in rheumatoid arthritis is limited, but the same risk factors would be anticipated. Liver function tests are also usually not reliable predictors of histological changes in this population.

In rheumatoid arthritis, advanced age at first use of methotrexate and increasing duration of therapy have been reported as risk factors for hepatotoxicity. Persistent abnormalities in liver function tests may precede appearance of fibrosis or cirrhosis in the rheumatoid population. Liver function tests should be performed at baseline and at 4-8 week intervals in patients receiving methotrexate for rheumatoid arthritis. Pretreatment liver biopsy should be performed for patients with a history of excessive alcohol consumption, persistently abnormal baseline liver function test values, or chronic hepatitis B or C infection. During therapy, liver biopsy should be performed if there are persistent liver function test abnormalities, or there is a decrease in serum albumin below the normal range (in the setting of well controlled rheumatoid arthritis).

If the results of a liver biopsy show mild changes (Roenigk grades I, II, IIIa), methotrexate may be continued and the patient monitored according to the recommendations listed above. Methotrexate should be discontinued in any patient who displays persistently abnormal liver function tests and refuses liver biopsy, or in any patient whose liver biopsy shows moderate to severe changes (Roenigk grade IIIb or IV).

**Respiratory**

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Pulmonary alveolar haemorrhage has been reported with methotrexate. This event may also be associated with vasculitis and other comorbidities. Prompt investigations should be considered when pulmonary alveolar haemorrhage is suspected to confirm the diagnosis.

**Monitoring and Laboratory Tests**

**General:**

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It is important that patients be identified within 48 hours since methotrexate toxicity may not be reversible if adequate leucovorin rescue is delayed for more than 42 to 48 hours.

**During therapy of rheumatoid arthritis and psoriasis, monitor:**

- **Hematologic:** Patients should have their blood tests checked at least monthly.
- **Hepatic:** Liver biopsies prior to methotrexate therapy are not indicated routinely.

  Liver function tests should be determined prior to the initiation of therapy with methotrexate and they should be monitored every 1 to 2 months. A relationship between abnormal liver function tests and fibrosis or cirrhosis of the liver has not been established. Transient liver function test abnormalities are observed frequently after methotrexate administration and are usually not cause for modification of methotrexate therapy. Persistent liver function test abnormalities just prior to dosing and/or depression of serum albumin may be indicators of serious liver toxicity and require evaluation.
- **Renal:** Renal function should be monitored every 1 to 2 months.

## ADVERSE REACTIONS

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|---|---|
| Gastrointestinal disorders: | Gingivitis, stomatitis, enteritis, anorexia, nausea, vomiting, diarrhea, hematemesis, melena, gastrointestinal ulceration and bleeding, pancreatitis, intestinal perforation, non-infectious peritonitis, glossitis. |
| General disorders and administration site conditions: | Anaphylactoid reactions, vasculitis, fever, conjunctivitis, infection, sepsis, nodulosis, hypogammaglobulinaemia, and sudden death. |
| Nervous system: | Cerebrospinal fluid pressure increased, […] |
| Renal and urinary disorders: | Renal failure, severe nephropathy or renal failure, azotemia, dysuria, cystitis, hematuria, urogenital dysfunction. Proteinuria has also been observed. |
| Respiratory, thoracic and mediastinal disorders: | Pneumonia, interstitial alveolitis/pneumonitis often associated with eosinophilia, pulmonary fibrosis, Pneumocystis carinii pneumonia, pleural effusion. Dyspnea, chest pain, hypoxia, respiratory fibrosis, pharyngitis, and chronic interstitial obstructive pulmonary disease, alveolitis and pulmonary alveolar haemorrhage have occasionally occurred. |

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**Post-Market Adverse Drug Reactions**

| System Organ Class | Adverse Reaction |
|---|---|
| Blood and Lymphatic System Disorders | Agranulocytosis; Pancytopenia; Leukopenia; Neutropenia; Lymphadenopathy and lymphoproliferative disorders (including reversible); Eosinophilia; Anemia megaloblastic; Renal vein thrombosis; Lymphoma; Aplastic anemia; Hypogammaglobulinemia |
| Nervous System Disorders | CSF pressure increased; Neurotoxicity; Arachnoiditis; Paraplegia; Stupor; Ataxia; Dementia; Dizziness; Paresthesia |
| Gastrointestinal Disorders | Intestinal perforation; Noninfectious peritonitis; Glossitis; Nausea; Pancreatitis |
| Reproductive System and Breast Disorders | Urogenital dysfunction |

# DRUG INTERACTIONS

**Amiodarone**

Amiodarone administration to patients receiving methotrexate treatment for psoriasis has induced ulcerated skin lesions.

**Packed Red Blood Cells**

Care should be exercised whenever packed red blood cells and methotrexate are given concurrently. Patients receiving 24-hr methotrexate infusion and subsequent transfusions have showed enhanced toxicity probably resulting from prolonged high serum-methotrexate concentrations.

**Psoralen Plus Ultraviolet Light (PUVA) Therapy**

Skin cancer has been reported in patients with psoriasis or mycosis fungoides (a cutaneous T-cell lymphoma) receiving a concomitant treatment with methotrexate plus PUVA therapy.

**Nitrous Oxide**

The use of nitrous oxide anesthesia potentiates the effect of methotrexate on folate metabolism, yielding increased toxicity such as severe, unpredictable myelosuppression, stomatitis, neurotoxicity (with intrathecal administration of methotrexate) and nephritis (see *CONTRAINDICATIONS* and *WARNINGS AND PRECAUTIONS: Renal*). In case of accidental co-administration, this effect can be reduced by the use of leucovorin rescue.

**Oral Antibiotics**

Oral antibiotics such as tetracycline, chloramphenicol, and nonabsorbable broad spectrum antibiotics, may decrease intestinal absorption of methotrexate or interfere with the enterohepatic circulation by inhibiting bowel flora and suppressing metabolism of the drug by bacteria. For example: Neomycin, Polymyxin B, Nystatin and Vancomycin decrease methotrexate absorption, whereas Kanamycin increases methotrexate absorption.

Trimethoprim/sulfamethoxazole has been reported rarely to increase bone marrow suppression in patients receiving methotrexate, probably by decreased tubular secretion and/or an additive antifolate effect. Concurrent use of the anti-protozoal *pyrimethamine* may increase the toxic effects of methotrexate because of an additive antifolate effect.

**Vitamins**

Vitamin preparations containing folic acid or its derivatives may decrease responses to methotrexate. Preliminary animal and human studies have shown that small quantities of intravenously administered leucovorin enter the cerebrospinal fluid primarily as 5-methyl tetrahydrofolate and, in humans, remain 1 to 3 orders of magnitude lower than the usual methotrexate concentrations following intrathecal administration.

However, high doses of leucovorin may reduce the efficacy of intrathecally administered methotrexate. In patients with rheumatoid arthritis or psoriasis, folic acid or folinic acid may reduce methotrexate toxicities such as gastrointestinal symptoms, stomatitis, alopecia, and elevated liver enzymes.

Before taking a folate supplement, it is advisable to check B12 levels, particularly in adults over the age of 50, since folate administration can mask symptoms of B12 deficiency.

Folate deficiency states may increase methotrexate toxicity.

**Drug-Lifestyle Interactions**

Use of alcohol with methotrexate is contraindicated (see *CONTRAINDICATIONS*). The effects of smoking, on the pharmacokinetics of methotrexate have not been specifically studied.
Some of the effects (e.g., dizziness and fatigue) may have an influence on the ability to drive or operate machinery.