



תאריך: מרץ 2025

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

התוויה כפי שאושרה בתעודת הרישום:

### **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.

[...]

#### 4.4 Special warnings and precautions for use

Methotrexate should be used with extreme care in infections, peptic ulcer disease, ulcerative colitis, **physical weakness** and in very young or very old persons. **If severe leukopenia occurs during therapy, there is a risk of bacterial infection. If infection occurs, discontinuation of treatment and adequate antibacterial therapy is indicated. If nephrotoxicity occurs, immediate discontinuation of treatment is also indicated. Severe bone marrow depression may require blood or platelet transfusion.**

[...]

**In children, periodic specific cognitive testing is recommended to detect cognitive impairment at an early stage.**

[...]

**Extra caution is required in patients with insulin-dependent diabetes mellitus, since in isolated cases during treatment with methotrexate, liver cirrhosis occurred without any increase in transaminases.**

[...]

#### *Teratogenicity - Risk to reproduction*

Methotrexate causes embryotoxicity, spontaneous abortion and fetal defects in humans. For this reason, possible effects on reproduction, miscarriage and congenital defects should be discussed with female patients of childbearing age (see section 4.6). In non-oncologic indications, before using Abitrexate Teva, it should be confirmed that the patient is not pregnant. If women of childbearing age are being treated, they should use effective contraception during treatment and **for at least six months afterwards.**

[...]

#### *Progressive multifocal leukoencephalopathy (PML)*

**Cases of progressive multifocal leukoencephalopathy (PML) have been reported in patients receiving methotrexate, usually in combination with other immunosuppressive medications. PML can be fatal and should be considered in the differential diagnosis in immunosuppressed patients with newly appearing or worsening neurologic symptoms.**

#### *Photosensitivity*

**Photosensitivity in the form of extreme sunburn reactions has been observed in some individuals taking methotrexate (see section 4.8). Exposure to bright sunlight or UV radiation should be avoided unless medically indicated. Patients should take appropriate measures to protect themselves from bright sunlight.**

#### 4.5 Interactions with other medicinal products and other forms of interaction

**Glutamine may cause a reduction in the tubular secretion of methotrexate and therefore potentiate the toxic effects of methotrexate.**

Non-steroidal anti-inflammatory drugs (NSAIDs) should not be administered before or simultaneously with high-dose methotrexate treatment (> 10 mg methotrexate per week). Increased serum levels of methotrexate have been reported with concomitant administration of some NSAIDs with high-dose methotrexate, resulting in death from severe hematologic and gastrointestinal toxicity.

NSAIDs, salicylates, other weak organic acids (such as probenecid) and penicillins (such as amoxicillin) may decrease the tubular secretion of methotrexate, which may increase toxicity. Use of methotrexate with these drugs should be done with caution and closely monitored. **The potential toxicity of methotrexate is particularly increased with concomitant use of NSAIDs when diuretics are also used.**

In rheumatology, combination therapy of low doses of methotrexate with an NSAID is common.

Plasma protein-bound methotrexate can be displaced by salicylates, NSAIDs, sulfonamides, phenytoin, tetracyclines, chloramphenicol, p-aminobenzoic acid, doxorubicin, bleomycin, cyclophosphamide, aminoglycosides, allopurinol, vincristine, hydrocortisone, prednisone, asparaginase, and cytosine arabinoside, resulting in increased plasma concentrations of unbound methotrexate.

Caution should be exercised when combining high-dose methotrexate with potentially nephrotoxic chemotherapy (e.g., with cisplatin).

The use of nitrous oxide potentiates the effect of methotrexate on folate metabolism and results in increased toxicity, such as severe unpredictable myelosuppression, stomatitis, and in the case of intrathecal administration, increased severe unpredictable neurotoxicity. Although this effect can be reduced by the administration of calcium folinate, **the concomitant use of nitrous oxide and methotrexate should be avoided. Oral antibiotics (including tetracyclines, chloramphenicol and non-absorbable broad-spectrum antibiotics) may affect intestinal flora and interfere with methotrexate absorption.**

Administration of additional hematotoxic drugs increases the risk of serious hematotoxic side effects of methotrexate. Co-administration of metamizole and methotrexate may exacerbate the hematotoxic effects of methotrexate, especially in the elderly. Therefore, concomitant administration should be avoided.

**Interaction with radiation in radiotherapy may occur** (see sections 4.4 and 4.8). **Pharmacodynamic interaction with other cytostatic agents may occur: therapeutic and toxic effects are enhanced.**

Vaccination with live virus should not be used in patients treated with methotrexate. Partial or complete protection can be obtained using inactivated vaccine.

Vitamin preparations containing folic acid or folic acid derivatives may decrease the effect of systemically administered methotrexate. Preliminary studies in humans and animals have shown that after intravenous administration of calcium folinate, a small amount penetrates the cerebrospinal fluid, mainly as 5-methyltetrahydrofolate, and that this amount in humans is 1 to 3 orders of magnitude lower than the normal methotrexate concentration after intrathecal administration. However, high doses of calcium folinate may decrease the efficacy of intrathecal methotrexate administration.

Folate deficiencies may increase the toxicity of methotrexate. In rare cases, potentiation of bone marrow suppression in methotrexate-treated patients with trimethoprim/sulfamethoxazole has been reported, probably due to additional folate antagonism. **The combined use of methotrexate and sulfonamides is therefore strongly discouraged.**

#### **4.6 Fertility, pregnancy and lactation**

[...]

##### **Contraception in men**

**It is not known whether methotrexate is present in semen. Methotrexate has been found to be genotoxic in animal studies. Therefore, the risk of genotoxic effects on sperm cannot be completely ruled out. Limited clinical evidence does not suggest an increased risk of malformations or miscarriage after paternal exposure to**



low doses of methotrexate (less than 30 mg/week). For higher doses, there are insufficient data to estimate the risk of malformations or miscarriage after paternal exposure.

As a precaution, sexually active male patients or their female partners are recommended to use reliable contraception during the male patient's treatment and for at least 3 months after methotrexate discontinuation. Men should not donate sperm during treatment or for at least 3 months after methotrexate discontinuation.

### **Pregnancy**

Methotrexate is contraindicated during pregnancy in non-oncologic indications (see section 4.3). If pregnancy occurs during methotrexate treatment or up to six months afterwards, medical advice should be given regarding the treatment-related risk of adverse effects to the child and ultrasound examinations should be performed to confirm normal fetal development. In animal studies, methotrexate has been shown to cause reproductive toxicity, especially during the first trimester (see section 5.3). Methotrexate has been shown to be teratogenic in humans; methotrexate has been reported to cause fetal death, miscarriages, and/or congenital anomalies (e.g., craniofacial, cardiovascular, of the central nervous system, and of limbs).

Methotrexate is a potent teratogen in humans, with an increased risk of spontaneous abortions, **intrauterine growth retardation** and congenital anomalies with exposure during pregnancy.

Spontaneous abortions were reported in 42.5% of pregnant women exposed to treatment with low doses of methotrexate (less than 30 mg/week), compared with a reported rate of 22.5% in disease-matched patients treated with drugs other than methotrexate.

Severe congenital anomalies occurred in 6.6% of live births in women exposed to treatment with low doses of methotrexate (less than 30 mg/week) during pregnancy, compared with approximately 4% of live births in disease-matched patients treated with drugs other than methotrexate.

Insufficient data are available on exposure to methotrexate during pregnancy at doses higher than 30 mg/week, but higher rates of spontaneous abortions and congenital anomalies are expected, especially at doses commonly used in oncologic indications.

When methotrexate treatment was discontinued prior to conception, normal pregnancies were reported.

When used in oncologic indications, methotrexate should not be administered during pregnancy, especially during the first trimester of pregnancy. The benefit of treatment must be weighed against the potential risk to the fetus on a case-by-case basis. If the drug is used during pregnancy or if the patient becomes pregnant while taking methotrexate, the patient should be informed of the potential risk to the fetus.

### **Fertility**

Methotrexate affects spermatogenesis and oogenesis and may reduce fertility. Methotrexate has been reported to cause oligospermia, menstrual dysfunction and **amenorrhea** in humans. These effects appear to be reversible in most cases after discontinuation of treatment. In oncologic indications, women who wish to become pregnant are advised to attend genetic consultation, if possible before starting treatment. Men should

seek advice on the possibility of sperm storage before starting treatment. Methotrexate may in fact be genotoxic in higher doses (see section 4.4).

#### **4.8 Undesirable effects**

[...]

##### ***Nervous system disorders***

Headache, drowsiness, blurred vision, aphasia, hemiparesis, paresis and seizures occurred after methotrexate administration.

There have been reports of leukoencephalopathy following intravenous administration of methotrexate to patients who had undergone craniospinal irradiation. Chronic leukoencephalopathy was also reported in patients with osteosarcoma who had received several high doses of methotrexate with calcium folinate rescue, even without craniospinal irradiation. Discontinuation of methotrexate treatment does not always lead to complete recovery.

A transient acute neurological syndrome was observed in patients treated with high doses of methotrexate. The manifestations of these neurological abnormalities may include abnormal behaviors, focal sensorimotor symptoms and abnormal reflexes. The exact cause of these is not known.

After intrathecal administration of methotrexate, the possible toxic side effects involving the central nervous system can be classified as follows:

- chemical arachnoiditis with symptoms such as headache, back pain, stiff neck and fever
- paresis, usually transient, with paraplegia involving one or more spinal nerve roots
- leukoencephalopathy with confusion, irritability, drowsiness, ataxia, dementia and sometimes severe seizures
- myelopathy.

*Very rare:* Paresthesia/hypesthesia.

##### ***Respiratory, thoracic and mediastinal disorders***

Death from interstitial pneumonitis was reported and chronic interstitial obstructive pulmonary disease occasionally occurred.

Pulmonary symptoms (especially a dry, nonproductive cough) or nonspecific pneumonitis during methotrexate treatment may indicate a potentially dangerous injury and require discontinuation of treatment along with a thorough examination. Although symptoms may be variable, the typical patient with methotrexate-induced lung disease presents with fever, cough, dyspnea, hypoxemia and an infiltrate on pulmonary radiography. An infection should be ruled out. This lesion can occur at any dose.

*Rare:* Methotrexate-associated lung abnormalities after intrathecal administration of methotrexate. If methotrexate-induced lung abnormalities occur, re-administration of methotrexate is contraindicated.

*Not known:* Diffuse alveolar hemorrhage has been reported with use of methotrexate for rheumatologic and related indications.

##### ***Gastrointestinal disorders***

Gingivitis, pharyngitis, stomatitis, anorexia, nausea, vomiting, diarrhea, hematemesis, melena, gastrointestinal ulceration, hemorrhage, abdominal pain and enteritis. If vomiting, diarrhea or stomatitis occur, with possible dehydration, methotrexate treatment should be stopped until recovery occurs.

[...]



#### ***Musculoskeletal and connective tissue disorders***

In combination with radiotherapy, there is an increased risk of soft tissue necrosis.

[...]

#### ***General disorders and administration site reactions***

*Rare:* Other reactions associated with or attributed to the use of methotrexate include opportunistic infections and sudden death, lymphomas, arthralgia/myalgia, diabetes, osteoporosis, and vasculitis. A few cases of anaphylactic reactions were reported.

Pancytopenia and sudden increase in rheumatoid nodules have also been reported in patients with rheumatoid arthritis.

*Not known:* edema, opportunistic infections.

[...]

#### **4.9 Overdose**

[...]

In case of intrathecal overdose, immediate lumbar puncture followed by ventriculolumbar perfusion and systemic Leucovorin Calciumtherapy can take place.

*Not known:* Osteonecrosis of the jaw (due to lymphoproliferative disorders).

[...]

#### **6.6 Special precautions for disposal and other instructions**

Solutions may be further diluted (in the range of 1 mg/ml to 10 mg/ml) with 0.9% sodium chloride solution or 5% Dextrose solution

[...]

העלון לרופא נשלח לפרסום במאגר התרופות שבאתר האינטרנט של משרד הבריאות

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