SUMMARY OF PRODUCT CHARACTERISTICS

Abitrexate Teva

Solution for Injection
For I.V., Intrathecal, I.M., Intra-Arterial and Intra-Ventricular Use

NAME OF THE MEDICINAL PRODUCT

Abitrexate Teva

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of solution contains 25 mg methotrexate.
Each vial of 2 ml of solution contains 50 mg methotrexate.
Each vial of 4 ml of solution contains 100 mg methotrexate.
Each vial of 8 ml of solution contains 200 mg methotrexate.
Each vial of 20 ml of solution contains 500 mg methotrexate.
Each vial of 40 ml of solution contains 1000 mg methotrexate.

PHARMACEUTICAL FORM

Solution for Injection.
Clear yellow-brown solution.

METHOD OF ADMINISTRATION

For I.V., intrathecal, I.M., intra-arterial and intra-ventricular use.

THERAPEUTIC INDICATIONS

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.

CONTRAINDICATIONS

Abitrexate Teva is contraindicated:

- In patients who are hypersensitive to the active substance or to any of the excipients listed in section *DOSAGE FORMS, COMPOSITION AND PACKAGING*.
- In patients with severe renal impairment including end stage renal disease with and without dialysis (see *WARNINGS AND PRECAUTIONS - Renal, Special populations* and *DOSAGE AND ADMINISTRATION*).
- In pregnant patients with psoriasis or rheumatoid arthritis and should be used in the treatment of neoplastic diseases only when the potential benefit outweighs the risk to the fetus.
- In women of childbearing potential until pregnancy is excluded.
- In nursing mothers.
- 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*).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- Abitrexate Teva should be used only by physicians whose knowledge and experience includes the use of antimetabolite therapy because of the possibility of serious toxic reactions (see *WARNINGS AND PRECAUTIONS: General*).
- Methotrexate has been reported to cause fetal death and/or congenital anomalies (see *Special Populations: Pregnant Women* section below). Therefore, use is contraindicated for women of childbearing potential until pregnancy is excluded and pregnant patients with psoriasis or rheumatoid arthritis (see *CONTRAINDICATIONS*).

General

Fatal toxicities related to inadvertent daily rather than weekly dosing have been reported, particularly in elderly patients. It should be emphasized to the patient that the recommended dose is taken weekly for rheumatoid arthritis and psoriasis, and that daily use of the weekly recommended dose has led to fatal toxicity.

Fatal toxicities related to intravenous dosing miscalculation have been reported. Special attention must be given to dose calculation.

Because of the possibility of serious toxic reactions (which can be fatal), methotrexate should be used only in neoplastic diseases (as indicated), or in patients with severe, recalcitrant, disabling psoriasis or severe rheumatoid arthritis that are not adequately responsive to other forms of therapy. The patient should be informed by the physician of the risks involved and should be under a physician's constant supervision.

The use of methotrexate high-dose regimens recommended for osteosarcoma requires meticulous care (see *DOSAGE AND ADMINISTRATION*). High dosage regimens for other neoplastic diseases are investigational and a therapeutic advantage has not been established.

Toxic effects may be related in frequency and severity to dose or frequency of administration but have been seen at all doses. Because they can occur at any time during therapy, it is necessary to follow patients on methotrexate closely. Most adverse reactions are reversible if detected early. When such reactions do occur, the drug should be reduced in dosage or discontinued and appropriate corrective measures should be taken. If necessary, this could include the use of leucovorin calcium and/or acute, intermittent hemodialysis with a high-flux dialyzer (see *OVERDOSAGE*). If methotrexate is re-instituted, it should be carried out with caution, with adequate consideration of further need for the drug and with increased alertness as to possible recurrence of toxicity.

Methotrexate may induce "tumour lysis syndrome" in patients with rapidly growing tumours. Appropriate supportive and pharmacologic measures may prevent or alleviate this complication.

Methotrexate exits slowly from third space compartments (e.g., pleural effusions or ascites). This results in a prolonged terminal plasma half-life and unexpected toxicity. In patients with significant third space accumulations, it is advisable to evacuate the fluid before treatment and to monitor plasma methotrexate levels.

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 non-steroidal anti-inflammatory drugs (NSAIDs) (see *DRUG INTERACTIONS*).

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 ($>1 g/m^2$), 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.

Methotrexate given concomitantly with radiotherapy may increase the risk of soft tissue necrosis and osteonecrosis.

Methotrexate should be used with extreme caution in the presence of debility.

The use of methotrexate high-dose regimens ($>500 mg/m^2$) recommended for osteosarcoma requires meticulous care. High-dosing regimens for other neoplastic diseases are investigational and a therapeutic advantage has not been established.

Drug Interactions with Proton Pump Inhibitors (PPI)

Use caution when administering high-dose methotrexate to patients receiving proton pump inhibitor (PPI) therapy. Case reports and published population pharmacokinetic studies suggest that concomitant use of some PPIs, such as omeprazole, esomeprazole, and pantoprazole, with methotrexate (primarily at high dose), may elevate and prolong serum levels of methotrexate and/or its metabolite hydromethotrexate, possibly leading to methotrexate toxicities. In two of these cases, delayed methotrexate elimination was observed when high-dose methotrexate was co-administered with PPIs, but was not observed when methotrexate was co-administered with ranitidine. However, no formal drug interaction studies of methotrexate with ranitidine have been conducted.

Carcinogenesis and Mutagenesis

Malignant lymphomas may occur in patients receiving low-dose methotrexate. These lymphomas may regress following withdrawal of methotrexate without requiring treatment.

No controlled human data exist regarding the risk of neoplasia with methotrexate. Methotrexate has been evaluated in a number of animal studies for carcinogenic potential with inconclusive results. Although there is evidence that methotrexate causes chromosomal damage to animal somatic cells and human bone marrow cells, the clinical

significance remains uncertain. Assessment of the carcinogenic potential of methotrexate is complicated by conflicting evidence of an increased risk of certain tumours in rheumatoid arthritis. Benefit should be weighed against this potential risk before using methotrexate alone or in combination with other drugs, especially in children or young adults. (See *TOXICOLOGY*).

Gastrointestinal

If vomiting, diarrhea, or stomatitis occurs, resulting in dehydration, methotrexate should be discontinued until recovery occurs. Diarrhea and ulcerative stomatitis require interruption of therapy; otherwise, hemorrhagic enteritis and death from intestinal perforation may occur.

methotrexate should be used with extreme caution in the presence of peptic ulcer disease or ulcerative colitis.

Use caution when administering high-dose methotrexate to patients receiving proton pump inhibitor (PPI) therapy as concomitant use of some PPIs, such as omeprazole, esomeprazole, and pantoprazole, with methotrexate (primarily at high dose), may elevate and prolong serum levels of methotrexate and/or its metabolite hydromethotrexate, possibly leading to methotrexate toxicities (see *DRUG INTERACTIONS: Drug-Drug Interactions*).

Hematologic

Methotrexate should be used with caution in patients with impaired bone marrow function and previous or concomitant wide field radiotherapy. Methotrexate may produce marked bone marrow depression with resultant anemia, aplastic anemia, pancytopenia, leucopenia, neutropenia, and/or thrombocytopenia. In controlled clinical trials in rheumatoid arthritis (n=128), leucopenia (WBC <3000/mm^3) was seen in 2 patients, thrombocytopenia (platelets <100,000/mm^3) in 6 patients, and pancytopenia in 2 patients.

The nadir of circulating leukocytes, neutrophils and platelets usually occurs between 5 and 13 days after an I.V. bolus dose (with recovery between 14 to 28 days). Leukocytes and neutrophils may occasionally show two depressions, the first occurring in 4-7 days and a second nadir after 12-21 days, followed by recovery. Clinical sequel such as fever, infections and hemorrhage from various sites may be expected.

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

Methotrexate has the potential for acute (elevated transaminases) and chronic (fibrosis and cirrhosis) hepatotoxicity. Acutely, liver enzyme elevations are frequently seen after methotrexate administration and are usually not a reason for modification of methotrexate therapy. Liver enzyme elevations are usually transient and asymptomatic, and also do not appear predictive of subsequent hepatic disease. Persistent liver abnormalities, and/or decrease of serum albumin may be indicators of serious liver toxicity. Chronic toxicity is potentially fatal; it generally has occurred after prolonged use (generally two years or more) and after a total cumulative dose of at least 1.5 grams. 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. 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. In studies in psoriatic patients, hepatotoxicity appeared to be a function of total cumulative dose and appeared to be enhanced by alcoholism, obesity, diabetes and advanced age. An accurate incidence rate has not been determined; the rate of progression and reversibility of lesions is not known. Special caution is indicated in the presence of pre-existing liver damage or impaired hepatic function.

Methotrexate has caused reactivation or worsening of hepatitis B and C infections, in some cases resulting in death. Some cases of hepatitis B reactivation have occurred after discontinuation of methotrexate. Prior to treatment with methotrexate, clinical and laboratory evaluation should be performed to evaluate preexisting hepatitis virus B and hepatitis virus C infection.

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).

There is a combined reported experience in 217 rheumatoid arthritis patients with liver biopsies both before and during treatment (after a cumulative dose of at least 1500 mg) and in 714 patients with a biopsy only during treatment. There are 64 (7%) cases of fibrosis and 1 (0.1%) case of cirrhosis. Of the 64 cases of fibrosis, 60 were deemed mild. The reticulin stain is more sensitive for early fibrosis and its use may increase these figures. It is unknown whether even longer use will increase these risks.

Immune

Methotrexate should be used with extreme caution in the presence of active infection, and is contraindicated in patients with overt or laboratory evidence of immunodeficiency syndromes (see *CONTRAINDICATIONS*).

Immunization may be ineffective when given during methotrexate therapy. Immunization with live virus vaccines is generally not recommended. Hypogammaglobulinemia has been reported rarely.

Neurologic

There have been reports of leukoencephalopathy following intravenous administration of methotrexate to patients who have had craniospinal irradiation. Serious neurotoxicity, frequently manifested as generalized or focal seizures, has been reported with unexpectedly increased frequency among pediatric patients with acute lymphoblastic leukemia who were treated with intravenous methotrexate (1 g/m^2). Symptomatic patients were commonly noted to have leukoencephalopathy and/or microangiopathic calcifications on diagnostic imaging studies.

Chronic leukoencephalopathy has also been reported in patients with osteosarcoma who received repeated doses of high-dose methotrexate with leucovorin rescue even without cranial irradiation.

There are also reports of leukoencephalopathy in patients who received low oral doses (4-8 mg/week) of methotrexate therapy for rheumatoid arthritis or psoriatic arthritis.

Discontinuation of methotrexate does not always result in complete recovery.

A transient acute neurologic syndrome has been observed in patients treated with high dosage regimens. Manifestations of this neurologic disorder may include behavioural abnormalities, focal sensorimotor signs, including transient blindness and abnormal reflexes. The exact cause is unknown.

After the intrathecal use of methotrexate, the central nervous system toxicity which may occur can be classified as follows: chemical arachnoiditis manifested by such symptoms as headache, back pain, nuchal rigidity, and fever; paresis, usually transient, manifested by paraplegia associated with involvement with one or more spinal nerve roots; leucoencephalopathy manifested by confusion, irritability, somnolence, ataxia, dementia, and occasionally major convulsions.

Intravenous administration of methotrexate may also result in acute encephalitis and acute encephalopathy with fatal outcome.

Cases of severe neurological adverse reactions that ranged from headache to paralysis, coma and stroke-like episodes have been reported mostly in juveniles and adolescents given methotrexate in combination with intravenous cytarabine.

Renal

Methotrexate is contraindicated in patients with severe renal impairment including end stage renal disease with and without dialysis (see *CONTRAINDICATIONS* and *DOSAGE AND ADMINISTRATION*). Methotrexate therapy in patients with mild and moderate renal impairment should be undertaken with extreme caution, and at reduced dosages, because renal dysfunction will prolong methotrexate elimination. Methotrexate may cause renal damage that may lead to acute renal failure. High doses of methotrexate used in the treatment of osteosarcoma may cause renal damage leading to acute renal failure.

Nephrotoxicity is due primarily to the precipitation of methotrexate and 7-hydroxymethotrexate in the renal tubules. Close attention to renal function including adequate hydration, urine alkalinization and measurement of serum methotrexate and creatinine levels are essential for safe administration.

Nephritis has been reported on co-administration with nitrous oxide anesthesia in rheumatoid arthritis patients (see *CONTRAINDICATIONS* and *DRUG INTERACTIONS: Drug-Drug Interactions*).

Respiratory

Methotrexate-induced lung disease, including acute or chronic interstitial pneumonitis, is a potentially dangerous lesion which may occur at any time during therapy and has been reported at low doses. It is not always fully reversible and fatalities have been reported. Cases of pleural effusion with or without interstitial pneumonitis have also been reported at any time during therapy at low doses. Pulmonary symptoms (especially a dry non-productive cough) or a non-specific pneumonitis occurring during methotrexate therapy may be indicative of a potentially dangerous lesion and require interruption of treatment and careful investigation. Although clinically variable, the typical patient with methotrexate-induced lung disease presents with fever, cough, dyspnea, hypoxemia, and an infiltrate on chest X-ray; infection (including pneumonia) needs to be excluded. This lesion can occur at all dosages.

Potentially fatal opportunistic infections, especially Pneumocystis carinii pneumonia, may occur with methotrexate therapy. When a patient presents with pulmonary symptoms, the possibility of *Pneumocystis carinii* should be considered.

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.

Sexual Function/Reproduction

Methotrexate causes embryotoxicity, abortion, and fetal defects in humans. It has also been reported to cause impairment of fertility, oligospermia and menstrual dysfunction in humans, during and for a short period after cessation of therapy (see *TOXICOLOGY*). The risk of effects on reproduction should be discussed with both male and female patients taking methotrexate. (See *TOXICOLOGY*).

Skin

Severe, occasionally fatal, dermatologic reactions, including toxic epidermal necrolysis (Lyell's Syndrome), Stevens-Johnson syndrome, exfoliative dermatitis, skin necrosis, and erythema multiforme, have been reported in

children and adults, within days of oral, intramuscular or intravenous methotrexate administration. Reactions were noted after single or multiple, low, intermediate or high doses of methotrexate in patients with neoplastic diseases, rheumatoid arthritis or psoriasis. Recovery has been reported with discontinuation of therapy.

Lesions of psoriasis may be aggravated by concomitant exposure to ultraviolet radiation. Radiation dermatitis and sunburn may be "recalled" by the use of methotrexate.

Special Populations

Pregnant Women: Methotrexate is contraindicated in pregnant patients with psoriasis or rheumatoid arthritis (see *CONTRAINDICATIONS* and *WARNINGS AND PRECAUTIONS: Serious Warnings and Precautions*) and should be used in the treatment of neoplastic diseases only when the potential benefit outweighs the risk to the fetus. Methotrexate has been reported to cause impairment of fertility, oligospermia and menstrual dysfunction in humans, during and for a short period after cessation of therapy. Methotrexate can cause fetal death, embryotoxicity, abortion, or teratogenic effects when administered to a pregnant woman.

Methotrexate is contraindicated in women of childbearing potential until pregnancy is excluded and should be fully counselled on the serious risk to the fetus should they become pregnant while undergoing treatment (see *CONTRAINDICATIONS*). Pregnancy should be avoided if either partner is receiving methotrexate. The optimal time interval between the cessation of methotrexate treatment of either partner and pregnancy has not been clearly established. Published literature recommendations for time intervals vary from 3 months to one year. The risk of effects on reproduction should be discussed with both male and female patients taking methotrexate .

Nursing Women:

Methotrexate is contraindicated in nursing mothers because of the potential for serious adverse reactions from methotrexate in breast-fed infants.

Pediatrics (<18 years of age):

Safety and effectiveness in pediatric patients have not been established, other than in cancer chemotherapy. Overdose by intravenous miscalculation of dosage (particularly in juveniles) have occurred. Special attention must be given to dose calculation.

Geriatrics (>65 years of age):

The clinical pharmacology of methotrexate has not been well studied in older individuals. Due to diminished hepatic and renal function, as well as decreased folate stores in this population, relatively low doses should be considered. Fatal toxicities related to inadvertent daily rather than weekly dosing have been reported, particularly in elderly patients. Elderly patients should be closely monitored for early signs of hepatic, bone marrow and renal toxicity.

Renal Impairment:

Methotrexate is contraindicated in patients with severe renal impairment (see *CONTRAINDICATIONS* and *DOSAGE AND ADMINISTRATION*).

Monitoring and Laboratory Tests

General: Patients undergoing methotrexate therapy should be informed of the early signs and symptoms of toxicity and closely monitored so that toxic effects are detected promptly. Serum methotrexate level monitoring can significantly reduce toxicity and mortality by allowing the adjustment of methotrexate dosing and the implementation of appropriate rescue measures. Patients subject to the following conditions are predisposed to developing elevated or prolonged methotrexate levels and benefit from routine monitoring of levels: e.g., pleural effusion, ascites, gastrointestinal tract obstruction, previous cisplatin therapy, dehydration, aciduria, and impaired renal function. Some patients may have delayed methotrexate clearance in the absence of these features. 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.

Monitoring of methotrexate concentrations should include determination of a methotrexate level at 24, 48, or 72

hours, and assessment of the rate of decline in methotrexate concentrations (to determine how long to continue leucovorin rescue).

Baseline assessment should include a complete blood count with differential and platelet counts, hepatic enzymes, renal function tests, and a chest X-ray. During initial or changing doses, or during periods of increased risk of elevated methotrexate blood levels (e.g., dehydration), more frequent monitoring may also be indicated.

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.
- **Respiratory:** Pulmonary function tests may be useful if methotrexate-induced lung disease (e.g. interstitial pneumonitis) is suspected, especially if baseline measurements are available.

During therapy of neoplastic disease:

More frequent monitoring is usually indicated during antineoplastic therapy for hematologic, hepatic, renal and respiratory.

Excipient information

Abitrexate Teva 2 ml, 4 ml and 8 ml vials contain less than 1 mmol sodium (23 mg) per vial, that is to say essentially 'sodium free'.
Abitrexate Teva 20 ml contains approximately 38.6 mg sodium per vial, equivalent to 1.93% of the WHO recommended maximum daily intake of 2 g sodium for an adult.
Abitrexate Teva 40 ml contains approximately 77.2 mg sodium per vial, equivalent to 3.86% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

In general, the incidence and severity of acute side effects are related to dose, frequency of administration, and the duration of the exposure to significant blood levels of methotrexate to the target organs. The most serious reactions are discussed under **WARNINGS AND PRECAUTIONS** section. The most frequently reported adverse reactions include ulcerative stomatitis, leucopenia, nausea, and abdominal distress. Other frequently reported adverse effects are malaise, undue fatigue, chills and fever, dizziness and decreased resistance to infection.
Ulcerations of the oral mucosa are usually the earliest signs of toxicity.

Adverse Drug Reactions by Organ System

Blood and lymphatic system disorders:	Leucopenia, anemia, aplastic anemia, thrombopenia, pancytopenia, agranulocytosis, lymphadenopathy and lymphoproliferative disorders (including reversible), neutropenia and eosinophilia have also been observed.

Cardiac disorders:	Pericarditis and pericardial effusion (damage to heart, rarely).
Eye disorders:	Conjunctivitis, blurred vision, serious visual changes of unknown etiology, and transient blindness/vision loss.
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.
Hepatobiliary disorders:	Hepatotoxicity, acute hepatitis, chronic fibrosis and cirrhosis, decrease in serum albumin, liver enzyme elevations, hepatic failure.
Infection:	Other reported infections included nocardiosis, histoplasmosis, cryptococcosis, and disseminated *H. simplex*, cytomegalovirus infection, including cytomegaloviral pneumonia.
Metabolism and nutrition disorders:	Diabetes mellitus.
Musculoskeletal, connective tissue and bone disorders:	Stress fractures, soft tissue necrosis, osteonecrosis, arthralgia, myalgia and osteoporosis.
Neoplasms benign, malignant and unspecified (including cysts and polyps):	Tumour lysis syndrome. 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 methotrexate first and, if the lymphoma does not regress, appropriate treatment should be instituted.
Nervous system:	Cerebrospinal fluid pressure increased, neurotoxicity, arachnoiditis, paresthesia, headache, dizziness, drowsiness, speech impediment including dysarthria and aphasia; hemiparesis, paresis and convulsions. Following low doses, there have been occasional reports of transient subtle cognitive dysfunction, mood alteration, or unusual cranial sensations, leukoencephalopathy, or encephalopathy.

Renal and urinary disorders:	Renal failure, severe nephropathy or renal failure, azotemia, dysuria, cystitis, hematuria, urogenital dysfunction. Proteinuria has also been observed.
Reproductive system and breast disorders:	Defective oogenesis or spermatogenesis, transient oligospermia, menstrual dysfunction, vaginal discharge and gynecomastia; infertility, abortion, fetal defects, loss of libido/impotence.
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.
Skin disorders:	Erythema, pruritus, photosensitisation, petechiae, loss of hair, skin necrosis, exfoliative dermatitis, painful erosion of psoriatic plaques, herpes zoster, vasculitis, urticaria, pigmentary changes, acne, ecchymosis, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), furunculosis and telangiectasia. Drug reaction with eosinophilia and systemic symptoms
Vascular disorders:	Hypotension, and thromboembolic events (including arterial thrombosis, cerebral thrombosis, deep vein thrombosis, retinal vein thrombosis, thrombophlebitis, and pulmonary embolus), vasculitis

Adverse Reactions Reported in Rheumatoid Arthritis:

- Alopecia (common)
- Diarrhea (common)
- Dizziness (common)
- Elevated liver enzymes (very common)
- Leucopenia (common)
- Nausea/vomiting (very common)
- Pancytopenia (common)
- Rash/pruritus/dermatitis (common)
- Stomatitis (common)
- Thrombocytopenia (common)

Adverse Reactions in Psoriasis:
The adverse reaction rates reported are very similar to those in the rheumatoid arthritis studies. Rarely, painful psoriatic plaque erosions may appear.

Abnormal Hematologic and Clinical Chemistry Findings
See *WARNINGS AND PRECAUTIONS: Monitoring and Laboratory Tests* section.

Post-Market Adverse Drug Reactions
Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

The following adverse events have also been reported during post-marketing experience with methotrexate:

System Organ Class	Adverse Reaction
Infections and Infestations	Infections (including fatal sepsis); Pneumonia; *Pneumocystis carinii* pneumonia; Nocardiosis; Histoplasmosis; Cryptococcosis; Herpes zoster; *H. simplex* hepatitis; Disseminated H. simplex; Cytomegalovirus infection (including cytomegaloviral pneumonia); Reactivation of hepatitis B infection; Worsening of hepatitis C infection
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
Respiratory, Thoracic and Mediastinal Disorders	Chronic interstitial pulmonary disease; Alveolitis; Dyspnea; Chest pain; Hypoxia; Cough; Plural effusion
Gastrointestinal Disorders	Intestinal perforation; Noninfectious peritonitis; Glossitis; Nausea; Pancreatitis
Hepatobiliary Disorders	Hepatic failure
Skin and Subcutaneous Tissue Disorders	Drug reaction with eosinophilia and systemic symptoms; Dermatitis; Petechiae
Musculoskeletal, Connective Tissue and Bone Disorders	Osteonecrosis
Renal and Urinary Disorders	Proteinuria
Pregnancy, Puerperium and Perinatal Conditions	Fetal death, Abortion
Reproductive System and Breast Disorders	Urogenital dysfunction
General Disorders and Administration Site Conditions	Pyrexia; Chills; Malaise; Fatigue; Anaphylactic reactions
Endocrine Disorders	Diabetes
Ophthalmologic Disorders	Transient blindness/vision loss

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form**:** https://sideeffects.health.gov.il.

DRUG INTERACTIONS

Serious Drug Interactions

The use of nitrous oxide anesthesia with methotrexate is contraindicated (see *CONTRAINDICATIONS*, *WARNINGS AND PRECAUTIONS - Renal and DRUG INTERACTIONS - Drug-Drug Interactions*).

Overview

Methotrexate competes with reduced folates for active transport across cell membranes by means of a single carrier-mediated active transport process. Impaired renal function, as well as concurrent use of drugs such as weak organic acids that undergo tubular secretion, can markedly increase methotrexate serum levels. Laboratory studies demonstrate that methotrexate may be displaced from plasma albumin by various compounds including sulfonamides, salicylates, tetracyclines, chloramphenicol and phenytoin.

Drug-Drug Interactions

Non-steroidal Anti-inflammatory Drugs (NSAIDs)
NSAIDs should not be administered prior to or concomitantly with high doses of methotrexate. Concomitant administration of NSAIDs with high-dose methotrexate therapy has been reported to elevate and prolong serum methotrexate levels, resulting in deaths from severe hematologic (including bone marrow suppression and aplastic anemia) and gastrointestinal toxicity. These drugs have been reported to reduce the tubular secretion of methotrexate, in an animal model, and may enhance its toxicity by increasing methotrexate levels.

Caution should be used when NSAIDs and salicylates are administered concomitantly with lower doses of methotrexate . In treating rheumatoid arthritis with methotrexate, the possibility of increased toxicity with concomitant use of NSAIDs including salicylates has not been fully explored. Despite the potential interactions, studies of methotrexate in patients with rheumatoid arthritis have usually included concurrent use of constant dosage regimens of NSAIDs without apparent problems. It should be appreciated however, that the doses used in rheumatoid arthritis (7.5 to 15 mg/week) are somewhat lower than those used in psoriasis and that larger doses could lead to toxicity.

Disease Modifying Antirheumatic drugs (DMARDs)
Combined use of methotrexate with gold, penicillamine, hydroxychloroquine, or sulfasalazine has not been studied and may increase the incidence of adverse effects.

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

L-asparaginase
The administration of L-asparaginase has been reported to antagonize the effect of methotrexate.

Diuretics
Bone marrow suppression and decreased folate levels have been described in the concomitant administration of triamterene and methotrexate.

Leflunomide
Methotrexate in combination with leflunomide may increase the risk of pancytopenia.

Drugs Highly Bound to Plasma Proteins

Methotrexate is partially bound to serum albumin, and toxicity may be increased because of displacement by other highly bound drugs, such as sulfonylureas, aminobenzoic acid, salicylates, phenylbutazone, phenytoin, sulfonamides, some antibiotics such as penicillins, tetracycline, pristinamycin, probenecid, and chloramphenicol.

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.

Probenecid
Renal tubular transport is also diminished by probenecid; use of methotrexate with this drug should be carefully monitored.

Proton Pump Inhibitors
Use caution when administering high-dose methotrexate to patients receiving proton pump inhibitor (PPI) therapy. Concomitant use of PPIs and high-dose methotrexate should be avoided especially in patients with renal impairment. Case reports and published population pharmacokinetic studies suggest that concomitant use of some PPIs, such as omeprazole, esomeprazole, and pantoprazole, with methotrexate (primarily at high dose), may elevate and prolong serum levels of methotrexate and/or its metabolite hydromethotrexate, possibly leading to methotrexate toxicities. In two of these cases, delayed methotrexate elimination was observed when high-dose methotrexate was co-administered with PPIs, but was not observed when methotrexate was co-administered with ranitidine. However, no formal drug interaction studies of methotrexate with ranitidine have been conducted.

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.

Nephrotoxic Drugs
In the treatment of patients with osteosarcoma, caution must be exercised if high-dose methotrexate is administered in combination with a potentially nephrotoxic chemotherapeutic agent (e.g., cisplatin). Methotrexate clearance is decreased by cisplatinum.

Although not documented, other nephrotoxic drugs such as aminoglycosides, Amphotericin B and Cyclosporin could theoretically increase methotrexate toxicity by decreasing its elimination.

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.

Penicillins and Sulfonamides
Penicillins and sulfonamides may reduce the renal clearance of methotrexate; hematologic and gastrointestinal toxicity have been observed in combination with methotrexate. Use of methotrexate with penicillins should be carefully monitored.

Ciprofloxacin
Renal tubular transport is diminished by ciprofloxacin; use of methotrexate with this drug should be carefully monitored.

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.

Theophylline
Methotrexate may decrease the clearance of theophylline; theophylline levels should be monitored when used concurrently with methotrexate.

Mercaptopurine
Methotrexate increases the plasma levels of mercaptopurine. Combination of methotrexate and mercaptopurine may therefore require dose adjustment.

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.

Radiotherapy
Methotrexate given concomitantly with radiotherapy may increase the risk of soft tissue necrosis and osteonecrosis.

Hepatoxins
The potential for increased hepatotoxicity when methotrexate is administered with other hepatotoxic agents has not been evaluated. However, hepatotoxicity has been reported in such cases. Therefore, patients receiving concomitant therapy with methotrexate and other potential hepatotoxic agents (e.g., leflunomide, azathioprine, sulfasalazine, retinoids) should be closely monitored for possible increased risk of hepatotoxicity.

Cytarabine and other cytotoxic agents
Methotrexate given concomitantly with I.V. cytarabine may increase the risk of severe neurologic adverse events such as headache, paralysis, coma and stroke-like episodes (see *WARNINGS AND PRECAUTIONS: Neurologic*).

Combined use of methotrexate with other cytotoxic agents has not been studied and may increase the incidence of adverse effects.

Drug-Herb Interactions
The effects of herbal products on the pharmacokinetics of methotrexate have not been studied.

Drug-Laboratory Interactions
Interactions with laboratory tests have not been established.

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.

DOSAGE AND ADMINISTRATION

WARNINGS
The dose must be adjusted carefully depending on the body surface area if methotrexate is used for the treatment of tumour diseases.
Fatal cases of intoxication have been reported after administration of incorrect calculated doses. Health care professionals and patients should be fully informed about toxic effects.

Treatment should be initiated by or occur in consultation with a doctor with significant experience in cytostatic treatment.

Abitrexate Teva may be administered by intramuscular, intravenous (bolus injection or infusion), intrathecal, intra-ventricular or intra-arterial route.
For intrathecal administration, Abitrexate Teva is administered as a 1 mg/ml solution, using an appropriate sterile preservative-free medium such as Sodium Chloride Injection.
Dosages are based on the patient's bodyweight or surface area, except in the case of intrathecal or intra-ventricular administration, when a maximum dose of 15 mg is recommended.
Dosage should be reduced in cases of hematological deficiency and hepatic or renal impairment. When administered by infusion, Abitrexate Teva should only be diluted with normal saline. Larger doses (more than 100 mg) are usually administered by intravenous infusion over periods not exceeding 24 hours. Part of the dose may be administered as an initial rapid intravenous injection.

Abitrexate Teva has been used with beneficial effects in a wide variety of neoplastic diseases, alone and in combination with other cytotoxic agents, hormones, immunotherapy, radiotherapy or surgery. Therefore, dosage schedules vary considerably depending on the clinical use, particularly when intermittent high-dose regimens are followed by the administration of calcium leucovorin in order to rescue normal cells from toxic effects. Dosage regimens for calcium leucovorin rescue are discussed at the end of this section.
The following are some examples of the dosages of Abitrexate Teva that have been used for particular indications:

Choriocarcinoma and Other Trophoblastic Tumors
By the intramuscular route, in doses of 15-30 mg daily for a 5-day course. Such courses are usually repeated 3-5 times as required, with rest periods of 1 or more weeks between courses, until any toxic symptoms subside.
The effectiveness of therapy is ordinarily evaluated by 24-hour quantitative analysis of urinary human chorionic gonadotrophin (HCG), which should return to normal or less than 50 IU/24 hours, usually after the 3rd or 4th course of treatment, and also usually followed by a complete resolution of measurable lesions in 4-6 weeks. After the normalization of HCG, 1 or 2 courses of Abitrexate Teva are usually recommended. Before each course of the drug, careful clinical assessment is essential.
Higher doses of up to 60 mg i.m. every 48 hours may be administered for 4 doses, followed by calcium leucovorin rescue. This course is repeated at 7-day intervals until levels of urinary HCG return to normal. Not less than 4 courses of treatment are usually necessary. Patients with complications, such as extensive metastases, may be treated with Abitrexate Teva in cyclic combination with other cytotoxic drugs.

Chorioadenoma Destruens and Hydatidiform Mole
Since hydatidiform mole may be followed by choriocarcinoma, prophylactic chemotherapy with Abitrexate Teva has been recommended.
Chorioadenoma destruens is considered to be an invasive form of hydatidiform mole. Abitrexate Teva is administered in these disease states in doses similar to those recommended for choriocarcinoma.

Lymphoblastic Leukemia
Daily administration of Abitrexate Teva 3.3 mg/m^2, in combination with prednisone 60 mg/m^2, is used as induction therapy in acute lymphatic (lymphoblastic) leukemia in children and young adolescents.
Abitrexate Teva alone, or in combination with other agents, appears to be a drug of choice for securing maintenance of drug-induced remissions.
When remission is achieved and supportive care has produced general clinical improvement, maintenance therapy is initiated with intramuscular methotrexate 30 mg/m^2, twice weekly. It has also been administered intravenously in doses of 2.5 mg/kg body weight, every 14 days. If relapse does occur, reinduction of remission can again usually be obtained by repeating the initial induction regimen.

Meningeal Leukemia
Administer 12 mg/m^2 intrathecally, or an empirical dose of 15 mg. Dilute methotrexate to a concentration of 1 mg/ml using a sterile, preservative-free medium such as 0.9% Sodium Chloride Injection. Administer at intervals of 2-5 days, and repeat until the CSF cell count returns to normal. Then administer one additional dose.

Administration at intervals of less than 1 week may result in increased subacute toxicity. For prophylaxis against meningeal leukemia, the dosage is the same as for treatment, except for the intervals of administration.
The CSF volume is dependent on age, and not on body surface area (BSA). The CSF is at 40% of the adult volume at birth and reaches the adult volume in several years.

Intrathecal methotrexate 12 mg/m^2 (maximum 15 mg) has resulted in low CSF methotrexate concentrations and reduced efficacy in children, and high concentrations and neurotoxicity in adults. The following dosage regimen is based on age instead of BSA, and appears to result in more consistent CSF methotrexate concentrations and less neurotoxicity.

Intrathecal Methotrexate Dosage According to Age.

Age (years)	Dose (mg)
Under 1	6
1	8
2	10
Over 3*	12

*equal or higher than 3 years of age.

Because the CSF volume and turnover may decrease with age, a dose reduction may be indicated in elderly patients.

Lymphomas
In stage III, give methotrexate concomitantly with other antitumor agents.
Treatment in all stages generally consists of several courses with 7-10 day rest periods between each course. Lymphosarcomas in stage III may respond to combined drug therapy with methotrexate 0.625-2.5 mg/kg body weight/day.

Mycosis Fungoides
Although the usual treatment is by orally-administered methotrexate, methotrexate has also been given intramuscularly in doses of 50 mg once a week, or 25 mg twice weekly.

Breast Cancer
Abitrexate Teva in intravenous doses of 10-60 mg/m^2 is commonly included in cyclical combination regimens with other cytotoxic drugs in the treatment of advanced breast cancer.
Similar regimens have also been used as adjuvant therapy in early cases following mastectomy and/or radiotherapy.

Osteosarcoma
Effective therapy requires several cytotoxic chemotherapeutic agents. In addition to high-dose methotrexate with leucovorin rescue, these agents may include doxorubicin, cisplatin and the combination of bleomycin, cyclophosphamide and dactinomycin (BCD) in the doses and schedule shown in the Table below.

The starting dose for high-dose methotrexate treatment is 12g/m^2. If this is insufficient to produce a peak serum concentration of 1,000 micromole per L (0.001 mol/l) at the end of the methotrexate infusion, the dose may be increased to 15g/m^2 in subsequent treatments. If the patient is vomiting or unable to tolerate leucovorin orally, administer leucovorin I.V. or I.M. at the same dose and schedule.

Chemotherapy Regimens for Osteosarcoma

DRUG*	DOSE*	TREATMENT WEEK AFTER SURGERY
Methotrexate	12 g/m^2 I.V. as 4-hour infusion (starting dose)	4,5,6,7,11,12,15, 16,29,30,44,45

Leucovorin	15 mg orally every 6 hours for 10 doses, starting 24 hours after start of methotrexate infusion	
Doxorubicin as a single drug**	30mg/m^2/day I.V. x 3 days	8,17
Doxorubicin**	50 mg/m^2 I.V.	20,23,33,36
Cisplatin**	100 mg/m^2 I.V.	20,23,33,36
Bleomycin**	15 units/m^2 I.V. x 2 days	2,13,26,39,42
Cyclophosphamide**	600 mg/m^2 I.V. x 2 days	2,13,26,39,42
Dactinomycin**	0.6 mg/m^2 I.V. x 2 days	2,13,26,39,42

* Link MP, Goorin AM, Miseer AW et al. The effect of adjuvant chemotherapy on relapse-free survival in patients with osteosarcoma of the extremity, N. Engl. J. Med. 1986;3 14(25):1600-6.

** See each respective monograph for more complete information.
Dosage modifications may be necessary because of drug-induced toxicity.

Bronchogenic Carcinoma

Intravenous infusions of 20-100 mg/m^2 of Abitrexate Teva have been included in cyclical combination regimens for the treatment of advanced tumors. Higher doses of Abitrexate Teva with calcium leucovorin rescue may also be employed as sole treatment.

Head and Neck Cancer

Intravenous infusions of 240-1,080 mg/m^2 of Abitrexate Teva with calcium leucovorin rescue may be used both as preoperative adjuvant therapy and in the treatment of advanced tumors.
Intra-arterial infusions of Abitrexate Teva are indicated for certain head and neck cancers, although this route of administration is not used extensively.

Bladder Carcinoma

Intravenous injections or infusions of Abitrexate Teva in doses up to 100 mg every 1-2 weeks may be used in the treatment of bladder carcinoma. Diuretics and hydration are employed in an attempt to reduce the excessive drug toxicity that may occur in patients with renal impairment.

Psoriasis

Patients should be fully informed of the potential risks involved, and should be under the constant supervision of the treating physician.
The usual dose in cases of severe, uncontrolled psoriasis unresponsive to conventional therapy is 10-25 mg, administered intramuscularly or intravenously once a week and adjusted according to the patient's response.

Rheumatoid Arthritis

Note: The following recommendation is based on clinical studies whose tabulated dosages, as well as the references appear at the end of the paragraph.
Initially, 10 mg/week may be administered either intramuscularly or intravenously. The dosage may be increased to 25 mg/week.
Duration of treatment varied in clinical studies from 6 weeks to 13 weeks. An intramuscular dosage of 15 mg/week has been administered over a period of 6 months. An initial dosage of 10 mg/week IV, increased to a maximum of 50 mg/week I.V. has been administered over a period of 2 months.

Tabulated Summary of Dosages for the Use of Methotrexate (Parenteral) in Rheumatoid Arthritis

STUDY	DOSE
Herman (1)	10 mg/m^2, I.V.
Ahern (2)	15 mg , oral 15 mg, I.V.
Campbell (3)	30 mg/m^2, oral 30 mg/m^2, I.V. 30 mg/m^2, I.M.
Steinson (4)	7.5 mg-25 mg per week; I.M./oral
Michaels (5)	10 mg-50 mg per week, I.V.
Andersen (6)	10 mg per week, I.M., increased up to 25 mg if required.
Thompson (7)	10 mg or 25 mg per week, I.M.
Hoffmeister (8)	10 mg-15 mg per week, oral and I.M.
Weinstein (9)	7.5 mg-25 mg per week, oral and I.M.
Szanto (10)	5 mg-15 mg per week oral/I.M.
Tishler (11)	12.5 mg (7.5 mg-15 mg) per week, oral/I.M.
Suarez-Almazor (12)	10 mg per week I.M.
Rau (13)	15 mg per week I.M.

References

1. Herman, R.A., Veng-Pedersen, P., Hoffman, J., Koehnke, R., and Furst, D.E.: Pharmacokinetics of Low-Dose Methotrexate in Rheumatoid Arthritis Patients. *J. Pharm. Sci.* 78: 165-171, 1989. **2.** Ahern, M., Booth, J., Loxton, A., McCarthy, P.M., Meffin, P., Kevant, S.: Methotrexate Kinetics in Rheumatoid Arthritis: Is there an Interaction with Nonsteroidal Anti-Inflammatory Drugs. *J. Rheumatol.* 15: 1356-1360, 1988. **3.** Campbell, M.A., Perrier, D.G., Dorr, R. T., et. al.: Methotrexate Bioavailability .*Cancer Treat. Rev.* 69: 833-838, 1985. **4.** Steinson, K., Weinstein, A., Korn, J., Abeles, M.: Low-Dose Methotrexate in Rheumatoid Arthritis. *J. Rheumatol.* 9: 860-866, 1982. **5.** Michaels, R. M., Nashel, D.J., Leonard, A., Sliwinski, A.J., Derbes, A. J.: Weekly Intravenous Methotrexate in the Treatment of Rheumatoid Arthritis. *Arthritis Rheum.* 25: 339-341, 1982. **6.** Andersen, P.A., West S.G., O'Dell, J. R., Via C.S.,Claypool, R. G., Kotzin B. L. Weekly Pulse Methotrexate in Rheumatoid Arthritis. Clinical and Immunologic Effects in a Randomized, Double-Blind Study. *Ann. Intern. Med.,* 103: 489-496, 1985. **7.** Thompson, R. N., Watts, C., Edelman, J., Russell, A. S.,: A Controlled Two-Center Trial of Parenteral Methotrexate Therapy for Refractory Rheumatoid Arthritis. *J. Rheumatol.* 11: 760-763, 1984. **8.** Hoffmeister, R. T., :Methotrexate in Rheumatoid Arthritis: 15 Years Experience. *Am. J. Med.* 75: 69-73, 1983. **9.** Weinstein, A., Marlowe, S., Korn, J., Farouhan, F. Low-Dose Methotrexate Treatment of Rheumatoid Arthritis. Long-Term Observations. *Am. J. Med.* 79: 331-337, 1985. **10.** Szanto, E., Low-Dose Methotrexate in Rheumatoid Arthritis: Effect and Tolerance. An Open Trial and a Double- Blind Randomized Study. *Scand. J. Rheumatol.* 15: 97-102, 1986. **11.** Tishler, M., Caspi, D., Rosenbach, T. O., Fishel, B., Wigler, I., Segal, R., Gazit, E., Yaron, M.: Methotrexate in Rheumatoid Arthritis; A Prospective Study in Israeli Patients with immunogenetic Correlations. *Ann. Rheum. Dis.* 47: 654-659, 1988. **12.** Suarz-Almazor M. E., Fitzgerald, A., Grace, M., Russell, A. S.: a Randomized Controlled Trial of Parenteral Methotrexate Compared with Sodium Aurothiomalate (Myochrysine) in the Treatment of Rheumatoid Arthritis. *J. Rheumatol.* 15: 753-756, 1988. **13.** Rau, R., Herborn, G., Kargen, T., Menninger, H., Elhardt, D.A Blinded Randomized Trial of Methotrexate and Gold Sodium Aurothiomalate in Early Erosive Rheumatoid Arthritis. *Arthritis Rheum.* 32: S43, 1981 (Abstract).

Particular attention should be given to the appearance of liver toxicity by performing liver function tests before initiating Abitrexate Teva treatment, and repeating the tests at 2-4 month intervals during therapy. Therapy should not be instituted, or should be discontinued, if any abnormality of liver function tests or of a liver biopsy is present or develops during therapy. Such abnormalities should return to normal within 2 weeks, after which, treatment may be recommended at the discretion of the physician.
The use of Abitrexate Teva may permit the return to conventional topical therapy which should be encouraged.

Calcium Leucovorin Rescue
When administering high doses of methotrexate, the following guidelines for methotrexate therapy with leucovorin

rescue should be closely observed:

- Methotrexate administration should be delayed until recovery if:
  - the WBC count is less than 1500mm^3
  - the neutrophil count is less than 500mm^3
  - the platelet count is less than 75,000mm^3
  - the serum bilirubin level is more than 1.2 mg/dl
  - the ALT level is more than 450 U
  - mucositis is present, until there is evidence of healing
  - persistent pleural effusion and ascite are present; drain dry prior to infusion
- Adequate renal function must be documented.
- Serum creatinine must be normal and creatinine clearance must be more than 60 ml/min. before the initiating of therapy.
- Serum creatinine must be measured prior to each subsequent course of therapy. If serum creatinine has increased by 50% or more in comparison to a prior value, the creatinine clearance must be measured and documented to be more than 60 ml/min. (even if the serum creatinine is still within the normal range).
- Patients must be well hydrated, and must be treated with sodium bicarbonate for urinary alkalinization. Administer 1,000 ml/m^2 of intravenous fluid over 6 hours prior to initiating of the methotrexate infusion. Continue hydration at 125 ml/m^2/hour (3L/m^2/day) during methotrexate infusion, and for 2 days after the infusion has been completed.
- Alkalinize urine to maintain a pH above 7.0 during methotrexate infusion and leucovorin calcium therapy by giving sodium bicarbonate orally or by incorporation into a separate I.V. solution.
- Repeat serum creatinine and serum methotrexate 24 hours after starting methotrexate, and at least once daily until the methotrexate level is below 5x10^{-8} mol/l (0.05 micromolar).

Leucovorin Rescue Schedules Following Treatment with Higher Doses of Methotrexate

CLINICAL SITUATION	LABORATORY FINDINGS	LEUCOVORIN CALCIUM DOSAGE AND DURATION
Normal Methotrexate Elimination	Serum methotrexate level approximately 10 micromolar at 24 hours after administration, 1 micromolar at 48 hours and less than 0.2 micromolar at 72 hours	15 mg PO or I.V. every 6 hours for 60 hours (10 doses starting at 24 hours after start of methotrexate infusion).
Delayed Late Methotrexate Elimination	Serum methotrexate level remaining above 0.2 micromolar at 72 hours and more than 0.05 micromolar at 96 hours after administration.	Continue 15 mg PO or I.V. every 6 hours until methotrexate level is less than 0.05 micromolar.
Delayed Early Methotrexate Elimination and/or Evidence of Acute Renal Injury.	Serum methotrexate level of equal or higher than 50 micromolar at 24 hours or equal or higher than 5 micromolar at 48 hours after administration, or a 100% or greater increase in serum creatinine level at 24 hours after methotrexate administration (e.g. an increase from 0.5 mg/dl to a level equal or higher than 1.0 mg/dl or more)	150 mg I.V. every 3 hours, until methotrexate level is less than 1 micromolar; then 15 mg I.V. every 3 hours, until methotrexate level is less than 0.05 micromolar.

Patients who experience delayed/early methotrexate elimination are likely to develop irreversible oliguric renal failure. In addition to appropriate leucovorin therapy, these patients require continuing hydration and urinary alkalinization and close monitoring of fluid and electrolyte status, until the serum methotrexate level has fallen to less

than 0.05 micromolar and the renal failure has resolved.

Some patients will have abnormalities in methotrexate elimination or abnormalities in renal function following methotrexate administration which are significant, but less severe, than those described in the Table. These abnormalities may, or may not be, associated with significant clinical toxicity.

If significant clinical toxicity is observed, leucovorin rescue should be extended for an additional 24 hours (total of 14 doses over 84 hours) in subsequent courses of therapy.

When laboratory abnormalities or clinical toxicities are observed, the possibility that the patient is taking other medications which interact with methotrexate should be considered.

Older People
Dose reduction should be considered in elderly patient due to reduced liver and kidney function as well as reserves which occur with increased age.

Hepatic Function Impairment
If the bilirubin is between 3-5, or AST more than 180, dosage should be reduced by 25%. If bilirubin is more than 5, omit the dose.
Methotrexate should be administered with great caution, if at all, to patients with significant current or previous liver disease, especially when caused by alcohol. Methotrexate is contraindicated if bilirubin values are >5 mg/dl (85.5 μmol/L).

Missed Dose
If a scheduled dose is missed, contact your doctor for instructions.

Administration
Do not use this medicine if the solution is not clear.
Abitrexate Teva solution can be further diluted with 0.9% Sodium Chloride Injection or 5% Dextrose Injection.
Abitrexate Teva diluted solution stored between 15-25^{0}C and protected from light has a chemical and physical in-use stability of 24 hours.
From a microbiological point of view, unless the method of dilution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

Since methotrexate is poorly soluble in acid media, use of potassium chloride solution is not advisable.
If a preservative-free diluent is used, the solution should be used immediately because of the possibility of microbial growth.
Due to the number of brands available, stability data of methotrexate in plastic syringes and bags are not available.
Unused preservative-free products should be discarded due to the possibility of microbial growth.

Incompatibilities:
Other drugs should not be mixed with methotrexate in the same infusion bottle. Methotrexate has been reported to be incompatible with cytarabine, fluorouracil, and prednisolone sodium phosphate; however, its incompatibility with fluorouracil has been questioned and subsequent studies documented in the literature indicate that methotrexate and cytarabine are physically and chemically stable in intravenous admixtures over a range of concentrations and in a variety of typical vehicles. A mixture of methotrexate with cytarabine and hydrocortisone sodium succinate in various infusion fluids has been reported to be visually compatible for at least 8 hours at 25°C, although precipitation did not occur on storage for several days. In general, compatibility of any medicinal product admixed with Abitrexate Teva must be assured prior to patient administration.
Contact with acidic solutions should be avoided since Abitrexate Teva is sparingly soluble in acid media and precipitation may occur (see *WARNINGS AND PRECAUTIONS* for clinical incompatibilities).

OVERDOSAGE

Overdose with methotrexate has occurred with intrathecal administration, although intravenous and intramuscular overdose have also been reported.

Discontinue or reduce dosage at the first sign of ulceration or bleeding, diarrhea, or marked depression of the hematopoietic system. Leucovorin is indicated to diminish the toxicity and counteract the effect of overdosages of methotrexate. Leucovorin administration should begin as promptly as possible. As the time interval between methotrexate administration and leucovorin initiation increases, the effectiveness of leucovorin in counteracting toxicity decreases. Monitoring of the serum methotrexate concentration is essential in determining the optimal dose and duration of treatment with leucovorin.

In cases of massive overdosage, hydration and urinary alkalinization may be necessary to prevent the precipitation of methotrexate and/or its metabolites in the renal tubules. Generally, neither standard hemodialysis nor peritoneal dialysis has been shown to improve methotrexate elimination. However, effective clearance of methotrexate has been reported with acute, intermittent hemodialysis using a high-flux dialyzer.

There are published case reports of intravenous carboxypeptidase G2 treatment to hasten clearance of methotrexate in cases of overdoses.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Methotrexate is a folate antagonist.

Methotrexate inhibits dihydrofolate reductase (DHFR), the enzyme that reduces folic acid to tetrahydrofolic acid. Tetrahydrofolate must be regenerated via the DHFR-catalyzed reaction in order to maintain the intracellular pool of tetrahydrofolate one-carbon derivatives for both thymidylate and purine nucleotide biosynthesis. The inhibition of DHFR by folate antagonists (methotrexate) results in a deficiency in the cellular pools of thymidylate and purines and thus in a decrease in nucleic acid synthesis. Therefore, methotrexate interferes with DNA synthesis, repair, and cellular replication.

Methotrexate is most active against rapidly multiplying cells, because its cytotoxic effects occur primarily during the S phase of the cell cycle. Since cellular proliferation in malignant tissues is greater than in most normal tissues, methotrexate may impair malignant growth without irreversible damage to normal tissues. As a result, actively proliferating tissues such as malignant cells, bone marrow, fetal cells, buccal and intestinal mucosa, and cells of the urinary bladder are in general more sensitive to DHFR inhibition effects of methotrexate.

The cytotoxicity of methotrexate results from three important actions: inhibition of DHFR, inhibition of thymidylate synthase, and alteration of the transport of reduced folates. The affinity of DHFR to methotrexate is far greater than its affinity for folic acid or dihydrofolic acid, therefore, large doses of folic acid given simultaneously will not reverse the effects of methotrexate. However, Leucovorin calcium, a derivative of tetrahydrofolic acid may block the effects of methotrexate if given shortly after the antineoplastic agent. Methotrexate in high doses, followed by leucovorin rescue, is used as a part of the treatment of patients with non-metastatic osteosarcoma.

The original rationale for high-dose methotrexate therapy was based on the concept of selective rescue of normal tissues by leucovorin. More recent evidence suggests that high dose methotrexate may also overcome methotrexate resistance caused by impaired active transport, decreased affinity of dihydrofolic acid reductase for methotrexate, increased levels of dihydrofolic acid reductase resulting from gene amplification, or decreased polyglutamination of methotrexate. The actual mechanism of action is unknown.

Methotrexate has immunosuppressive activity. This may be a result of inhibition of lymphocyte multiplication. The mechanisms of action in the management of rheumatoid arthritis of the drug are not known, although suggested mechanisms have included immunosuppressive and/or anti-inflammatory effects.

In psoriasis, the rate of production of epithelial cells in the skin is greatly increased over normal skin. This

differential in proliferation rates is the basis for the use of methotrexate to control the psoriatic process.

Pharmacokinetics

Absorption: Methotrexate is generally completely absorbed following parenteral administration, and after intramuscular injection peak serum concentrations occur in 30 to 60 minutes.

Distribution: Methotrexate is widely distributed into body tissues with highest concentrations in the kidneys, gallbladder, spleen, liver and skin. Methotrexate in serum is approximately 50% proteinbound. After intravenous administration, the initial volume of distribution is approximately 0.18 L/kg (18% of body weight) and steady-state volume of distribution is approximately 0.4 to 0.8 L/kg (40% to 80% of body weight). Methotrexate does not penetrate the blood-cerebrospinal fluid barrier in therapeutic amounts when given parenterally.

Metabolism: At low doses, methotrexate does not appear to undergo significant metabolism; following high-dose therapy, methotrexate undergoes hepatic and intracellular metabolism to polyglutamated forms that can be converted back to methotrexate by hydrolase enzymes.

These polyglutamates act as inhibitors of dihydrofolate reductase and thymidylate syntheses. Small amounts of methotrexate polyglutamates may remain in tissues for extended periods. The retention and prolonged drug action of these active metabolites vary among different cells, tissues and tumours. A small amount of metabolism to 7-hydroxymethotrexate may occur at doses commonly prescribed. The aqueous solubility of 7-hydroxymethotrexate is 3 to 5 fold lower than the parent compound.

Excretion: Renal excretion is the primary route of elimination and is dependent upon dosage and route of administration. Total clearance averages 12 L/h, but there is wide interindividual variation. Excretion of single daily doses occurs through the kidneys in amounts from 80% to 90% within 24 hours. Repeated daily doses result in more sustained serum levels and some retention of methotrexate over each 24-hour period, which may result in accumulation of the drug within the tissues. The liver cells appear to retain certain amounts of the drug for prolonged periods even after a single therapeutic dose. Methotrexate is retained in the presence of impaired renal function and may increase rapidly in the serum and in the tissue cells under such conditions. Methotrexate does not penetrate the blood- cerebrospinal fluid barrier in therapeutic amounts when given parenterally. High concentrations of the drug, when needed, may be attained by direct intrathecal administration.

The terminal half-life reported for methotrexate is approximately 3 to 10 hours for patients receiving treatment for psoriasis, rheumatoid arthritis or low dose antineoplastic therapy (less than 30 mg/m^2). For patients receiving high doses of methotrexate, the terminal half-life is 8 to 15 hours.
Methotrexate clearance rates vary widely and are generally decreased at higher doses.

Special Populations and Conditions

Nursing Women: Methotrexate has been detected in human breast milk and is contraindicated during breast-feeding. The highest breast milk to plasma concentration ratio reached was 0.08:1.
Pediatrics: In pediatric patients receiving methotrexate for acute lymphocytic leukemia (6.3 to 30 mg/m^2), the terminal half-life has been reported to range from 0.7 to 5.8 hours.

Geriatrics: The clinical pharmacology of methotrexate has not been well studied in older individuals. Due to diminished hepatic and renal function as well as decreased folate stores in this population, relatively low doses (especially in RA and psoriasis indications) should be considered and these patients should be closely monitored for early signs of toxicity.

Renal Impairment: Since the renal excretion of methotrexate is the primary route of elimination with 80% to 90% of the single daily doses of methotrexate excreted through the kidneys within 24 hours, methotrexate is retained in the presence of impaired renal function and may increase rapidly in the serum and in the tissue cells under such conditions, thus in patients with renal impairment the health care provider may need to adjust the dose to prevent accumulation of drug.

Hepatic Impairment: Hepatic excretion of methotrexate is a minor route of elimination. However, the liver cells

appear to retain certain amounts of the drug for prolonged periods even after a single therapeutic dose. Special caution is indicated in the presence of pre-existing liver damage or impaired hepatic function.

STORAGE AND STABILITY

Keep in a safe place out of the reach of children.

Store in a dry place at room temperature (15-25°C) in a well closed packaging. Protect from light.

Use immediately after preparation and discard unused portion. It is recommended that the vial remains in the carton until time of use. Abitrexate Teva vial should be inspected for damage and visible signs of leaks. If there are signs of breakage or leakage from the vial, do not use. Incinerate the unopened package.
For storage conditions after dilution see *DOSAGE AND ADMINISTRATION – Administration.*

SPECIAL HANDLING INSTRUCTIONS

General: Individuals who have contact with anti-cancer drugs, or work in areas where these drugs are used, may be exposed to these agents in air or through direct contact with contaminated objects.
Safe Handling and Disposal: Good medical practice will minimize exposure of persons involved with frequent handling of this drug as outlined below:
Handling**:**

1. Methotrexate has no vesicant properties and does not show acute toxicity on topical contact with the skin or mucous membranes. However, persons involved with handling cytotoxic drugs should avoid contact with skin and inhalation of airborne particles.
2. Preparation of antineoplastic solutions should be done in a vertical laminar flow hood (Biological Safety Cabinet - Class II).
3. Personnel preparing methotrexate solutions should wear PVC gloves, safety glasses and protective clothing such as disposable gowns and masks.
4. Personnel regularly involved in the preparation and handling of antineoplastics should have bi-annual blood examinations.

Disposal:

1. Avoid contact with skin and inhalation of airborne particles by use of PVC gloves and disposable gowns and masks.
2. All needles, syringes, vials and other materials for disposal which have come in contact with Abitrexate Teva should be segregated in plastic bags, sealed and marked as hazardous waste. Incinerate at 1000°C or higher. Sealed containers may explode if a tight seal exists.
3. If incineration is not available, rinse all needles, syringes, tubing and other materials for disposal which have come in contact with methotrexate solutions with water and discard in the sewer system with running water.

Rinse vials with the appropriate quantity of water with the aid of a hypodermic syringe. Withdraw the solution and discard in the sewer system with running water. Dispose of rinsed equipment and vials in a safe manner.
Cleaning: Non-disposable equipment that has come in contact with Abitrexate Teva may be rinsed with water and washed thoroughly with soap and water.
Spillage/Contamination: Wear gloves, mask and protective clothing. Place spilled material in an appropriate container (i.e. cardboard for broken glass) and then in a polyethylene bag; absorb remains with gauze pads or towels; wash area with water and absorb with gauze or towels again and place in bag; seal, double bag and mark as a hazardous waste. Dispose of waste by incineration or by other methods approved for hazardous materials. Personnel involved in clean up should wash with soap and water.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Abitrexate Teva is available as a 25 mg/ml solution in 2 ml, 4 ml, 8 ml, 20 ml and 40 ml colorless type I glass vials. Not all packs may be marketed.

Composition: Each milliliter contains 25 mg of methotrexate with the following non-medicinal ingredients: sodium chloride, sodium hydroxide (for pH adjustment), hydrochloric acid (for pH adjustment), water for injections.

Excipient with known effect:
Each ml contains approximetly 1.93 mg sodium.

The solution is preservative-free.

PRODUCT REGISTRATION NO.:

048.96.23819

LICENSE HOLDER AND MANUFACTURER

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This leaflet was revised in January 2022 according to MOHs guidelines.