# הודעה על החמרה (מידע בטיחות) בעלון לרופא
(מעודכן 3102.50)

**__ February 1, 2015 __ תאריך**

**שם תכשיר באנגלית ומספר הרישום**

**ABITREXATE 25 mg/ml Solution for Injection**
**ABITREXATE 1g/10 ml (100 mg/ml) Solution for Injection**

**מספרי רישום** **25mg/ml: 048 96 23819 05**
**1g/10ml: 100 38 24914 05**

**שם בעל הרישום** **Salomon, Levin & Elstein Ltd, POBox 3696, Petach Tikva 49133_**

טופס זה מיועד לפרוט ההחמרות בלבד !

**ההחמרות המבוקשות**

| טקסט חדש | טקסט נוכחי | פרק בעלון |
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| | | **Indication** |
| Methotrexate should not be used in pregnancy, and in patients in a poor state of nutrition. Methotrexate is furthermore contraindicated in patients with serious renal (Creatinine clearance less than 20 ml/min) severe liver disorders, bone marrow hypoplasia, leucopenia, thrombocytopenia, anaemia, alcohol abuse, methotrexate hypersensitivity and lung toxicity due to methotrexate. During methotrexate therapy no breastfeeding should be given.<br>Serious, acute or chronic infections such as tuberculosis and HIV.<br>Ulcers of the oral cavity and known active gastrointestinal ulcer disease.<br>Concurrent vaccination with live vaccines | Methotrexate should not be used in pregnancy, and in patients in a poor state of nutrition. Methotrexate is furthermore contraindicated in patients with serious renal liver disorders, bone marrow hypoplasia, leucopenia, thrombocytopenia, anaemia, alcohol abuse, methotrexate hypersensitivity and lung toxicity due to methotrexate. During methotrexate therapy no breastfeeding should be given. | **Contraindications** |
| **WARNINGS**<br>The dose must be adjusted carefully depending on the body surface area if methotrexate is used for the treatment of tumour diseases.<br>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<br>Treatment should be initiated by or occur in consultation with a doctor with significant experience in cytostatic treatment.<br><br>*Older People*<br>Dose reduction should be considered in elderly patient due to reduced liver and kidney functin as well as reserves which occur with increased age.<br><br>*Hepatic Function Impairment*<br>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.<br>Methotrexate should be administered with great caution, if at all, to patients with significant current or previous liver disease, especially when caused by alcohol.<br>Methotrexate is contraindicated if bilirubin values are >5 mg/dl (85.5 µmol/L). | *Hepatic Function Impairment*<br>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. | **Posology, dosage & administration** |

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| Fatal toxicity in association with intravenous and intrathecal administration due to dose miscalculation has been reported. Particular caution should be exercised when calculating the dose.<br><br>Because of the risk of severe toxic reactions (which can be fatal), methotrexate must only be used in life-threatening neoplastic diseases. Deaths have been reported during treatment of malignancies with methotrexate. The doctor should inform the patient of the risks of treatment and the patient should be monitored constantly by the doctor.<br><br>Methotrexate has reportedly caused fetal death and/or congenital malformations. Treatment of neoplastic diseases is not recommended in women of childbearing potential unless there are clear medical indications that the benefits of treatment can be expected to outweigh the conceivable risks. Methotrexate affects spermatogenesis and oogenesis during the period in which it is administered, which can result in reduced fertility. These effects may be reversible on discontinuing treatment.<br><br>***Tumor lysis syndrome***<br>Like other cytotoxic agents, methotrexate can induce tumour lysis syndrome in patients with rapidly growing tumours. Appropriate supportive treatment and pharmacological measures can prevent or alleviate such complications.<br><br>***Methotrexate and NSAIDs***<br>Unexpected severe (including fatal) myelosuppression, aplastic anaemia and gastrointestinal toxicity have been reported in connection with concomitant treatment with methotrexate (usually at a high dose) and non-steroidal anti-inflammatory agents (NSAIDs).<br><br>Concomitant methotrexate treatment and radiotherapy can increase the risk of soft tissue necrosis and osteonecrosis.<br><br>Intrathecal and intravenous administration of methotrexate can result in acute encephalitis and acute encephalopathy, possibly with a fatal outcome. Patients with periventricular CNS lymphoma who are given methotrexate intrathecally have reportedly developed cerebral herniation.<br><br>***Methotrexate and pleural effusion/ascites***<br>Methotrexate is eliminated slowly from collections of fluid (e.g. pleural effusion, ascites). This results in a prolonged terminal half-life and unexpected toxicity. In patients with significant collections of fluid, drainage of the fluid before treatment is started and monitoring of plasma methotrexate levels are recommended.<br><br>If stomatitis, diarrhoea, haematemesis or black stool occurs, therapy with methotrexate should be discontinued due to the danger of haemorrhagic enteritis or death from intestinal perforation or dehydration.<br><br>Conditions in which there is folic acid deficiency can increase the risk of methotrexate toxicity.<br><br>In association with intrathecal administration or in high dose treatment, methotrexate must not be mixed with solutions which contain preservatives.<br><br>Solutions of methotrexate which contain the preservative benzyl alcohol are not recommended for use in infants. Gasping syndrome with fatal outcome has been reported in infants following intravenous treatment with solutions containing the preservative benzyl alcohol. Symptoms include rapid onset of respiratory problems, hypotension, bradycardia and cardiovascular collapse. | | **Special Warnings and Special Precautions for Use** |

***Infection or immunological conditions***
Methotrexate must be used with great care in connection with active infection and is usually contraindicated in patients with manifest suppression of the immune response or where immunodeficiency is demonstrated by laboratory tests.

Pneumonia (which in certain cases can lead to respiratory failure) can occur. Potentially fatal opportunistic infections including Pneumocystis carinii pneumonia can occur in association with methotrexate treatment. When a patient exhibits pulmonary symptoms, the possibility of Pneumocystis carinii pneumonia should be considered.

***Immunisation***
Methotrexate may interfere with results of immunological tests Immunisation after a vaccination may be less effective in association with methotrexate treatment. Particularly caution should be exercised in the presence of inactive, chronic infections (e.g. herpes zoster, tuberculosis, hepatitis B or C) due to possible activation. Immunisation with live viruses is not normally recommended.

***Skin toxicity***: Due to the risk of phototoxicity, the patient must avoid sunlight and solarium.

**Monitoring treatment**
Patients on methotrexate treatment must be closely monitored so that toxic effects can be detected immediately. Analyses before treatment must include a full blood count with differential and platelet counts, liver enzymes, testing for hepatitis B and C infections, renal function test and x-ray of the lungs. Toxic effects of methotrexate can occur even with low doses and therefore it is important to monitor treated patients carefully. Most undesirable effects are reversible if detected early.

After initiation of treatment or when there is a change in the dose, or during periods in which there is an increased risk of elevated levels of methotrexate (e.g. in dehydration), monitoring should be performed.

Bone marrow biopsy must be performed as necessary.

**Serum methotrexate level monitoring** can significantly reduce methotrexate toxicity and routine monitoring of serum methotrexate level is necessary depending on dosage or therapy protocol.

**Leucopenia and thrombocytopenia** occur usually 4 -14 days after administration of methotrexate. In rare cases recurrence of leucopenia may occur 12 - 21 days after administration of methotrexate. Methotrexate therapy should only be continued if the benefit outweighs the risk of severe myelosuppression.

**Haematopoietic suppression**: Haematopoietic suppression induced by methotrexate may occur abruptly and at apparently safe doses. In the event of any significant drop in leukocytes or platelets, treatment must be discontinued immediately and appropriate supportive therapy instituted. Patients must be instructed to report all signs and symptoms suggestive of infection. In patients concomitantly taking haematotoxic medications (e.g. leflunomide), the blood count and platelets should be closely monitored.

**Liver function tests**: Particular attention should be paid to the onset of liver toxicity. Treatment should not be initiated or should be discontinued if there are any abnormalities in liver function tests or liver biopsies, or if these develop during therapy. Such abnormalities should return to normal within two weeks; after which, treatment may be resumed at the discretion of the doctor. Further research is needed to establish whether serial liver chemistry tests or propeptide of type III collagen can detect hepatotoxicity sufficiently. This assessment should differentiate between patients without any risk factors and patients with risk factors, e.g. excessive prior alcohol consumption, persistent elevation of liver enzymes, history of liver disease, family history of hereditary liver disorders, diabetes mellitus, obesity and previous contact with hepatotoxic drugs or chemicals and prolonged methotrexate treatment or cumulative doses of 1.5 g or more.

Screening for liver-related enzymes in serum: A transient rise in transaminase levels to twice or three times the upper limit of normal has been reported with a frequency of 13 - 20%. In the event of a constant increase in liver related enzymes, consideration should be given to reducing the dose or discontinuing therapy.

Patients suffering from insulin-dependent diabetes should be carefully monitored because liver cirrhosis and an increase in transaminase can occur.

Due to the potentially toxic effect on the liver, additional hepatotoxic medications should not be given during treatment with methotrexate unless clearly necessary and alcohol consumption should be avoided or greatly reduced. Closer monitoring of liver enzymes should be undertaken in patients concomitantly taking other hepatotoxic medications (e.g. leflunomide). The same should also be taken into consideration if haematotoxic medications are co-administered.

Malignant lymphomas may occur in patients receiving low-dose methotrexate; in which case, methotrexate must be discontinued. If lymphomas should fail to regress spontaneously, initiation of cytotoxic therapy is required.

**Renal function**: methotrexate treatment in patients with impaired renal function should be monitored via renal function tests and urinalysis, since impaired renal function reduces the elimination of methotrexate, which may result in severe adverse reactions.

In cases of possible renal impairment (e.g. in elderly patients), close monitoring of renal function is required. This is particularly applies to the co-administration of medicinal products which affect methotrexate excretion cause kidney damage (e.g. non-steroidal anti-inflammatory drugs) or which can potentially lead to haematopoietic disorder. Dehydration may also potentiate the toxicity of methotrexate. Alkalinisation of the urine and increase a high diuresis is recommended.

**Respiratory System**: Acute or chronic interstitial pneumonitis, often associated with blood eosinophilia, may occur and deaths have been reported. Symptoms typically include dyspnoea, cough (especially a dry non-productive cough) and fever for which patients should be monitored at each follow-up visit. Patients should be informed of the risk of pneumonitis and advised to contact their doctor immediately should they develop persistent cough or dyspnoea.

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| Methotrexate should be withdrawn from patients with pulmonary symptoms and a thorough investigation (including chest x-ray) should be made to exclude infection. If methotrexate induced lung disease is suspected treatment with corticosteroids should be initiated and treatment with methotrexate should not be restarted.<br><br>Pulmonary symptoms require a quick diagnosis and discontinuation of methotrexate therapy. Pneumonitis can occur at all doses.<br><br>**Vitamin preparations** or other products containing folic acid, folinic acid or their derivatives may decrease the effectiveness of methotrexate.<br><br>***Children***<br>Methotrexate should be used with caution in paediatric patients. Treatment should follow currently published therapy protocols for children. Serious neurotoxicity, frequently manifested as generalised or focal seizures has been reported with unexpectedly increased frequency among paediatric patients with acute lymphoblastic leukaemia who were treated with intermediate-dose intravenous methotrexate (1 g/m$^2$). Symptomatic patients were commonly noted to have leukoencephalopathy and/or microangiopathic calcifications on diagnostic imaging studies.<br><br>***Elderly***<br>Because of deterioration in liver and kidney function as well as reduced folic acid reserves, relatively low doses should be considered in elderly patients. These patients must be closely monitored for early signs of toxicity.<br><br>***Sodium***<br>Abitrexate solution or injection contains sodium as follows:<br>***Abitrexate Injection 25 mg/ml Solution for Injection***<br>Each ml contains 1.93 mg sodium.<br><br>***Abitrexate Injection 1g/10 ml (100 mg/ml) Solution for Injection***<br>Sodium content:<br>Each ml contains 10 mg sodium.<br><br>This should be taken into consideration by patients on a controlled sodium diet. | | |
| Oral antibiotics (including tetracyclines, chloramphenicol and non-absorbable broad-spectrum antibiotics) may influence the intestinal flora and inhibit methotrexate (re)absorption.<br>In isolated cases, trimethoprim/sulfamethoxazole has reportedly increased myelosuppression in patients treated with methotrexate, probably due to reduced tubular secretion and/or an additive antifolate effect<br><br>*Ciprofloxacin:* Excretion of methotrexate possibly reduced (increased risk of toxicity).<br><br>*Leflunomide:* Methotrexate in combination with leflunomide can increase the risk of pancytopenia.<br><br>*Probenecid:* Renal tubular transport is diminished by probenecid, and its use together with methotrexate must be avoided.<br><br>*Penicillins:*Penicillins can reduce renal clearance | Oral antibiotics (including tetracyclines, chloramphenicol and non-absorbable broad-spectrum antibiotics) may influence the intestinal flora and inhibit methotrexate (re)absorption. | **Interaction with Other Medicaments and Other Forms of Interaction** |

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| of methotrexate. Haematological and gastrointestinal toxicity have been observed in combination with high and low dose methotrexate.<br><br>*Chemotherapeutic products:* An increase in renal toxicity can be observed when high doses of methotrexate are given in combination with potentially nephrotoxic chemotherapeutic agents (e.g. cisplatin).<br><br>*Cytarabine:* Concomitant therapy with cytarabine and methotrexate can increase the risk of severe neurological side effects ranging from headache to paralysis, coma and stroke-like episodes.<br><br>*Hepatotoxic products:* The risk of increased hepatotoxicity when methotrexate is administered concurrently with other heptatotoxic products has not been studied. Hepatotoxicity has however been reported in such cases. Patients receiving concomitant treatment with drugs with a known hepatotoxic effect (e.g. leflunomide, azathioprine, sulfasalazine, retinoids) must be carefully monitored for signs of any increase in hepatotoxicity.<br><br>*Theophylline:* Methotrexate can reduce clearance of theophylline. Theophylline levels must therefore be monitored during concomitant treatment with methotrexate.<br><br>*Mercaptopurine:* Methotrexate increases plasma content of mercaptopurine. The combination of methotrexate and mercaptopurine can therefore require dose adjustment.<br><br>*Drugs with high plasma protein binding:* Methotrexate is partially bound to serum albumin. Other highly bound drugs such as salicylates, phenylbutazone, phenytoin and sulfonamides can increase the toxicity of methotrexate by means of displacement.<br><br>*Furosemide:* Concomitant administration of furosemide and methotrexate can result in increased levels of methotrexate due to competitive inhibition of tubular secretion.<br><br>*Proton pump inhibitors:* Literature data indicate that co-administration of proton pump inhibitors and methotrexate, especially at high dose, may result in elevated and prolonged plasma levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicity. | | |
| Because methotrexate may cause blurred vision, paresis and hemiparesis, fatigue and dizziness, the ability to drive and use machines may be adversely affected. | Because methotrexate may cause blurred vision, paresis and hemiparesis, the ability to drive and use machines may be adversely affected. | **Effect on ability to drive and use machines** |

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| (see Contraindications)<br><br>*Pregnancy*<br>Methotrexate can cause foetal death, embryotoxicity, abortion or teratogenic effects when administered to pregnant women. During pregnancy, especially in the first trimester, cytotoxic drugs must only be given when strictly indicated, weighing the needs of the mother against the risks to the foetus. Treatment with methotrexate during the first trimester has resulted in a high risk of malformations (in particular cranial malformation and malformation of the extremities).<br><br>*Breastfeeding*<br>Methotrexate passes into breast milk in quantities such that there is a risk to the child even at therapeutic doses. Breast feeding must therefore be discontinued during treatment with methotrexate.<br><br>*Fertility*<br>Methotrexate may be genotoxic. Women of childbearing potential must not be treated with methotrexate until pregnancy has been excluded. Since in men spermatogenesis can be affected by methotrexate, pregnancy should be avoided if either partner is receiving methotrexate. The optimum time interval between discontinuation of methotrexate therapy in either partner and pregnancy has not been established. The recommended interval in published literature varies between three months and one year. Both men and women receiving methotrexate should be informed of the potential risk of adverse effects on reproduction. Women of childbearing potential should be fully informed of the potential hazard to the fetus should they become pregnant during methotrexate therapy.<br><br>~~Methotrexate has been observed to be foetotoxic in humans: abortion, mortality of the foetus and congenital defects have occurred in pregnant women receiving methotrexate, especially in the first three months of pregnancy. During methotrexate therapy, breast-feeding should not be given.~~ | Methotrexate has been observed to be foetotoxic in humans: abortion, mortality of the foetus and congenital defects have occurred in pregnant women receiving methotrexate, especially in the first three months of pregnancy. During methotrexate therapy, breast-feeding should not be given. | **Fertility, pregnancy and Lactation** |
| *Conventional and high dose therapy*<br>The frequency and degree of severity of undesirable effects depends on the dose administered, the duration of exposure and method of administration, but side effects have been seen at all doses and can occur at any time during treatment. Most undesirable effects are reversible when detected at an early stage. When severe reactions occur, the dose should be reduced or treatment discontinued and appropriate measures initiated. If treatment with methotrexate is resumed, this should be done with caution after adequate consideration of the further need for the drug. Increased vigilance with regard to any recurrence of toxicity is required.<br><br>The most frequently reported undesirable effects include ulcerative stomatitis, leukopenia, nausea and bloating. Other frequently reported undesirable effects are feeling unwell, unusual tiredness, chills and fever, dizziness, reduced resistance to infections. Treatment with folinic acid during high dose therapy can counteract or alleviate a number of undesirable effects. Temporary discontinuation of therapy is recommended if there are signs of leukopenia. | In general the incidence and severity of acute side effects is related to the dosage and frequency of administration. The most frequent adverse effects are ulcerative stomatitis, leucopenia, nausea and gastrointestinal problems. Other frequently occurring side-effects are feeling unwell, inexplicable fatigue, chills and fever, dizziness and reduced resistance to diseases.<br>In view of the oncological background by the combined therapy and the underlying disease makes it difficult to attribute a certain reaction to this drug.<br><br>The undesirable effects with methotrexate are summarized by organ system.<br><br>**Blood and lymphatic system disorders**<br>Methotrexate may suppress haematopoiesis and cause anaemia, leucopenia and/or thrombocytopenia. In patients with existing haematopoietic insufficiencies this drug should be used with care, or not at all.<br>In psoriasis treatment should be | **Adverse events** |

| Organ system class | Very common (≥1/10) | Common (≥1/100 to <1/10) | Uncommon (≥1/1,000 to <1/100) | Rare (≥1/10,000 to <1/1,000) | Very rare (<1/10,000) | Not known (cannot be estimated from the available data) |
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| Infections and infestations | | Herpes zoster | | | Sepsis, opportunistic infections (may be fatal in some cases), infections caused by the cytomegaly virus | |
| Cardiac disorders | | | | Pericarditis, pericardial effusion, pericardial tamponade | | |
| Blood and lymphatic syste | | leukocytopenia, thrombo- | Pancytopenia, agranulo-cyto | Megaloblastic anaemia | Severe courses of bone marr | Haemorrhage, haematoma |

discontinued immediately in case of a significant drop in the blood count. In the treatment of neoplasia methotrexate may only be continued if the possible cure justifies the risk of serious myelosuppression. Myelosuppression may also occur after intrathecal administration of methotrexate. Patients with serious granulocytopenia and fever should undergo immediate examination and usually require parenteral broad-spectrum antibiotics.

**Immune system disorders**
Methotrexate should be used with extreme care in case of active infection and usually is contra-indicated in patients with immunodeficiency syndromes. During a methotrexate treatment immunisation may not be effective. Immunisation with live vaccine is usually not recommended. Disseminated vaccinia infections have been reported after a small pox immunization in patients undergoing methotrexate treatment.
Hypogammaglobulinaemia has been observed rarely.
**Nervous system disorders**
Headache, drowsiness, blurred vision, aphasia, hemiparesis, paresis and convulsions have been reported after methotrexate administration.
There are reports of leucoencephalopathy after intravenous administration of methotrexate to patients who underwent craniospinal irradiation.
Chronic leucoencephalopathy was also reported in patients with osteosarcoma who were administered high dosages of methotrexate with calcium folinate rescue therapy, even without cranial irradiation. Discontinuation of methotrexate treatment does not always result in complete recovery.
A transient acute neurological syndrome has been observed in patients who underwent high dose methotrexate treatment. The clinical manifestations may consist of abnormal behaviour, focal sensomotoric phenomena, and abnormal reflexes. The exact cause of these symptoms is unknown.
After intrathecal administration of methotrexate, the possible toxic side-effects pertaining to the central nervous system may be classified in the following way:

- chemical arachnoiditis with symptoms as headache, backache, neck stiffness and fever
- paresis, usually transient, with paraplegia involving one or more spinal nerve roots
- leucoencephalopathy with confusion, agitation, somnolence, ataxia, dementia and sometimes serious convulsions.

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| m disorders | | cytopenia and anaemia | sis, haematopoietic disorders | | ow depression aplastic anaemia Lymph-adenopathy, lymphoproliferative disorders (partly reversible) eosinophilia and neutropenia | |
| Immune system disorders | | | Anaphylactoid reactions, allergic vasculitis | | Immuno-suppression hypogamma-globulinaemia | |

| **Organ system class** | **Very common (≥1/10)** | **Common (≥1/100 to <1/10)** | **Uncommon (≥1/1,000 to <1/100)** | **Rare (≥1/10,000 to <1/1,000)** | **Very rare (<1/10,000)** | **Not known (cannot be estimated from the available data)** |
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| Psychiatric disorders | | | | | Insomnia, cognitive dysfunction | psychosis |
| Nervous system disor | | Headache fatigue | Vertigo confusion | Severely impaired visio | Pain, muscular asthenia | |

**Respiratory, thoracic and mediastinal disorders**
Death by interstitial pneumonitis has been reported and chronic interstitial obstructive lung disease sometimes occurred. Pulmonary symptoms (in particular a dry, non-productive cough) or a non-specific pneumonitis during the methotrexate treatment may indicate a potentially dangerous lesion and require discontinuation of the treatment and a thorough examination. Although symptoms may be varying a patient with methotrexate induced lung disease typically shows fever, cough, dyspnoea, hypoxemia and infiltration in lung radiography. An infection should be excluded. This condition may occur at any dosage. Methotrexate related lung pathology has rarely been described after intrathecal administration of methotrexate. At the onset of methotrexate induced lung disease, the re-administration of methotrexate is contra-indicated.

**Gastrointestinal disorders**
Gingivitis, pharyngitis, stomatitis, anorexia, nausea, vomiting, diarrhoea, haematemesis, melena, gastrointestinal ulceration, bleeding and enteritis.

When vomiting, diarrhoea, or stomatitis occurs, with possible dehydratation, methotrexate treatment should be discontinued until recovery.
Methotrexate should be used with extreme care in case of peptic ulceration or ulcerative colitis.

**Hepato-biliary disorders**
Methotrexate may cause acute (increase in transaminases) or chronic (fibrosis and cirrhosis) hepatoxicity. Chronic toxicity is potentially lethal. It usually occurs after chronic use (mostly 2 years or longer) and after a total dose of at least 1.5 g. In studies with psoriasis patients hepatotoxicity appeared to be determined by the total cumulative dose. The effect is potentiated by alcoholism, obesity, diabetes and advanced age. A correct correlation has not yet been determined.
Information on progression and reversibility of lesions is not available. Care should be taken in the presence of existing liver damage or decreased liver function.
Liver function tests, including serum albumin should be carried out regularly prior to administration. Test results are often normal in cases of fibrosis and cirrhosis. These conditions can only be diagnosed by biopsy.
In case of psoriasis and rheumatoid arthritis it is recommended to perform a liver biopsy after a total cumulative dose of 1.5 g. Intermediate fibrosis or any

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| ders | | drowsiness | depression seizures convulsion encephalo-pathy | nmood alterations paresis, effect on speech including dysarthria and aphasia, myelopathy | orparesthesia of the extremities, myasthenia, changes in sense of taste (metallic taste), meningism (paralysis, vomiting), acute aseptic meningitis | | cirrhosis usually prompts discontinuation of the therapy. Although mild changes usually are no reason to avoid or discontinue methotrexate treatment, the drug should be used with care.<br><br>**Skin and subcutaneous disorders**<br>Erythema, pruritis, urticaria, photosensivity, depigmentation, alopecia, ecchymosis, telangiectasia, acne, furunculosis. Psoriatric lesions may worsen by exposure to UV-radiation. Radiation dermatitis and sunburn may flare up by methotrexate administration.<br><br>**Musculoskeletal, connective tissue and bone disorders**<br>In combination with radiotherapy there is an increased risk of soft tissue necrosis.<br><br>**Renal and urinary disorders**<br>Serious nephropathy or renal insufficiency, azotemia, cystitis and hematuria; High dosages of methotrexate may cause renal toxicity with acute renal insufficiency. Nephrotoxicity is usually caused by the deposition of methotrexate and 7-hydroxymethotrexate in the renal tubuli.<br><br>**Reproductive system and breast disorders**<br>Defective oogenesis or spermatogenesis, transient oligospermia, menstrual dysfunction and vaginal discharge, infertility, abortion, foetal deviations, suppression of spermatogenesis, loss of libido, and impotence may occur.<br><br>Other rare adverse effects related to or ascribed to the use of methotrexate are arthralgia/myalgia, diabetes, osteoporosis, lymphomas, opportunistic infections, vasculitis, and sudden death. Incidental cases of anaphylactic reactions have been reported.<br>Also pancytopenia and sudden increase in the number of rheumatoid nodules have been reported in patients with rheumatoid arthritis.<br><br>A few cases of toxic epidermal necrolysis and Steven-Johnson syndrome were reported. | |
| Eye disorders | | | | visual disturbances, blurred vision | Conjunctivitis Retinopathy, transient blindness/loss of vision, periorbital oedema, blepharitis, epiphora, photophobia | | | |
| Neoplasms benign, malignant and | | | individual cases of lymphoma | | Tumour lysis syndrome | | | |

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| unspecified (incl cysts and polyps) | | | which abated in a number of cases once methotrexate treatment had been discontinued. In a recent study, it was not possible to establish that methotrexate therapy increases the incidence of lymphomas | | | | | |
| Vascular disorders | | | Vasculitis | hypotension thrombo-embolic events reactions (incl. arterial thrombosis, cerebral thrombosis, | | Cerebral oedema, petechie | | |

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| | | | | thrombo-phlebitis, deep vein thrombosis, retinal vein thrombosis, pulmonary embolism) | | |

| **Organ system class** | **Very common** (≥1/10) | **Common** (≥1/100 to <1/10) | **Uncommon** (≥1/1,000 to <1/100) | **Rare** (≥1/10,000 to <1/1,000) | **Very rare** (<1/10,000) | **Not known** (cannot be estimated from the available data) |
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| Respiratory, thoracic and mediastinal disorders | | Pulmonary complications due to interstitial alveolitis/pneumonitis and related deaths (independent of dose and duration of methotrexate | Pulmonary fibrosis | Pharyngitis, apnoea, bronchial asthma | Pneumocystis carinii pneumonia, shortness of breath, chronic obstructive pulmonary disease. Infections including pneumonia have also been | Acute pulmonary oedema |

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| | | treatment). Typical symptoms may be: general illness; dry, irritating cough; shortness of breath progressing to rest dyspnoea, chest pain, fever. If such complications are suspected, methotrexate treatment must be discontinued immediately and infections (including pneumonia) must be excluded. | | | observed. Pleural effusion | | | |
| Gast | Loss | Diar | gastr | Ging | Hae | Toxi | | |

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| roint estin al disor ders | of appe tite, naus ea, vom iting , abdo mina l pain, infla mma tion and ulcer ation s of the muc ous mem bran e of mou th and thro at (esp ecial ly duri ng the first 24- 48 hour s after admi nistr ation of meth otre xate) . Sto mati tis, dysp epsi a | rhoe a (esp ecial ly duri ng the first 24- 48 hour s after admi nistr ation of meth otre xate) . | ointe stina l blee ding and ulcer s, panc reati tis | ivitis , Ente ritis, mela ena (blo ody stool s), mala bsor ptio n | mate mesi s (vo miti ng bloo d), toxic meg acol on | c meg acol on |

| **Org an syst em class** | **Ver y com mon** (≥1/ 10) | **Co mm on** (≥1/ 100 to <1/1 0) | **Unc om mon** (≥1/ 1,00 0 to <1/1 00) | **Rar e** (≥1/ 10,0 00 to <1/1 ,000 ) | **Ver y rare** (<1/ 10,0 00) | **Not kno wn** (can not be esti mate d from the avail able data) |
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| Hepato-biliary disorders | Increase in liver-related enzymes (ALAT, ASAT, alkaline phosphatase nd bilirubin). | | Development of liver fattening, fibrosis and cirrhosis (occurs frequently despite regularly monitored, normal values of liver enzymes); diabetic metabolism; drop of serum albumin. | Acute hepatitis and hepatotoxicity | Reactivation of chronic hepatitis, acute liver degeneration. Furthermore, herpes simplex hepatitis and liver insufficiency have been observed (also see the notes regarding liver biopsy in section 4.4). | Metabolic disorder | | |
| Skin and subcutaneous tissue disorders | | Exanthema, erythema, itching | Urticaria, photo-sensibility, enhanced pigmentation of the skin, hair loss, increase of rheumatic nodu | Increased pigmentary changes of nails, acne, petechiae, ecchymoses, erythema multiforme, | Furunculosis, telea ngiectasis, acute paronychia, Furthermore, nocardiosis, histoplasma and cryptoco | Exfoliative dermatitis, skin necrosis, | | |

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| | | | les, herpes zoster, painful lesions of psoriatic plaque; severe toxic reactions: vasculitis, herpetiform eruption of the skin, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome). | cutaneous erythematous eruptions. | ccus mycosis and disseminated herpes simplex have been reported. Allergic vasculitis, hidradenitis | |
| Musculoskeletal system, connective tissue and bone disorders | | | Osteoporosis, Arthralgia, myalgia | Stress fracture | | |
| Renal and urinary disorders | | | Inflammation and ulceration of the urin | Renal failure, oliguria, anuria, azot | Proteinuria | |

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| | | | ary bladder (possibly with haematuria), dysuria. | aemia, hyper-uricaemia, elevated serum creatinine and urea level | | |

| **Organ system class** | **Very common (≥1/10)** | **Common (≥1/100 to <1/10)** | **Uncommon (≥1/1,000 to <1/100)** | **Rare (≥1/10,000 to <1/1,000)** | **Very rare (<1/10,000)** | **Not known (cannot be estimated from the available data)** |
|---|---|---|---|---|---|---|
| Reproductive system and breast disorders | | | Inflammation and ulceration of the vagina | | Loss of libido, impotence, oligospermia, impaired menstruation, Vaginal discharge, infertility, gynaecomastia | |
| General disorders and administration site conditions | | | Severe allergic reactions progressing to anaphylactic | | Fever, impaired wound healing | |

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| | | | shock; | | | |
| Metabolism and nutrition disorders | | | | Diabetes Mellitus | | |

The following undesirable effects have also been reported, but their frequency has not been established: Pneumocystis carinii pneumonia, (including reversible cases), foetal death, damage to the foetus, abortion.

***Systemic organ toxicity***

*Lymphoma*

Malignant lymphoma which can go into remission after discontinuation of the treatment with methotrexate can occur in patients on low dose therapy, and may not therefore require any cytotoxic treatment. Methotrexate should be discontinued first and appropriate treatment initiated if the lymphoma does not regress.

*Haematological*

Methotrexate can suppress haematopoiesis and cause anaemia, aplastic anaemia, pancytopenia, leukopenia, neutropenia and/or thrombocytopenia. Methotrexate must be administered with caution to patients with malignancies and underlying factors affecting haematopoiesis. When treating neoplastic conditions, treatment with methotrexate should only be given provided the potential benefits outweigh the risk of myelosuppression.

*Lungs*

Lung disease caused by methotrexate, including acute or chronic interstitial pneumonitis, is a potentially dangerous complication, which can occur at any time during the course of treatment. This undesirable effect has been reported at low doses and is not always totally reversible. Deaths have been reported.

Signs of pulmonary involvement or symptoms such as dry non-productive cough, fever, chest pains, dyspnoea, hypoxemia and infiltrate on x-ray of the lungs, or non-specific pneumonitis which occurs in connection with methotrexate therapy, may indicate potentially serious damage and requires discontinuation of treatment and careful investigation. Lung changes can occur at all doses. The possibility of infection (including pneumonia) must be excluded.

*Gastrointestinal*

If vomiting, diarrhoea or stomatitis occur, with resulting dehydration, methotrexate therapy must be discontinued until the patient has recovered. Haemorrhagic enteritis and deaths caused by intestinal perforation can occur. Methotrexate must be used with great caution in patients with peptic ulcers or ulcerative colitis. Stomatitis can be prevented or alleviated by folinic acid mouthwashes.

*Liver*

Methotrexate involves a potential risk of acute hepatitis

and chronic (fibrosis and cirrhosis) hepatotoxicity. Chronic toxicity is potentially fatal and occurs commonly after long-term use (in general after 2 years or more) and after a total cumulative dose greater than 1.5 g. In studies of psoriasis patients hepatotoxicity was seen to be proportional to the cumulative dose and was potentiated by alcoholism, overweight, diabetes and age.

Transient deterioration in liver enzyme values is frequently seen after methotrexate treatment and does not usually necessitate adjustment of treatment. Existing abnormal liver values and/or reduction in serum albumin can indicate severe hepatotoxicity.

Methotrexate has caused reactivation of hepatitis B infections and exacerbation of hepatitis C infections, in some cases with fatal outcome. Some cases of hepatitis B reactivation have occurred following discontinuation of methotrexate. Clinical and laboratory tests should be performed to investigate any occurrence of liver disease in patients with prior hepatitis B or C infections. Based on these investigations, treatment with methotrexate may prove unsuitable for certain patients.

In the event of impaired liver function, the undesirable effects of methotrexate (in particular stomatitis) can be exacerbated.

*Kidneys*
Methotrexate can cause kidney damage which can result in acute renal failure. Renal function can be exacerbated following high dose therapy to such an extent that the excretion of methotrexate is inhibited, as a result of which systemic methotrexate toxicity can occur. In order to prevent renal failure, alkalinisation of the urine and adequate fluid intake (at least 3 l/day) are recommended. Measurement of serum methotrexate and renal function is recommended.

*Skin*
Serious, in some cases fatal skin reactions, including toxic epidermal necrolysis (Lyell's syndrome), Stevens-Johnson syndrome and erythema multiforme have been reported within a few days of oral, intramuscular, intravenous or intrathecal treatment with methotrexate in single or repeat doses. Radiation dermatitis and sunburn can be accentuated after use of methotrexate.

*CNS*
There are reports of leukoencephalopathy after intravenous treatment with methotrexate in patients who have undergone craniospinal radiotherapy. Severe neurotoxicity, often manifested as generalised or focal seizures have been reported with an unexpected increase in frequency in children with acute lymphoblastic leukaemia treated with a moderately high dose of intravenous methotrexate (1 g/m2). Symptomatic patients frequently had leukoencephalopathy and/or microangiopathic calcifications in x-ray investigations.

Chronic leukoencephalopathy has also been reported in patients treated with repeated high doses of methotrexate together with folinic acid, even without concomitant cranial radiotherapy. Discontinuation of the methotrexate therapy did not always result in full recovery. Leukoencephalopathy has also been reported in patients treated with methotrexate tablets.

One transient acute neurological syndrome has been observed in patients undergoing high dose therapy. Manifestations of this neurological syndrome can include abnormal behaviour, focal sensorimotor symptoms including transient blindness, and abnormal

reflexes. The exact cause is unclear.

Cases of neurological side effects ranging from headache to paralysis, coma and stroke-like episodes have been reported, primarily in children and adolescents receiving concomitant medication with cytarabine.

*Intrathecal therapy*

The subacute neurotoxicity is usually reversible after discontinuing methotrexate.

| **Organ system class** | **Common (>1/100)** |
|---|---|
| Central and peripheral nervous system disorders | Headache, chemical arachnoiditis, subacute neurotoxicity, necrotising demyelinating leukoencephalopathy |
| Gastrointestinal disorders | Nausea and vomiting |
| General disorders and administration site conditions | Fever |

*Chemical arachnoiditis*, which can occur a few hours after intrathecal administration of methotrexate is characterised by headache, back pain, stiff neck, vomiting, fever, meningism and pleocytosis in the cerebrospinal fluid similar to that in bacterial meningitis. Arachnoiditis generally disappears within a few days.

*Subacute neurotoxicity,* common after frequently repeated intrathecal administration, mainly affects the motor functions in the brain or spinal cord. Paraparesis/paraplegia, with involvement of one or more spinal nerve roots, tetraplegia, cerebellar dysfunction, cranial nerve paralysis and epileptic seizures can occur.

*Necrotising demyelinating leukoencephalopathy* can occur several months or years after starting intrathecal therapy. The condition is characterised by progressive neurological deterioration with insidious onset, confusion, irritability and somnolence. Ultimately severe dementia, dysarthria, ataxia, spasticity, seizures and coma can occur. The condition can be fatal. Leukoencephalopathy occurs primarily in patients who have received large quantities of intrathecal methotrexate in combination with cranial radiotherapy and/or systemically administered methotrexate.

Signs of neurotoxicity (meningeal inflammation, transient or permanent paresis, encephalopathy) must be followed up after intrathecal administration of methotrexate.

**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. Healthcare professionals are asked to report any suspected adverse reactions to the Ministry of Health according to the National Regulation by using an online form (http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.health.gov.il ) or by email (adr@MOH.HEALTH.GOV.IL ).

In general the incidence and severity of acute side-effects is related to the dosage and frequency of administration. The most frequent adverse effects are ulcerative stomatitis, leucopenia, nausea and gastrointestinal problems. Other frequently occurring side-effects are feeling unwell, inexplicable fatigue, chills and fever, dizziness and reduced resistance to diseases.
In view of the oncological background by the combined therapy and the underlying disease makes it difficult to attribute a certain reaction to this drug.

The undesirable effects with methotrexate are summarized by organ system.

**Blood and lymphatic system disorders**
Methotrexate may suppress haematopoiesis and cause anaemia, leucopenia and/or thrombocytopenia. In patients with existing haematopoietic insufficiencies this drug should be used with care, or not at all.

In psoriasis treatment should be discontinued immediately in case of a significant drop in the blood count. In the treatment of neoplasia methotrexate may only be continued if the possible cure justifies the risk of serious myelosuppression. Myelosuppression may also occur after intrathecal administration of methotrexate. Patients with serious granulocytopenia and fever should undergo immediate examination and usually require parenteral broad-spectrum antibiotics.

**Immune system disorders**
Methotrexate should be used with extreme care in case of active infection and usually is contra-indicated in patients with immunodeficiency syndromes. During a methotrexate treatment immunisation may not be effective.
Immunisation with live vaccine is usually not recommended. Disseminated vaccinia infections have been reported after a small pox immunization in patients undergoing methotrexate treatment.
Hypogammaglobulinaemia has been observed rarely.
**Nervous system disorders**
Headache, drowsiness, blurred vision, aphasia, hemiparesis, paresis and convulsions have been reported after methotrexate administration.
There are reports of leucoencephalopathy after intravenous administration of methotrexate to patients who underwent craniospinal irradiation.
Chronic leucoencephalopathy was also reported in patients with osteosarcoma who were administered high dosages of methotrexate with calcium folinate rescue therapy, even without cranial irradiation. Discontinuation of methotrexate treatment does not always result in complete recovery.
A transient acute neurological syndrome has been observed in patients who underwent high dose methotrexate treatment. The clinical manifestations may consist of abnormal behaviour, focal sensomotoric phenomena, and abnormal reflexes. The exact cause of these symptoms is unknown.
After intrathecal administration of methotrexate, the possible toxic side-effects pertaining to the central nervous system may be classified in the following way:
- chemical arachnoiditis with symptoms as headache, backache, neck stiffness and fever
- paresis, usually transient, with paraplegia involving one or more spinal nerve roots
- leucoencephalopathy with confusion, agitation, somnolence, ataxia, dementia and sometimes serious convulsions.

**Respiratory, thoracic and mediastinal disorders**
Death by interstitial pneumonitis has been reported and

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| chronic interstitial obstructive lung disease sometimes occurred. Pulmonary symptoms (in particular a dry, non-productive cough) or a non-specific pneumonitis during the methotrexate treatment may indicate a potentially dangerous lesion and require discontinuation of the treatment and a thorough examination. Although symptoms may be varying a patient with methotrexate induced lung disease typically shows fever, cough, dyspnoea, hypoxemia and infiltration in lung radiography. An infection should be excluded. This condition may occur at any dosage. Methotrexate related lung pathology has rarely been described after intrathecal administration of methotrexate. At the onset of methotrexate induced lung disease, the re-administration of methotrexate is contra-indicated.<br><br>**Gastrointestinal disorders**<br>Gingivitis, pharyngitis, stomatitis, anorexia, nausea, vomiting, diarrhoea, haematemesis, melena, gastrointestinal ulceration, bleeding and enteritis. When vomiting, diarrhoea, or stomatitis occurs, with possible dehydratation, methotrexate treatment should be discontinued until recovery. Methotrexate should be used with extreme care in case of peptic ulceration or ulcerative colitis.<br><br>**Hepato-biliary disorders**<br>Methotrexate may cause acute (increase in transaminases) or chronic (fibrosis and cirrhosis) hepatoxicity. Chronic toxicity is potentially lethal. It usually occurs after chronic use (mostly 2 years or longer) and after a total dose of at least 1.5 g. In studies with psoriasis patients hepatotoxicity appeared to be determined by the total cumulative dose. The effect is potentiated by alcoholism, obesity, diabetes and advanced age. A correct correlation has not yet been determined.<br><br>Information on progression and reversibility of lesions is not available. Care should be taken in the presence of existing liver damage or decreased liver function. Liver function tests, including serum albumin should be carried out regularly prior to administration. Test results are often normal in cases of fibrosis and cirrhosis. These conditions can only be diagnosed by biopsy. In case of psoriasis and rheumatoid arthritis it is recommended to perform a liver biopsy after a total cumulative dose of 1.5 g. Intermediate fibrosis or any cirrhosis usually prompts discontinuation of the therapy. Although mild changes usually are no reason to avoid or discontinue methotrexate treatment, the drug should be used with care.<br><br>**Skin and subcutaneous disorders**<br>Erythema, pruritis, urticaria, photosensivity, depigmentation, alopecia, ecchymosis, telangiectasia, acne, furunculosis. Psoriatric lesions may worsen by exposure to UV-radiation. Radiation dermatitis and sunburn may flare up by methotrexate administration.<br><br>**Musculoskeletal, connective tissue and bone disorders**<br>In combination with radiotherapy there is an increased risk of soft tissue necrosis.<br><br>**Renal and urinary disorders**<br>Serious nephropathy or renal insufficiency, azotemia, cystitis and hematuria; High dosages of methotrexate may cause renal toxicity with acute renal insufficiency. Nephrotoxicity is usually caused by the deposition of methotrexate and 7-hydroxymethotrexate in the renal tubuli.<br><br>**Reproductive system and breast disorders**<br>Defective oogenesis or spermatogenesis, transient | | |

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| ~~oligospermia, menstrual dysfunction and vaginal discharge, infertility, abortion, foetal deviations, suppression of spermatogenesis, loss of libido, and impotence may occur.~~<br><br>~~Other rare adverse effects related to or ascribed to the use of methotrexate are arthralgia/myalgia, diabetes, osteoporosis, lymphomas, opportunistic infections, vasculitis, and sudden death. Incidental cases of anaphylactic reactions have been reported.~~<br>~~Also pancytopenia and sudden increase in the number of rheumatoid nodules have been reported in patients with rheumatoid arthritis.~~<br><br>~~A few cases of toxic epidermal necrolysis and Steven-Johnson syndrome were reported.~~ | | |
| | | **Pharmacodynamic properties** |
| | | **Pharmacokinetic properties** |
| Experience of overdose with the product has in general been associated with oral and intrathecal treatment, although overdose in association with intravenous and intramuscular administration has also been reported. Reports of oral overdose have often been due to accidental daily instead of weekly ingestion. Commonly reported symptoms following oral overdose include the symptoms and signs seen at pharmacological doses, in particular haematological and gastrointestinal reactions such as leukopenia, thrombocytopenia, anaemia, pancytopenia, neutropenia, myelosuppression, mucositis, stomatitis, oral ulceration, nausea, vomiting, gastrointestinal ulceration, gastrointestinal bleeding. In certain cases no symptoms were reported. There are reports of deaths associated with overdose. In these cases there were also reports of conditions involving sepsis or septic shock, renal failure and aplastic anaemia.<br><br>The most common symptoms of intrathecal overdose are CNS symptoms including headache, nausea and vomiting, seizures or convulsions and acute toxic encephalopathy. In certain cases, no symptoms were reported. There have been reports of deaths following intrathecal overdose. In these cases there were also reports of cerebellar herniation accompanying elevated intracranial pressure and toxic encephalopathy.<br><br>*Recommended treatment*<br><br>*Antidote therapy:* Folinic acid should be given parenterally at a dose at least the size of the methotrexate dose and should wherever possible be administered within an hour. Folinic acid is indicated to minimise toxicity and counter the effect of methotrexate overdose. Folinic acid treatment should be initiated as soon as possible. The longer the interval between the administration of methotrexate and the initiation of folinic acid, the less the effect of folinic acid in suppressing the toxic effect. Monitoring of serum methotrexate concentrations is necessary to be able to determine the optimum dose of folinic acid and the length of the treatment.<br><br>In the event of a major overdose, hydration and alkalinisation of the urine may be required to prevent precipitation of methotrexate and/or its metabolites in the renal tubules. Neither standard haemodialysis nor peritoneal dialysis have been shown to increase the elimination of methotrexate. Acute intermittent haemodialysis with the use of highly permeable dialyser | Symptoms of overdosage include one or more adverse effects to a serious extent. With prolonged treatment the toxic effects will be more pronounced. In case of overdosage folinic acid should be administered as soon as possible: at least 15 mg every 3 hours intravenously. The dose frequency and dose height of folinic acid can be adapted to the amount of methotrexate given and the methotrexate plasma concentration (see also high-dose methotrexate). An intrathecal overdosage can be treated by immediate lumbar puncture, subsequent ventriculolumbar perfusion and systemic folinic acid therapy. If necessary, general supportive measures should be taken and blood transfusion should be given. | **Overdose** |

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| may be attempted for methotrexate intoxication.<br><br>Intrathecal overdose may require intensive systemic supportive measures such as systemic administration of high doses of folinic acid, alkaline diuresis, acute CSF drainage and ventricular lumbar perfusion.<br><br>~~Symptoms of overdosage include one or more adverse effects to a serious extent. With prolonged treatment the toxic effects will be more pronounced. In case of overdosage folinic acid should be administered as soon as possible: at least 15 mg every 3 hours intravenously. The dose frequency and dose height of folinic acid can be adapted to the amount of methotrexate given and the methotrexate plasma concentration (see also high-dose methotrexate). An intrathecal overdosage can be treated by immediate lumbar puncture, subsequent ventriculolumbar perfusion and systemic folinic acid therapy. If necessary, general supportive measures should be taken and blood transfusion should be given.~~ | | |
| Animal studies show that methotrexate impairs fertility and that it is embryotoxic, foetotoxic and teratogenic. Methotrexate is mutagenic in vivo and in vitro, but the clinical significance is unknown since rodent carcinogenicity studies have produced differing results. Chronic toxicity studies in mice, rats and dogs showed toxic effects in the form of gastrointestinal lesions, myelosuppression and hepatotoxicity.<br><br>~~No particulars.~~ | No particulars. | **Preclinical safety data** |