

Read all of this patient information leaflet carefully; it contains important information about the drug.

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This product has been prescribed for you personally and must not be passed on to anyone else.

In this leaflet:

1. What Methotrexate 25 mg/ml solution for injection is and what it is used for
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Methotrexate 25 mg/ml solution for injection

Each 1 ml of this sterile solution for injection contains methotrexate sodium equivalent to 25 milligrams of active substance methotrexate.

Other ingredients are sodium hydroxide, sodium chloride, water for injections and nitrogen.

Marketing Authorisation Holder:

hameln pharma plus gmbh
Langes Feld 13
31789 Hameln, Germany

Manufacturer:

Haupt Pharma Wolfkratshausen GmbH
Pfaffenrieder Str. 5
82515 Wolfkratshausen, Germany

Distributor:

hameln pharmaceuticals ltd
Gloucester, UK

1. What Methotrexate 25 mg/ml solution for injection is and what it is used for

Methotrexate 25 mg/ml solution for injection is a yellow and sterile solution in clear glass vials.

Methotrexate is one of a group of medicines known as antimetabolites. It is used in the treatment of cancer as well as psoriasis including psoriatic arthritis. It stops a substance called dihydrofolate reductase from working. This substance is an enzyme, which is important in "cell growth (replication)". By inhibiting the enzyme, cancer cells will eventually "die".

Methotrexate helps patients with psoriasis by killing the cells in the skin that are growing too fast. It is these rapidly growing cells that cause the raised patches of skin in psoriasis.

Pack sizes:

The solution for injection is available in

- packs of 1, 5 or 10 vial(s) containing 2 ml solution. This corresponds to 50 mg of active substance methotrexate per vial.
- packs of 1, 5 or 10 vial(s) containing 20 ml solution. This corresponds to 500 mg of active substance methotrexate per vial.
- packs of 1 or 5 vial(s) containing 40 ml solution. This corresponds to 1,000 mg of active substance methotrexate per vial.
- a pack of 1 vial containing 200 ml solution. This corresponds to 5,000 mg of active substance methotrexate per vial.

2. Before receiving Methotrexate 25 mg/ml solution for injection

2.1 You should not receive Methotrexate 25 mg/ml solution for injection

- if you have ever had any allergic reaction to methotrexate or any of the ingredients of this product
- if you have severe problems with your kidneys
- if you have severe problems with your liver, including alcoholic liver disease, abnormal blood counts, fibrosis, cirrhosis or recent active hepatitis
- if you suffer from alcoholism
- if you have any serious blood disorders (anaemia, a reduction in white cell number (leucopenia) or platelet number (thrombocytopenia))
- if you have an active infection
- if you have a medical condition, or are receiving medication, which lowers your resistance to infection
- if you are pregnant or intend to become pregnant, or are breast-feeding, as the drug can harm unborn and breast-fed infants.

2.2 Take special care with Methotrexate 25 mg/ml solution for injection

- if you have impaired respiratory function
- if you have mild to moderate kidney or liver problems, or a mild to moderate blood disorder
- if you have diarrhoea
- if you have ulcers in your mouth, stomach or intestine (large bowel)
- if you have ascites (collection of liquid in the free abdominal cavity) and/or pleural effusions (collection of liquid in the pleural cavity)

- if you are receiving or intend to receive any vaccine, as methotrexate can reduce their effect
- if you have had radio- or chemotherapy before (especially of the pelvis), or are receiving radiotherapy concurrently
- if you have an impaired general condition (if you feel weak or infirm)
- if you are of advanced age
- if Methotrexate 25 mg/ml solution for injection is given to very young children.

Please consult your doctor, even if these statements were applicable to you at any time in the past.

2.3 Interactions with other drugs

Please inform your doctor if you are taking or have recently taken any other medicines, even those not prescribed.

Medications which can be influenced by or can influence the effect of methotrexate negatively:

- pain-killers such as salicylates (e.g. aspirin), amidopyrine derivatives, phenylbutazone and leflunomide
- diphenylhydantoin (e.g. phenytoin, an antiepileptic agent)
- barbiturates and tranquillisers (sedative agents)
- antibiotics (medication against bacteria), e.g. tetracyclines, penicillins, chloramphenicol, cotrimoxazole and sulphonamides
- cytostatics (medication against cancer), e.g. doxorubicin, mercaptopurine, procarbazine, cisplatin, L-asparaginase and 5-fluorouracil
- Disease-modifying antirheumatic drugs (DMARD; drugs that are used to treat rheumatoid arthritis)
- probenecid (uricosuric agent used in the prophylaxis of gout)
- p-aminobenzoic acid (used in sun creams)
- non-steroidal anti-inflammatory drugs (NSAIDs; medications against "rheumatism", e.g. indomethacin, ibuprofen)
- anti-folate drugs (e.g. nitrous oxide or co-trimoxazole)
- p-aminohippuric acid (substance to check kidney function)
- pyrimethamine (medication against malaria)
- cholestyramine (lipid-lowering agent)
- acitretin or other retinoids (for psoriasis or skin disorders)
- theophylline (used mainly in bronchial asthma)
- erythrocyte concentrates (for blood transfusion)
- nitrous oxide-based anaesthetics
- omeprazole (used in the therapy of gastric ulcers)
- sulphasalazine (for ulcerative colitis)
- tetrahydrofolic acid preparations
- oral antidiabetics (medications to treat diabetes) and diuretics (increase urine output)
- hypoglycaemics (lower blood sugar levels)
- other medicinal products with nephrotoxic and hepatotoxic potential (incl. alcohol)
- vaccinations
- azathioprine (an immunosuppressive drug)
- vitamin preparations containing folic acid or its derivatives

Please note that these statements may also apply to products used some time ago or at some time in the future.

2.4 Pregnancy

Do not take Methotrexate 25 mg/ml solution for injection if you are pregnant because it causes a variety of malformations or even the death of the foetus. Women must not get pregnant during treatment with Methotrexate 25 mg/ml solution for injection. If you get pregnant during treatment with Methotrexate 25 mg/ml solution for injection, please inform your doctor immediately!

Special indications for contraception:

Methotrexate temporarily influences sperm and egg production. During treatment and up to 6 months after treatment is stopped, you must practice effective contraception. In this respect, it is of no importance whether the male or the female partner takes Methotrexate 25 mg/ml solution for injection!

2.5 Breast-feeding

Do not take Methotrexate 25 mg/ml solution for injection during breast-feeding, since methotrexate is excreted into the breast milk. Methotrexate can seriously harm breast-fed infants.

3. How Methotrexate 25 mg/ml solution for injection is administered

Your doctor or nurse will give you Methotrexate 25 mg/ml solution for injection injecting it either into the central nervous system (intraventricular or intrathecal administration only for the 2 ml vial), into one of your veins (e.g. as bolus or infusion), arteries, or a muscle.

During your treatment, you will have a number of tests, such as regular blood tests to check that appropriate blood levels of methotrexate are attained and that your kidneys are eliminating excess drug properly. Other tests are performed routinely at the start and during the course of therapy (e.g. chest X-ray, liver function test, full blood count and urinalysis).

Your doctor may instruct you to take sodium bicarbonate or acetazolamide tablets while receiving your injections to help make sure that methotrexate is not concentrated in the kidneys. If you receive methotrexate in high doses, you will receive calcium folinate as well to lessen the side effects of methotrexate. Your doctor will decide on a suitable dose for you. Doses vary considerably and will depend on the underlying disease. It is possible that you will only get methotrexate. In the case of cancer, it is also possible that you will receive so-called combination therapy in which you must take several medications. Your body weight, age, general condition of health, your response to the drug and whether other medicines are required at the same time will also influence the dose you receive.

4. Possible Side Effects

Like all medicines Methotrexate 25 mg/ml solution for injection can have side effects:

Methotrexate has the potential for serious, sometimes fatal toxicity. Because the toxic reactions can occur at any time during therapy, your doctor should observe you closely and must inform you of early signs and symptoms of toxicity.

If you think you have an infection, a sore throat, fever or chills during treatment, you should tell your doctor immediately.

The most common undesirable effects are ulcerative stomatitis, leucopenia, nausea, and abdominal discomfort.

Unwanted effects of Methotrexate 25 mg/ml solution for injection are

- Blood picture changes - e.g. your vulnerability for infections may increase, you may suffer from unusual bleeding or bruising and you may observe signs of anaemia (weakness, tiredness, difficulties in breathing)
- disorders of the mouth, stomach and intestines like mucositis (mucus membrane inflammation, e.g. inflammation of the gums, tongue, throat, mouth, intestines as well as ulcerations), lack of appetite, feeling sick, vomiting, diarrhoea, unusual bleeding from the mouth, stomach and intestines, inflammation of the pancreas, increased risk of perforation, melaena (red to black stools), malabsorption (disturbances of uptake of nutrition with consequences such as body weight loss), and toxic megacolon (severe complication with massive dilatation of the colon and severe pain, for example)
- renal failure, impairment of renal function, inflammation of the urinary bladder, blood in the urine, reduced or faulty formation of sperm and egg cells, menstrual dysfunction (periods may become less frequent or even stop completely), infertility, abortion, malformations of the foetus and pain or difficulty in passing urine
- damage to the liver such as fibrosis (increase in the connective tissue), cirrhosis (transformation of the tissue with hardening and abolition of the normal structure of the organ), hepatitis (inflammation of the liver), acute liver cell death, fatty degeneration of the liver or other histologic (tissue) changes in the liver
- damage to the lungs such as inflammation and fibrosis (increase in the connective tissue); the pulmonary toxicity may manifest as fever, cough (especially dry and nonproductive), difficulties or increase in the frequency of breathing, chest pain, hypoxaemia (lack of oxygen in the blood), and/or abnormal findings on chest radiography and/or tests of respiratory function, and infections.
- adverse reactions of the skin such as formation of blisters, becoming red and inflamed, loss of skin tissue, vasculitis (inflammation of blood vessels), rash, itching, nettle rash, photosensitivity, pigmentary changes (discolouration of the skin), telangiectasia (expansion

of small superficial blood vessels in the skin), acne, formation of boils, point-like or small flat bleeding, an increase in rheumatic nodules, loss of hair, worsening of psoriasis (with concomitant UV therapy), increased colouration or inflammation or detachment of the nails, a "recall" of radiation dermatitis (inflammation of the skin) and sunburn

- leucoencephalopathy (inflammation of the brain), manifested by ventricular enlargement (expansion of the fluid spaces inside the brain), confusion, shaking, irritability, sleepiness, ataxia (disturbance of balance and co-ordination), dementia, feeling sick, fever, and occasionally seizures or coma, significant intellectual deficit, headache, drowsiness, speech disorder, incomplete palsy affecting one or both sides of the body, fits, dizziness, vomiting, mental disturbance, pain, muscle weakness, paraesthesia (pins-and-needles sensation), subtle cognitive dysfunction (easily disturbed attention), mood swings, unusual sensations in the head, and even death
- unwanted reactions of the eyes like swelling, inflammation of the eyelid edges, conjunctivitis (inflammation of the eye conjunctiva), unusual formation of tears, photophobia, and impairment of vision
- allergic reactions, cerebral oedema (swelling of the brain), haematoma, nodulosis (formation of nodules under the skin), loss of interest in sex / impotence, chills, fever without any detectable cause, decreased resistance to infection, upper respiratory tract infection, abnormal tissue cell changes, metabolic disorders, hyperuricaemia (increased blood levels of uric acid, possibly leading to gout), diabetes, osteoporosis and other bone disorders, including aseptic necrosis of the femoral head (loss of bone tissue in the hip joint), pains in the joints, muscle pain, malaise and undue fatigue, development of the breast gland in males, ringing in the ears, sweating, vaginal discomfort, in rare cases pericarditis (inflammation of the outer lining of the heart), pericardial effusion and tamponing (collection of fluid and blood, respectively, in the space between the outer lining of the heart and the heart muscle), low blood pressure, complications resulting from the formation of blood clots in veins and arteries, tumour lysis syndrome (renal failure due to massive destruction of rapidly growing tumour cells) and even sudden death
- in cases of acute lymphocytic leukaemia, methotrexate can cause pain in the left epigastric region (the area overlying the stomach, below the left lower border of the rib cage; inflammation of the space above the spleen due to destruction of the leukaemic cells)
- other possible complications from administration into the central nervous system include Guillain-Barré syndrome (inflammation of the central nervous system), nerve palsies, and cerebellar dysfunction, arachnoiditis (inflammation of one of the membranes surrounding the spinal cord) manifested as headache, back pain, neck stiffness, and/or fever, subacute myelopathy (disorder affecting the spinal cord) manifested as complete or incomplete palsy of the lower limbs (paraparesis or paraplegia).

There have been reports on the manifestation of lymphomas which were, in some cases, reversible after discontinuing methotrexate therapy. The potential of methotrexate to produce other cancers in humans has been evaluated in several studies, but the results do not confirm a cancerogenic risk.

You should inform your doctor immediately if you notice any unwanted effects.

If you notice any side effects not mentioned in this patient information leaflet, or if you are unsure of the effect of this product, please consult your doctor or pharmacist.

5. Storing Methotrexate 25 mg/ml solution for injection

- Keep the medicine out of the reach and sight of children.
- Keep the vial in the outer carton in order to protect from light.
- Do not store above 25°C.
- For single dose use only. Discard any unused solution immediately and safely after initial use.
- This medicine should only be administered by a medically qualified person, e.g. a doctor.
- Methotrexate 25 mg/ml solution for injection should not be used after the expiry date printed on the label.
- Any unused product or waste should be disposed of in accordance with local requirements for example by incineration.

Remember this medicine is for you only. Only a doctor or a nurse can give you the injection.

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