Methotrexate 25mg/ml Solution for Injection or Infusion
Methotrexate

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their sign of illness are the same as yours.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet.
- The full name of this medicine is Methotrexate 25mg/ml Solution for Injection or Infusion but within the leaflet it will be referred to as Methotrexate Solution.

In this leaflet:

1 What Methotrexate Solution is and what it is used for
2 What you need to know before you use
3 How to use
4 Possible side effects
5 How to store
6 Contents of the pack and other information

1 What Methotrexate Solution is and what it is used for

Methotrexate Solution is a substance with the following properties:
- it interferes with the growth of tumour cells in the body that reproduce quickly (anti-tumour agent)
- it reduces undesired reactions of the body's own defence mechanism (immunosuppressant)
- it has anti-inflammatory effects.

Methotrexate Solution is used to treat cancer, such as:
- lymphatic leukaemia (disease of the blood or bone marrow with increased number of white blood cells)
- breast cancer
- bone cancer (osteosarcoma)
- head and neck cancer
- gynaecologic cancer (choriocarcinoma, throphoblastic disease – tumour development directly associated with pregnancy)
- cancer of the lymphatic system (Non-Hodgkin's lymphoma).

2 What you need to know before you use

Do not use Methotrexate Solution if you
- are **allergic** to methotrexate or any of the other ingredients of this medicine (listed in section 6)
- you have **significant kidney** disease
- you have **significant liver** disease
- have **disorders of the blood-forming system**
- have **increased alcohol consumption**
- have severe or existing **infections**
- have gastro-intestinal **ulcers** or ulcers of the oral cavity
- are **pregnant or breast-feeding** (see section "Pregnancy and breast-feeding").

You should not be given **live vaccines** during treatment with Methotrexate Solution.

Tell your doctor before you use Methotrexate Solution if you think any of the above applies to you.

Warning and precautions
Take special care with Methotrexate Solution if you
- have/had any **liver or kidney** disease
- have problem with your **lung** function
- have **abnormal accumulation** of liquid in the abdomen or in the cavity between the lungs and chest wall (ascites, pleural effusions)
- are **dehydrated** or suffer from conditions leading to dehydration (vomiting, diarrhoea, stomatitis)
- have **diabetes** mellitus treated with insulin
- have inactive, **prolonged infections** (e.g. tuberculosis, hepatitis B or C, shingles (herpes zoster))
- experience any **sign or symptoms** suggestive of **infection**, e.g. fever.

Inform your doctor in case any of the above applies to you.

You should avoid solarium and direct sun light during treatment, as the skin is more sensitive.

Methotrexate may be genotoxic. This means that the medicine may cause genetic mutation. Methotrexate can affect sperm and egg production with the potential to cause birth defects. You and your partner must avoid conception (becoming pregnant or fathering children) if currently receiving methotrexate and for at least six months after your treatment with methotrexate has stopped. See also section "Pregnancy and lactation". Since treatment with methotrexate may lead to infertility, it might be advisable for male patients to look into the possibility of sperm preservation before starting treatment.

Even if methotrexate is administered at low dosage, severe side effects can occur. In order to diagnose them early, regular monitoring by the doctor at short-term intervals is necessary. Before treatment is started your doctor may carry out blood tests, and also to check how well your kidneys and liver are working. You may also have a chest X-ray. Further tests may also be done during and after treatment. Do not miss appointments for blood tests.
If the results of any of these tests are abnormal, treatment will only be resumed when all readings are back to normal.

Other medicines and Methotrexate Solution
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription and herbal or natural medicinal products. Remember to tell your doctor about your treatment with Methotrexate Solution, if you are prescribed another medicine while the treatment is still ongoing. It is especially important to tell your doctor if you are using:
- other treatments for rheumatoid arthritis or psoriasis such as leflunomide, sulphasalazine (also used for ulcerative colitis), salicylates such as acetylsalicylic acid, phenylbutazone, or amidopyrine
- alcohol (should be avoided)
- live vaccinations
- azathioprine (used to prevent rejection after an organ transplant)
- retinoids (used to treat skin disorders)
- anticonvulsant drugs (prevent fits)
- cancer treatments
- barbiturates (sleeping injection)
- tranquillisers
- oral contraceptives
- probenecid (for gout)
- antibiotics
- pyrimethamine (used to prevent and treat malaria)
- vitamin preparations, which contain folic acid
- proton-pump inhibitors (used to treat severe heartburn or ulcers)
- theophylline (used to treat asthma).

Methotrexate Solution with food, drink and alcohol
During Methotrexate Solution treatment you should avoid any alcohol consumption as well as excessive consumption of coffee, caffeine-containing beverages or black tea. Also make sure you drink plenty of liquids during treatment with Methotrexate Solution because dehydration (reduction in body water) can increase the toxicity of Methotrexate Solution.

Pregnancy, breast-feeding and fertility
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

You must not use Methotrexate Solution during pregnancy. Men and women should use an effective method of birth control during treatment and during a further six months after treatment with Methotrexate Solution has been discontinued.

In women of child-bearing age, any existing pregnancy must be excluded with certainty by taking appropriate measures e.g. pregnancy test, prior to therapy.

As methotrexate can be genotoxic, all women who wish to become pregnant are advised to consult a genetic counselling centre, if possible already prior to therapy, and men should seek advice about the possibility of sperm preservation before starting therapy, see also section "Take special care with Methotrexate Solution".

Methotrexate passes into breast milk. Breast-feeding should be stopped prior to and during treatment with Methotrexate Solution.

Driving and using machines
Tiredness and dizziness can occur during treatment. If affected you should not drive or operate machinery.

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The following information is intended for medical or healthcare professionals only:

Methotrexate 25mg/ml Solution for Injection or Infusion
Instructions

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.

Handling and disposal
- Handling must be in accordance with local requirements. Cytostatics handling should only be carried out by specially trained staff and should only take place in locations fitted for this purpose. Work surfaces should be covered by plastified absorbant paper, which can be discarded after use.
- Protective gloves and glasses should be used in order to avoid potential contact with eyes, skin or mucosa. In the event of contact with the eyes, irrigate with copious amounts of water or sodium chloride 0.9%. Seek medical evaluation. Methotrexate is not blister forming and should therefore not cause damage to skin. However, if the compound should get in contact with the skin or mucosa, the affected area should still be rinsed immediately with plenty of water. Transient stinging can be treated with a mild cream. If there is a danger that larger quantities of methotrexate have been absorbed (regardless of absorption method), treatment with leucovorin should be carried out.
- Adequate procedures should be in place for accidental contamination due to spillage; staff exposure to antineoplastic agents should be recorded and monitored.
- Cytostatics should not be handled by pregnant staff.
- All contaminated waste materials (including sharps, container, absorbent materials, unused solution) should be placed in a designated sealed and labelled impervious waste disposal bag or rigid waste container, and incinerated in accordance with local procedures for destruction for hazardous waste.

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colours/plates:
1. Black
2.
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4.
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6.
Non Printing Colours
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Methotrexate Solution contains
The medicinal product contains 0.192mmol sodium per ml solution (4.425mg/ml). Doses less than 5ml contain less than 1 mmol sodium (23mg) per dose and are i.e. essentially "sodium-free", but to be taken into consideration by patients on a controlled sodium diet in case the dose exceeds 5ml.

3 How to use

Treatment with methotrexate should be initiated by or in consultation with a doctor with considerable experience in cancer treatment. The dose is usually calculated based on various factors e.g. the patient general health and body surface area and the type of disease. The overall duration of treatment and intervals between administrations is decided by the physician.
Methotrexate can be given intramuscularly (in a muscle), intravenously (in a vein), intra-arterially (in an artery and intra-thecally.
Higher doses are usually given as an infusion over 24 h, either alone or in combination with other medicinal products used to treat cancer.
Your doctor may instruct you to take sodium bicarbonate or acetazolamide tablets while receiving your medicine 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.

Use in children: This medicine should be used with caution in children and in line with standard therapy recommendations.

Methotrexate should not come into contact with the surface of the skin or mucosa. In the event of contamination, the affected area must be rinsed immediately with plenty of water.

If you use more Methotrexate Solution than you should
Your doctor decides on the dosage, which is given by healthcare staff. Overdose is therefore unlikely.
An overdose of methotrexate can lead to severe toxic reactions. Overdose symptoms may include easy bruising or bleeding, unusual weakness, mouth sores, nausea, vomiting, vomiting blood or black or bloody stools. The antidote in case of an overdose is calcium folinate.

If you forget or stop using Methotrexate Solution
You should not interrupt or discontinue Methotrexate Solution treatment, unless you have discussed this with your doctor. In case you forget your appointment for next dose, contact your doctor as soon as possible to schedule a new appointment. If you suspect severe side effects, contact your doctor immediately for advice.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4 Possible side effects

Like all medicines, Methotrexate Solution can cause side effects, although not everybody gets them. Tell your doctor straight away if you get any sudden wheeziness, difficulty in breathing, swelling of the eyelids, face or lips, rash or itching (especially affecting your whole body).

Serious side effects
If you develop any of the following side effects, contact your doctor immediately:
- lung complaints (symptoms may be general illness; dry, irritating cough; shortness of breath, breathlessness at rest, chest pain, or fever)
- severe peeling or blistering of the skin
- unusual bleeding (including vomiting blood) or bruising
- severe diarrhoea
- ulcers in mouth
- black or tarry stools
- blood in the urine or stools
- tiny red spots on the skin
- fever
- yellowing of the skin (jaundice)
- pain or difficulty in passing urine
- thirst and/or frequent urination
- fits (convulsions)
- loss of consciousness
- blurred or decreased vision.

The following side effects have also been reported:

Very common (more than 1 in 10):
Inflammation of the mouth, indigestion, loss of appetite, nausea (feeling sick), vomiting, tummy pain, inflammation and ulcers in the mouth and throat. Increase in liver enzymes (can be detected by a test carried out by a doctor).

Common (between 1 in 100 and 1 in 10):
Changes in the number of blood cells and platelets (can be detected by a test carried out by a doctor). Headache, tiredness, sleepiness. Diarrhoea. Measles-like rash (alone), redness, and itching.

Uncommon (between 1 in 1,000 and 1 in 100):
Spinning sensation, confusion, depression, fits. Brain disorder (leukoencephalopathy/ encephalopathy). Lung damage. Ulcers and bleeding in the digestive tract. Liver disorders (can be detected by a test carried out by a doctor), diabetes, decreased blood protein (can be detected by a test carried out by a doctor). Nettle rash (alone), light sensitivity, brown skin, hair loss, increase of rheumatic nodules (lumps of tissues), shingles, painful psoriasis. Joint or muscle pain, brittle bones, inflammation. Ulcers in the bladder (possibly with blood in the urine), painful urination. Severe allergic reactions. Inflammation and ulcers of the vagina.

Rare (between 1 in 1,000 and 1 in 10,000):
Inflammation of the lining of the heart, fluid around the heart. Severely visual disturbance, mood alterations. Low blood pressure, blood clots. Sore throat, interruption of breathing, asthma. Inflammation of the digestive tract, bloody stools, inflamed gums, abnormal digestion. Changed colour of nails, acne, red or purple spots. Bone fracture. Kidney failure, little or no urine produced, waste products in the blood.

Very rare (less than 1 in 10,000 and unknown):
Infections. Severe failure of the bone marrow (can be detected by a test carried out by a doctor). Swollen glands. Sleeplessness. Pain, muscle weakness, pins and needles, changes in sense of taste (metallic taste), inflammation of the lining of the brain causing paralysis or vomiting. Red eyes, damage to the retina of the eye. Fluid on the lungs. Vomiting blood. Cold sores. Protein in the urine (can be detected by a test carried out by a doctor). Loss of sex drive, problems having an erection, low sperm production, abnormal periods, vaginal discharge, infertility. Infection around a fingernail, severe complication of the digestive tract, fungal infections, boils, dilated small blood vessels in the skin, damage to the blood vessels of the skin. Lumps in the armpit or groin. Slow wound healing.

Other: After injection into a muscle, there may be a burning sensation or damage at the injection site.

If you get any side effects, talk to your doctor. This includes any side effects not listed in this leaflet.

5 How to store

Keep this medicine out of the sight and reach of children.
Do not use this medicine after the expiry date which is stated on the label and carton after EXP. The expiry date refers to the last day of the month.
Use immediately after first opening.
Store in the original package in order to protect from light.
Store below 25°C.
You must not use Methotrexate Solution, if the solution is not clear and contains particles.
This medicine and its packaging must not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines or packaging no longer required. These measures will help to protect the environment.

6 Contents of the pack and other information

What Methotrexate Solution contains
- The active substance is: Methotrexate. 1ml of solution for injection contains 25mg methotrexate.
  2ml vial contains 50mg methotrexate; 10ml vial contains 250mg methotrexate; 20ml vial contains 500mg methotrexate; 40ml vial contains 1,000mg methotrexate.
- The other ingredients are: sodium chloride, sodium hydroxide (for pH adjustment), hydrochloric acid (for pH adjustment) and water for injections.

What Methotrexate Solution looks like and contents of the pack
Methotrexate Solution is a clear, yellowish solution for injection.

Pack sizes:
1 x 2ml vial
1 x 20ml vial
1 x 40ml vial

Marketing Authorisation Holder
Actavis Group PTC ehf.
Reykjavíkurvegi 76-78
220 Hafnarfjörður
Iceland

Manufacturer
S.C. Sindan- Pharma S.R.L
11 Ion Mihalache Blvd
011171 Bucharest
Romania

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The solution is to be visually inspected prior to use. Only clear solutions practically free from particles should be used.

Incompatibilities
Strong oxidants and acids. Precipitation or formation of a cloudy solution has been seen during combinations with chlorpromazine hydrochloride, droperidol, idarubicin, Metoclopramide hydrochloride, heparin solution, prednisolone sodium phosphate and promethazine hydrochloride.

Parenteral methotrexate preparations can be prepared with the following intravenous solutions for infusion: 9mg/ml (0.9%) sodium chloride, 50mg/ml (5%) glucose. Other pharmaceuticals should not be mixed with Methotrexate Solution in the same infusion container.

Storage and shelf-life after first opening/dilution
Vials before opening: Store below 25°C. Store in the original package in order to protect from light.
Vials after first opening: Use immediately.

Solution after dilution: Chemical and physical in-use stability have been demonstrated for solutions containing either 4.0 or 8.0mg/ml methotrexate in 9mg/ml (0.9%) sodium chloride and in 50mg/ml (5%) glucose for 30 days at 2-8°C protected from light and at 25°C under normal lighting conditions. Chemical and physical in-use stability have been demonstrated for solution containing 0.1mg/ml methotrexate in 9mg/ml (0.9%) sodium chloride and in 50mg/ml (5%) glucose for 30 days at 2-8°C protected from light and for 5 days at 25°C, under normal lighting conditions.
From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

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