PACKAGE LEAFLET: INFORMATION FOR THE USER

Methotrexate 500 mg/20 ml Injection

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 signs 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.

What is in this leaflet:

1. What Methotrexate Injection is and what it is used for

Methotrexate 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), and
- it has anti-inflammatory effects.

Methotrexate 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, trophoblastic disease – tumour development directly associated with pregnancy)
- cancer of the lymphatic system (Non-Hodgkin´s lymphoma).

Methotrexate can also be used to treat severe psoriasis (a skin disease with thickened patches of inflamed red skin, often covered by silvery scales) when it has not responded to other treatments

2. What you need to know before you use Methotrexate Injection

Methotrexate 500mg/20ml Injection must not be injected intrathecally (into the spine).

Do not use Methotrexate Injection 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 breast-feeding and additionally, for non-oncologic indications (for non-cancer treatment) if you are pregnant (see section "Pregnancy, breast-feeding and fertility").

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

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

Warnings and precautions

Take special care with Methotrexate Injection if you

- have/had any liver or kidney disease
- have problems with your lung function
- have an 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
- are a child, elderly or debilitated.

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

Acute bleeding from the lungs in patients with underlying rheumatologic disease has been reported with methotrexate. If you experience symptoms of spitting or coughing up blood you should contact your doctor immediately.

If you, your partner or your caregiver notice new onset or worsening of neurological symptoms including general muscle weakness, disturbance of vision, changes in thinking, memory and orientation leading to confusion and personality changes contact your doctor immediately because these may be symptoms of a very rare, serious brain infection called progressive multifocal leukoencephalopathy (PML).

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

Methotrexate temporarily affects sperm and egg production. Methotrexate can cause miscarriage and severe birth defects. You should avoid having a baby if you are being given methotrexate at the time and for at least 6 months after the end of your treatment with methotrexate if you are a woman. If you are a man you should avoid fathering a child if you are being given methotrexate at the time and for at least 3 months after the end of your treatment. See also section "Pregnancy, breast-feeding and fertility".

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.

Recommended follow-up examinations and precautions
Even if methotrexate is used in low doses, serious side effects can occur. In order to detect them in time, your doctor must perform monitoring examinations and laboratory tests.

Prior to the start of therapy:
Before you start treatment, your blood will be checked to see if you have enough blood cells. Your blood will also be tested to check your liver function and to find out if you have hepatitis. Furthermore, serum albumin (a protein in the blood), hepatitis (liver infection) status and kidney function will be checked. The doctor may also decide to run other liver tests, some of these may be images of your liver and others may need a small sample of tissue taken from the liver in order to examine it more closely. Your doctor may also check to see if you have tuberculosis and they may X-ray your chest or perform a lung function test.

During the treatment:
Your doctor may perform the following examinations:
- examination of the oral cavity and the pharynx for changes in the mucous membrane such as inflammation or ulceration
- blood tests/ blood count with number of blood cells and measurement of serum methotrexate levels
- blood test to monitor liver function
- imaging tests to monitor liver condition
- small sample of tissue taken from the liver in order to examine it more closely
- blood test to monitor kidney function
- respiratory tract monitoring and, if necessary, lung function test

It is very important that you appear for these scheduled examinations.

If the results of any of these tests are conspicuous, your doctor will adjust your treatment accordingly.

Elderly patients
Elderly patients under treatment with methotrexate should be monitored closely by a physician so that possible side effects can be detected as early as possible. Age-related impairment of liver and kidney function as well as low body reserves of the vitamin folic acid in old age require a relatively low dosage of methotrexate.

Other medicines and Methotrexate Injection
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 Injection, if you are prescribed other 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 (prevents 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)
- hypoglycaemic drugs (used to treat diabetes)
- diuretics (that make you pass more urine)
- anti-inflammatory drugs
- nitrous oxide ('laughing gas' that is inhaled to give pain relief).

Methotrexate Injection with food, drink and alcohol
During Methotrexate Injection 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 Injection because dehydration (reduction in body water) can increase the toxicity of Methotrexate Injection.

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.

Do not use Methotrexate during pregnancy except if your doctor has prescribed it for oncology treatment. Methotrexate can cause birth defects, harm the unborn child or cause miscarriage. It is associated with malformations of the skull, face, heart and blood vessels, brain, and limbs. It is therefore very important that methotrexate is not given to pregnant women or to women who are planning to become pregnant unless used for oncology treatment.

For non-oncological indications, in women of child-bearing age the possibility of a pregnancy must be ruled out, e.g. by pregnancy tests, before treatment is started.

Do not use Methotrexate if you are trying to become pregnant. You must avoid becoming pregnant during treatment with methotrexate and for at least 6 months after the end of treatment. Therefore, you must ensure that you are taking effective contraception for the whole of this period (see also section "Warnings and precautions").

If you become pregnant during treatment or suspect you might be pregnant, speak to your doctor as soon as possible. If you do become pregnant during treatment, you should be offered advice regarding the risk of harmful effects on the child through treatment.
If you want to become pregnant, you should speak with your doctor, who may refer you for specialist advice before the planned start of treatment.

Male fertility
The available evidence does not indicate an increased risk of malformations or miscarriage if the father takes methotrexate less than 30 mg/week. However, a risk cannot be completely excluded and there is no information regarding higher methotrexate doses. Methotrexate can have a genotoxic effect. This means that the medicine can cause genetic mutations. Methotrexate can affect the production of sperm, which is associated with the possibility of birth defects.

You should avoid fathering a child or donating semen during treatment with methotrexate and for at least 3 months after the end of treatment. As treatment with methotrexate at higher doses commonly used in cancer treatment can cause infertility and genetic mutations, it may be advisable for male patients treated with methotrexate doses higher than 30 mg/week to consider sperm preservation before the beginning of treatment (see also section "Warnings and precautions").

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

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

Methotrexate Injection contains sodium
Methotrexate 500 mg/20 ml Injection contains 41.1 mg sodium (main component of cooking/table salt) per vial. This is equivalent to 2.06% of the recommended maximum daily dietary intake of sodium for an adult.

3. How to use Methotrexate Injection

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’s general health, body surface area and the type of disease. The overall duration of treatment and intervals between administration is decided by the physician.

Methotrexate can be given intramuscularly (in a muscle), intravenously (in a vein), or intra-arterially (in an artery). Higher doses are usually given as an infusion over 24 hours, either alone or in combination with other medicinal products used to treat cancer.

Methotrexate 500 mg/20 ml is not suitable for injection intrathecally (into the spine).

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.

Dose in severe psoriasis:
Take Methotrexate only **once a week.**

Important warning about the dose of Methotrexate Injection:

Use Methotrexate Injection **only once a week** for the treatment of psoriasis. Using too much of Methotrexate Injection may be fatal. Please read section 3 of this leaflet very carefully. If you have any questions, please talk to your doctor or pharmacist before you take this medicine.

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 are must be rinsed immediately with plenty of water.

If you use more Methotrexate Injection 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 Injection
You should not interrupt or discontinue Methotrexate Injection treatment, unless you have discussed this with your doctor. In case you forget your appointment for the 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 Injection 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)
- spitting or coughing blood*
- severe peeling or blistering of the skin
- unusual bleeding (including vomiting blood) or bruising
- severe diarrhoea
- severe abdominal pain
- ulcers in the 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
- weakness on one side of your body
- fits (convulsions)
- loss of consciousness
- blurred or decreased vision

*(has been reported for methotrexate used in patients with underlying rheumatologic disease)

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 10 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 1000 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 1000 and 1 in 10,000):
Inflammation of the lining of the heart, fluid around the heart. Severe 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. Change in colour of the nails, acne, red or purple spots. Bone fracture, little or no urine produced, waste products in the blood.

Very rare (less than 1 in 10,000):
Infections. Severe failure of the bone marrow (can be detected by a test carried out by a doctor). Swollen glands. Sleeplessness. Pain, muscle weakness, sensation of numbness or tingling, having less sensitivity to stimulation than normal, changes in the 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. Lymphoproliferative disorders (excessive growth of white blood cells).

Not known (frequency cannot be estimated from available data):
Blood poisoning (septicaemia), difficulty/inability to talk, dizziness. Ringing in the ears. Skin reaction at the site of previous radiotherapy or sun exposure, exacerbation of psoriasis by ultraviolet light, redness and shedding of the skin. Death of bone tissue (osteonecrosis). Defective sperm and egg production, miscarriage, birth defects. Bleeding from the lungs*. Bone damage in the jaw (secondary to excessive growth of white blood cells). Swelling, Death.

*(has been reported for methotrexate used in patients with underlying rheumatologic disease)

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

Reporting of side effects
If you get any side effects, talk to your doctor. This includes any side effects not listed in this leaflet. You can also report side effects directly (see details below). By reporting side effects you can help provide more information on the safety of this medicine.

Ireland
HPRA Pharmacovigilance. Website: www.hpra.ie

Malta
ADR Reporting Website:
www.medicinesauthority.gov.mt/adrportal

5. How to store Methotrexate Injection

Keep this medicine out of the sight and reach of children

Expiry
Do not use this medicine after the expiry date which is stated on the vial label and carton after 'EXP'. The expiry date refers to the last day of that month.

Storage
The vials should be kept in the outer carton and stored at, or below, 25°C. The vials should not be frozen.

This product should only be used if the solution appears clear and yellow in colour.

Unused portions of opened vials must not be stored for later use.

Prepared infusions should be used immediately, however, if this is not possible they can, in certain circumstances, be stored for up to 30 days in a refrigerator provided they have been prepared in a way to exclude microbial contamination.

6. Contents of the pack and other information

What Methotrexate Injection contains
The active substance is methotrexate. Each millilitre (ml) of solution contains 25 milligrams (mg) of methotrexate, as methotrexate sodium which is formed *in situ*.

The other ingredients are sodium chloride, sodium hydroxide (see section 2 "Methotrexate Injection contains sodium") and Water for Injections.

What Methotrexate Injection looks like and contents of the pack
Methotrexate Injection is a clear, yellow solution for injection which comes in glass containers called vials.

It may be supplied in packs containing:
- 1 x 500 mg/20 ml vial

Marketing Authorisation Holder

Ireland
Pfizer Healthcare Ireland,
9 Riverwalk,

National Digital Park,
Citywest Business Campus,
Dublin 24,
Ireland

Malta
Pfizer Hellas S.A.
243 Messoghion Ave.
154 51 N. Psychiko
Greece

Manufacturer responsible for batch release
Pfizer Service Company BV
Hoge Wei 10,
Zaventem, 1930
Belgium

Manufacturer
Hospira Australia Pty Ltd, 1-5, 7-23 and 25-39 Lexia Place, Mulgrave, Victoria 3170, Australia

This medicine is authorised in the Member States of the European Economic Area under the following names:

Ireland	Methotrexate 500 mg/20 ml Injection
Malta	Methotrexate 500 mg/20 ml Injection
Cyprus	Methotrexate 500 mg/20 ml ενέσιμο διάλυμα

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The following information is intended for healthcare professionals only:

Methotrexate 500 mg/20 ml Injection
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 **incorrectly calculated** doses.

Further to the information included in section 3, practical information on the preparation/handling of the medicinal product is provided here.

Incompatibilities
Immediate precipitation or turbidity results when combined with certain concentrations of droperidol, heparin sodium, metoclopramide hydrochloride, ranitidine hydrochloride in syringe.

Instructions for use and handling
The 500 mg/20 ml presentation is not suitable for intrathecal administration.

Single use only. Discard any unused contents.

After dilution, chemical and physical in-use stability has been demonstrated in dextrose 5% and sodium chloride 0.9% infusion solutions for 30 days at 4°C in PVC containers when protected from light.

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 2-8°C, unless dilution has taken place in controlled and validated aseptic conditions.