PACKAGE LEAFLET: INFORMATION FOR THE USER

Methotrexate 25 mg/ml Injection

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

In this leaflet:

1. WHAT METHOTREXATE INJECTION IS AND WHAT IT IS USED FOR

Methotrexate Injection is an anti-metabolite medicine (medicine which affects how the body's cells grow) and immunosuppressant (medicine which reduces the activity of the immune system).

Methotrexate is used in large doses (on its own or in combination with other medicines) to treat certain types of cancer such as breast cancer. In smaller doses it can 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. BEFORE YOU ARE GIVEN METHOTREXATE INJECTION

You will not be given Methotrexate Injection if you
- **are allergic (hypersensitive) to Methotrexate or any of the other ingredients of Methotrexate Injection**
- have significant kidney or liver problems
- have been told you have (or think you have) a blood disorder such as low levels of white blood cells, red blood cells (anaemia) or platelets
- have any infection
- your immune system is not working as well as it should
- are breast-feeding and additionally, for non-oncologic indications (for non-cancer treatment) if you are pregnant (see section 'Pregnancy, breast-feeding and fertility')

Tell your doctor if any of the above applies to you before this medicine is used.

Warnings and precautions
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).

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'.

Methotrexate may make your skin more sensitive to sunlight. Avoid intense sun and do not use sun-beds or a sun-lamp without medical advice. To protect your skin from intense sun, wear adequate clothing or use a sunscreen with a high protection factor.

Take special care with Methotrexate Injection if you

- have a stomach ulcer or ulcerative colitis (inflammation and ulceration of the gut)
- have an infection
- have mild kidney problems
- have a medical condition which causes a build-up of fluid in the lining of your lungs or in your abdomen (the fluid will need to be drained before methotrexate treatment is started)
- are to have radiotherapy (risk of tissue and bone damage may be increased)
- are to have any vaccinations

Tell your doctor if any of the above applies to you before this medicine is used.

Special care will also be taken in children, the elderly and in those who are in poor physical condition.

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.

Taking/using other medicines
Special care is needed if you are taking/using other medicines as some could interact with methotrexate, for example:

- non-steroidal anti-inflammatory medicines e.g. ibuprofen (medicines taken for pain relief)
- aspirin or similar medicines (known as salicylates)
- omeprazole, esomeprazole and pantoprazole (medicines used to reduce the production of stomach acid)
- diuretics (water tablets)
- medicines taken for diabetes (including insulin and tablets)
- antibiotics such as penicillins, sulphonamides, co-trimoxazole, trimethoprim, tetracycline, chloramphenicol and para-aminobenzoic acid
- phenytoin (medicine often used to treat epilepsy)
- vitamin supplements containing folic acid
- probenecid (medicine used to treat gout)
- nitrous oxide (used for general anaesthesia and pain relief). Nitrous oxide increases the effect of Methotrexate and can lead to an increase in some side effects (such as reduced number of blood cells and platelets and inflammation of mouth). Following injection into the spine it can have an effect on your nervous system
- metamizole (synonyms novaminsulfon and dipyrone) (medicine against severe pain and /or fever)
- retinoids, such as acitretin (a medicine used to treat psoriasis) or isotretinoin (used to treat severe acne)
- other drugs that may cause damage to your kidneys
- other drugs that may cause damage to your liver
- live virus vaccines
- mercaptopurine (medicine used in the treatment of blood cell cancer)
- theophylline (medicine used in the treatment of asthma)

Please tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Using Methotrexate Injection and drinking alcohol
Do not drink alcohol whilst being treated with Methotrexate as alcohol increases the risk of liver damage.

Pregnancy, breast-feeding and fertility
Tell your doctor if you are pregnant, trying to become pregnant or breast-feeding before this medicine is used.

<u>Pregnancy</u>

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.

Mothers should not breast-feed whilst treatment with methotrexate is ongoing.

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").

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
Do not drive or use machines if you experience any side effect (e.g. dizziness, drowsiness or blurred vision) which may lessen your ability to do so.

Information on sodium content in Methotrexate Injection
Methotrexate 50 mg/2 ml and 250 mg/10 ml contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially ‘sodium-free’.

Methotrexate 500 mg/20 ml 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.

Methotrexate 1 g/40 ml contains 82.2 mg sodium (main component of cooking/table salt) per vial. This is equivalent to 4.11% of the recommended maximum daily dietary intake of sodium for an adult.

3. HOW YOU ARE GIVEN METHOTREXATE INJECTION

This medicine may be given by injection into a vein (intravenous injection), into muscle (intramuscular injection), into an artery (intraarterial injection) or into the spine (intrathecal injection)*. It may also be given by infusion (drip) into a vein. It may be diluted before it is given.

* Of the presentations available (see section 6) only the 50 mg/2 ml is suitable for intrathecal injection.

Recommended dose
Your doctor will work out the correct dose of Methotrexate Injection for you and how often it must be given.

The dose of medicine given to you will depend on the disease being treated, your medical condition, your age, your size and how well your kidneys are working.

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.

If you are given too much or too little Methotrexate Injection
This medicine will be given to you in a hospital, under the supervision of a doctor. It is unlikely that you will be given too much or too little, however, tell your doctor or nurse if you have any concerns.

4. POSSIBLE SIDE EFFECTS

Methotrexate is a very toxic medicine and patients have died, or become very ill, whilst being treated with it. During treatment you should watch for any side effects and report them to the doctor.

If any of the following happen, tell your doctor immediately:
- severe allergic reaction - you may experience a sudden itchy rash (hives), swelling of the hands, feet, ankles, face, lips, mouth or throat (which may cause difficulty in swallowing or breathing), and you may feel you are going to faint
- inflammation of the lung with breathlessness – you may develop a persistent cough, experience pain or difficulty breathing, or become breathless. This may be associated with changes in a particular type of white cell in your blood.
- spitting or coughing blood*
- symptoms of an infection e.g. fever, chills, achiness, sore throat
- unexpected bleeding e.g. bleeding gums, blood in the urine or in vomit, or the appearance of unexpected bruises or broken blood vessels (broken veins)
- black tarry stools

- a sore mouth, particularly if you have a number of ulcers or blisters inside of the mouth or on the tongue
- skin rashes or blistering to the surfaces of the eyes, nose, vagina or anus (back passage)
- diarrhoea
- stroke/ weakness on one side of the body
- weakness in the legs that spreads to the upper limbs and the face, which may result in paralysis
- abdominal pain, fatty stools, vomiting
- chest pain (which may be due to heart or lung problems)

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

These are serious side effects. You may need urgent medical attention.

If any of the following happen, tell your doctor as soon as possible:
- low blood pressure (you may feel faint)
- fits
- blurred vision
- dizziness
- difficulty/inability to talk
- muscle weakness
- you may feel the need to drink more than usual (diabetes)
- abnormally easily broken bones (osteoporosis)
- pain or redness of the blood vessels (vasculitis)
- itching or the appearance of lightened patches on the skin, bruises, boils
- sunburn-like reactions due to increased sensitivity of the skin to sunlight (frequency uncommon)
- acne
- yellowing of the skin and whites of the eyes (jaundice)
- pain in the stomach, loins or abdomen
- you may need to pass urine more often than normal, which may be painful (cystitis)
- headaches
- drowsiness
- generally feeling tired or unwell
- reduced appetite, feeling or being sick
- irregular periods in women (periods may stop completely)
- hair loss
- effects on learning and memory
- ringing in the ears
- joint and muscle pain
- blood clot which causes pain, swelling or redness (cerebral, deep vein, retinal vein or arterial vein)
- mood alterations
- inflammation of the lungs, which causes breathlessness, cough and raised temperature, pneumonia
- shingles (Herpes Zoster)
- bleeding from the lungs (frequency not known)*
- lymphoproliferative disorders (excessive growth of white blood cells) (frequency very rare)
- bone damage in the jaw (secondary to excessive growth of white blood cells) (frequency not known)
- redness and shedding of skin (frequency not known)

- sensation of numbness or tingling, having less sensitivity to stimulation than normal (frequency very rare)
- swelling (frequency not known)
- injection site reaction (frequency not known)**
- dark red or black patches of skin around the injection site, often accompanied with pain (Injection site necrosis) (frequency not known)**

*(has been reported for methotrexate used patients with underlying rheumatologic disease).
**(parenteral only).

Some different side effects may occur following injection into the spine. These are
- headache
- back or shoulder pain
- difficulty with bending your head down
- fever
- temporary paralysis or weakness
- problems with a particular part of your brain, leading to shaking, abnormal balance or staggering.
- Irritability and confusion
- Stiffness
- Fits
- Confusion and loss of memory
- Sleepiness
- Coma
- Death

Methotrexate may lead to problems with your blood, liver and kidneys. Your doctor will take blood samples to check for these problems and may ask you to have an operation to have a small sample of your liver removed.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

Effects on fertility
Treatment with methotrexate may reduce fertility in men and women. Fertility is thought to go back to normal after methotrexate treatment is stopped. Tell your doctor if you have concerns.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can report side effects directly via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. By reporting side effects, you can help provide more information on the safety of this medicine.

5. HOW TO STORE METHOTREXATE INJECTION

Keep out of the reach and sight of children

Expiry
This medicine must not be used after the expiry date which is stated on the vial label and carton after 'EXP'. Where only a month and year is stated, the expiry date refers to the last day of that month.

Storage
The vials should be kept in the outer carton, in order to protect from light, and stored at, or below, 25°C. The vials should not be frozen.
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. FURTHER INFORMATION

What Methotrexate Injection contains
The active substance is methotrexate. Each millilitre (ml) of solution contains 25 milligrams (mg) of methotrexate.

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:
- 5 x 50 mg/2 ml vials
- 1 x 500 mg/20 ml vial

Not all packs may be marketed.

Marketing Authorisation Holder
Hospira UK Limited
Walton Oaks
Walton-On-The-Hill
Dorking Road
Tadworth
Surrey
KT20 7NS
UK

Manufacturer
Pfizer Service Company BV
Hoge Wei 10
1930 Zaventem
Belgium

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Methotrexate 25 mg/ml Injection
The following information is intended for medical or healthcare professionals only

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
Only the 50 mg/2 ml presentation is 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.