PATIENT INFORMATION LEAFLET

2364
05.08.21[25]

Metoject® 50 mg/ml solution for 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 or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. WHAT METOJECT 50 MG/ML IS AND WHAT IT IS USED FOR

Metoject contains methotrexate as active substance.

Methotrexate is a substance with the following properties:
- it interferes with the growth of certain cells in the body that reproduce quickly
- it reduces the activity of the immune system (the body's own defence mechanism)
- it has anti-inflammatory effects

Metoject 50 mg/ml is indicated for the treatment of
- active rheumatoid arthritis in adult patients.
- polyarthritic forms of severe, active juvenile idiopathic arthritis, when the response to nonsteroidal anti-inflammatory drugs (NSAIDs) has been inadequate.
- severe recalcitrant disabling psoriasis, which is not adequately responsive to other forms of therapy such as phototherapy, PUVA, and retinoids, and severe psoriatic arthritis in adult patients.
- mild to moderate Crohn's disease in adult patients when adequate treatment with other medicines is not possible.

Rheumatoid arthritis (RA) is a chronic collagen disease, characterised by inflammation of the synovial membranes (joint membranes). These membranes produce a fluid which acts as a lubricant for many joints. The inflammation causes thickening of the membrane and swelling of the joint.

Juvenile arthritis concerns children and adolescents less than 16 years. Polyarthritic forms are indicated if 5 or more joints are affected within the first 6 months of the disease.

Psoriatic arthritis is a kind of arthritis with psoriatic lesions of the skin and nails, especially at the joints of fingers and toes.

Psoriasis is a common chronic skin disease, characterised by red patches covered by thick, dry, silvery, adherent scales.

Metoject 50 mg/ml modifies and slows down the progression of the disease.

Crohn's disease is a type of inflammatory bowel disease that may affect any part of the gastrointestinal tract causing symptoms such as abdominal pain, diarrhoea, vomiting or weight loss.

2. WHAT YOU NEED TO KNOW BEFORE YOU USE METOJECT 50 MG/ML

Do not use Metoject 50 mg/ml:
- if you are allergic to methotrexate or any of the other ingredients of this medicine (listed in section 6).
- if you suffer from severe liver or kidney diseases or blood diseases,
- if you regularly drink large amounts of alcohol,
- if you suffer from a severe infection, e.g. tuberculosis, HIV or other immunodeficiency syndromes,
- if you suffer from ulcers in the mouth, stomach ulcer or intestinal ulcer,
- if you are pregnant or breast-feeding (see section "Pregnancy, breast-feeding and fertility"),
- if you receive vaccinations with live vaccines at the same time.

Warnings and precautions

Talk to your doctor or pharmacist before using Metoject 50 mg/ml if:
- you are elderly or if you feel generally unwell and weak.
- your liver function is impaired.
- you suffer from dehydration (water loss).

Special precautionary measures for treatment with Metoject 50 mg/ml

Methotrexate temporarily affects sperm and egg production, which is reversible in most cases. Methotrexate can cause miscarriage and severe birth defects. You must avoid becoming pregnant when using methotrexate and for at least six months after treatment has stopped. See also section "Pregnancy, breast-feeding and fertility".

Recommended follow-up examinations and safety measures

Even when Metoject 50 mg/ml is administered in low doses, severe side effects can occur. In order to detect them in time, check-ups and laboratory tests have to be carried out by your doctor.

Before therapy

Before starting the treatment, blood samples will be taken in order to check that you have enough blood cells, and tests will be carried out to check your liver function, serum albumin (a protein in the blood) and kidney function. Your doctor will also check if you suffer from tuberculosis (infectious disease in combination with little nodules in the affected tissue) and a chest X-ray will be taken.

During therapy

You will have the following tests at least once a month during the first six months and at least every three months thereafter:
- Examination of the mouth and throat for alterations of the mucosa
- Blood tests
- Check of liver function
- Check of kidney function
- Check of respiratory system and if necessary lung function test

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.

Methotrexate may affect your immune system and vaccination results. It may also affect the result of immunological tests. Inactive, chronic infections (e.g. herpes zoster [shingles], tuberculosis, hepatitis B or C) may flare up. During therapy with Metoject 50 mg/ml you must not be vaccinated with live vaccines.

Radiation-induced dermatitis and sun-burn can reappear under methotrexate therapy (recall-reaction). Psoriatic lesions can exacerbate during UV-irradiation and simultaneous administration of methotrexate. Enlarged lymph nodes (lymphoma) may occur and therapy must then be stopped.

Diarrhoea can be a toxic effect of Metoject 50 mg/ml and requires an interruption of therapy. If you suffer from diarrhoea please speak to your doctor.

Certain brain disorders (encephalopathy/leukoencephalopathy) have been reported in cancer patients receiving methotrexate. Such side effects cannot be excluded when methotrexate is used to treat other diseases.

Other medicines and Metoject 50 mg/ml

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Please note that this also applies to medicines that you will take in the future.

The effect of the treatment may be affected if Metoject 50 mg/ml is administered at the same time as certain other medicines:
- **Antibiotics** such as: tetracyclines, chloramphenicol, and non-absorbable broad-spectrum antibiotics, penicillines, glycopeptides, sulphonamides, ciprofloxacin and cefalotin (medicines to prevent/fight certain infections)
- **Non-steroidal anti-inflammatory** drugs or **salicylates** (medicines against pain and/or inflammation such as acetylsalicylic acid, diclofenac and ibuprofen or pyrazole)
- **Probenecid** (medicine against gout)
- Weak organic acids like loop **diuretics** ("water tablets")
- Medicines which may have adverse effects on the **bone marrow**, e.g. trimethoprim-sulphamethoxazole (an antibiotic) and pyrimethamine
- Other **medicines used to treat rheumatoid arthritis** such as leflunomide, sulfasalazine and azathioprine.
- Mercaptopurine (a **cytostatic** medicine).
- Retinoids (medicine against **psoriasis** and other dermatological diseases).
- Theophylline (medicine against **bronchial asthma** and other lung diseases).
- Some medicines against **stomach trouble** such as omeprazole and pantoprazole.
- Hypoglycaemics (medicines that are used to **lower the blood sugar**).

Vitamins containing **folic acid** may impair the effect of your treatment and should only be taken when advised by your doctor.

Vaccination with live vaccine must be avoided.

Metoject 50 mg/ml with food, drink and alcohol

Alcohol as well as large amounts of coffee, caffeine-containing soft drinks and black tea should be avoided during treatment with Metoject 50 mg/ml.

Pregnancy, breast-feeding and fertility

Pregnancy

Do not use Metoject 50 mg/ml during pregnancy or if you are trying to become pregnant. 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. Therefore, it is very important that methotrexate is not given to pregnant patients or patients planning to become pregnant. In women of child-bearing age, any possibility of pregnancy must be excluded with appropriate measures, e.g. pregnancy test before starting treatment.

You must avoid becoming pregnant whilst taking methotrexate and for at least 6 months after treatment is stopped by using reliable contraception throughout this time (see also section "Warnings and precautions").

If you do become pregnant during treatment or suspect you might be pregnant, speak to your doctor as soon as possible. You should be offered advice regarding the risk of harmful effects on the child through treatment.

If you wish to become pregnant you should consult your doctor, who may refer you for specialist advice before the planned start of treatment.

Breast-feeding

Stop breast-feeding prior to and during treatment with Metoject 50 mg/ml.

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. Methotrexate may be genotoxic. This means that the medicine may cause genetic mutation. Methotrexate can affect sperm production with the potential to cause birth defects. Therefore, you should avoid fathering a child or to donate semen whilst taking methotrexate and for at least 6 months after treatment is stopped.

Driving and using machines

Treatment with Metoject 50 mg/ml may cause adverse reactions affecting the central nervous system, e.g. tiredness and dizziness. Thus the ability to drive a vehicle and/or to operate machines may, in certain cases, be compromised. If you feel tired or drowsy you should not drive or use machines.

Metoject 50 mg/ml contains sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially "sodium-free".

3. HOW TO USE METOJECT 50 MG/ML

Important warning about the dose of Metoject 50 mg/ml (methotrexate):
Use Metoject 50 mg/ml **only once a week** for the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, psoriasis and psoriatic arthritis, and Crohn's disease. Using too much of Metoject 50 mg/ml (methotrexate) 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.

Always use this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Your doctor decides on the dose, which is adjusted individually. Usually it takes 4 – 8 weeks before there is any effect of the treatment.

Metoject 50 mg/ml is administered by or under the supervision of a physician or healthcare staff as an injection under the skin (subcutaneous injection) **once a week only**. Together with your doctor you decide on a suitable weekday each week on which you receive your injection.

Use in children and adolescents

The doctor decides on the appropriate dose in children and adolescents with polyarthritic forms of juvenile idiopathic arthritis.
Metoject is not recommended in children less than 3 years of age due to insufficient experience in this age group.

Method and duration of administration

Metoject is injected subcutaneously **once weekly!**
The duration of the treatment is determined by the treating physician. Treatment of rheumatoid arthritis, juvenile idiopathic arthritis, psoriasis vulgaris, psoriatic arthritis and Crohn's disease with Metoject is a long-term treatment.

At the start of your treatment, Metoject may be injected by medical staff. However, your doctor may decide that you can learn how to inject Metoject under the skin yourself. You will receive appropriate training for you to do this. Under no circumstances should you attempt to inject yourself, unless you have been trained to do so.
Please refer to the instructions for use at the end of the leaflet.

The manner of handling and disposal must be consistent with that of other cytostatic preparations in accordance with local requirements. Pregnant health care personnel should not handle and/or administer Metoject 50 mg/ml.

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 Metoject than you should

If you use more Metoject than you should, talk to your doctor immediately.

If you forget to use Metoject

Do not take a double dose to make up for a forgotten dose.

If you stop using Metoject

If you stop using Metoject, talk to your doctor immediately.

If you have the impression that the effect of Metoject 50 mg/ml is too strong or too weak, you should talk to your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, this medicine can cause side effects, although not everybody gets them.
The frequency as well as the degree of severity of the side effects depends on the dosage level and the frequency of administration. As severe side effects may occur even at low dosage, it is important that you are monitored regularly by your doctor. Your doctor will do **tests to check for abnormalities** developing in the blood (such as low white blood cells, low platelets, and lymphoma) and changes in the kidneys and the liver.

Tell your doctor immediately if you experience any of the following symptoms, as these may indicate a serious, potentially life-threatening side effect, which require urgent specific treatment:
- **persistent dry, non-productive cough, shortness of breath and fever;** these may be signs of an inflammation of the lungs (common)
- **spitting or coughing blood;** these might be signs of bleeding from the lungs (not known)
- **symptoms of liver damage such as yellowing of the skin and whites of the eyes**; methotrexate can cause chronic liver damage (liver cirrhosis), formation of scar tissue in the liver (liver fibrosis), fatty degeneration of the liver [all uncommon], inflammation of the liver (acute hepatitis) [rare] and liver failure [very rare]
- **allergy symptoms such as skin rash including red itchy skin, swelling of the hands, feet, ankles, face, lips, mouth or throat (which may cause difficulty in swallowing or breathing) and feeling you are going to faint;** these may be signs of severe allergic reactions or an anaphylactic shock [rare]
- **symptoms of kidney damage such as swelling of the hands, ankles or feet or changes in frequency of urination or decrease (oliguria) or absence of urine (anuria);** these may be signs of kidney failure [rare]
- **symptoms of infections, e.g. fever, chills, achiness, sore throat;** methotrexate can make you more susceptible to infections. Severe infections like a certain type of pneumonia (*Pneumocystis jirovecii pneumonia*) or blood poisoning (sepsis) may occur [rare]
- **symptoms such as weakness of one side of the body (stroke) or pain, swelling, redness and unusual warmth in one of your legs (deep vein thrombosis); This may happen when a dislodged blood clot causes a blockage of a blood vessel** (thromboembolic event) [rare]
- **fever and serious deterioration of your general condition, or sudden fever accompanied by a sore throat or mouth, or urinary problems**; methotrexate can cause a sharp fall in certain white blood cells (agranulocytosis) and severe bone marrow suppression [very rare]
- **unexpected bleeding, e.g. bleeding gums, blood in the urine, vomiting blood or bruising,** these can be signs of a severely reduced number of blood platelets caused by severe courses of bone marrow depression [very rare]
- **symptoms such as severe headache often in combination with fever, neck stiffness, feeling sick, vomiting, disorientation and sensitivity to light** may indicate an inflammation of the membranes of the brain (acute aseptic meningitis) [very rare]
- certain brain disorders (encephalopathy/leukoencephalopathy) have been reported in cancer patients receiving methotrexate. Such side effects cannot be excluded when methotrexate therapy is used to treat other diseases. Signs of this kind of brain disorders may be **altered mental state, movement disorders (ataxia), visual disturbances or disturbances of memory** [not known]
- **severe skin rash or blistering of the skin (this can also affect your mouth, eyes and genitals**); these may be signs of conditions called Stevens Johnson syndrome or burned skin syndrome (toxic epidermal necrolysis/Lyell's syndrome) [very rare]

In the following, please find the other side effects that may occur:

Very common: may affect more than 1 in 10 people
- Inflammation of the mouth lining, indigestion, feeling sick, loss of appetite, abdominal pain.
- Abnormal liver function test (ASAT, ALAT, bilirubin, alkaline phosphatase).

Common: may affect up to 1 in 10 people
- Mouth ulcers, diarrhoea.
- Rash, reddening of the skin, itching.
- Headache, tiredness, drowsiness.
- Reduced blood cell formation with decrease in white and/or red blood cells and/or platelets.

Uncommon: may affect up to 1 in 100 people
- Throat inflammation.
- Inflammation of the bowels, vomiting, inflammation of pancreas, black or tarry stools, gastrointestinal ulcers and bleeding.
- Increased sensitivity to light, loss of hair, increased number of rheumatic nodules, skin ulcers, shingles, inflammation of blood vessels, herpes-like skin rash, hives.
- Onset of diabetes mellitus.
- Dizziness, confusion, depression.
- Decrease in serum albumin.
- Decrease in the number of all blood cells and platelets.
- Inflammation and ulcer of the urinary bladder or vagina, reduced kidney function, disturbed urination.
- Joint pain, muscle pain, reduction of bone mass.

Rare: may affect up to 1 in 1,000 people
- Inflammation of gum tissue.
- Increased skin pigmentation, acne, blue spots on the skin due to vessel bleeding (ecchymosis, petechiae), allergic inflammation of blood vessels.
- Decreased number of anti-bodies in the blood.
- Infection (incl. reactivation of inactive chronic infection), red eyes (conjunctivitis).
- Mood swings (mood alterations).
- Visual disturbances.
- Inflammation of the sac around the heart, accumulation of fluid in the sac around the heart, obstruction of cardiac filling due to fluid in the sac around the heart.
- Low blood pressure.
- Formation of scar tissue in the lung (pulmonary fibrosis), shortness of breath and bronchial asthma, accumulation of fluid in the sac around the lung.
- Stress fracture.
- Electrolyte disturbances.
- Fever, wound-healing impairment.

Very rare: may affect up to 1 in 10,000 people
- Acute toxic dilatation of the gut (toxic megacolon).
- Increased pigmentation of the nails, inflammation of the cuticles (acute paronychia), deep infection of hair follicles (furunculosis), visible enlargement of small blood vessels.
- Local damage (formation of sterile abscess, changes in the fatty tissue) of injection site.
  Pain, loss of strength or sensation of numbness or tingling/having less sensitivity to stimulation than normal, changes in taste (metallic taste), convulsions, paralysis, meningism.
- Impaired vision, non-inflammatory eye disorder (retinopathy).
- Loss of sexual drive, impotence, male breast enlargement, defective sperm formation (oligospermia), menstrual disorder, vaginal discharge.
- Enlargement of lymphatic nodes (lymphoma).
- Lymphoproliferative disorders (excessive growth of white blood cells).

Not known: frequency cannot be estimated from the available data
- Increased number of certain white blood cells.
- Nosebleed.
- Proteins in urine.
- Feeling of weakness.
- Bone damage in the jaw (secondary to excessive growth of white blood cells).
- Tissue destruction at injection site.
- Redness and shedding of skin.
- Swelling.

Subcutaneous application of methotrexate is locally well tolerated. Only mild local skin reactions were observed, decreasing during therapy.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the Yellow Card Scheme Website: 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 METOJECT 50 MG/ML
- Keep out of the sight and reach of children.
- Do not store above 25 °C.
- Keep the pre-filled syringes in outer carton in order to protect from light.
- Do not use after the expiry date stated on the packaging. The expiry date refers to the last day of that month.
- If your pre-filled syringe shows any signs of deterioration, consult your doctor or pharmacist who will tell you what to do.
- Medicines should not be disposed via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. The measures will help to protect the environment

6. CONTENTS OF THE PACK AND OTHER INFORATION
What Metoject 50 mg/ml contains
The active substance is methotrexate. 1 ml of solution contains methotrexate disodium corresponding to 50 mg methotrexate.

1 pre-filled syringe of 0.20 ml contains 10 mg methotrexate.
1 pre-filled syringe of 0.25 ml contains 12.5 mg methotrexate.
1 pre-filled syringe of 0.30 ml contains 15 mg methotrexate.
1 pre-filled syringe of 0.35 ml contains 17.5 mg methotrexate.
1 pre-filled syringe of 0.40 ml contains 20 mg methotrexate.
1 pre-filled syringe of 0.45 ml contains 22.5 mg methotrexate.
1 pre-filled syringe of 0.50 ml contains 25 mg methotrexate.

The other ingredients are sodium chloride, sodium hydroxide, water for injections.

What Metoject 50 mg/ml looks like and contents of the pack
A pre-filled colourless glass syringe of 1 ml capacity, filled with a clear, yellow-brown solution. It is embedded with an injection needle with a plunger stopper of rubber and plastic rods inserted on the stopper to form the syringe. Also contains alcohol pads.

The following pack sizes are available:
- Pre-filled syringes containing 0.20 ml, 0.25 ml, 0.30 ml, 0.35 ml, 0.40 ml, 0.45 ml and 0.50 ml of solution.
- They are available in a packsize of 4 syringes and 1 syringe with embedded SC needle. Also contains alcohol pads in the package.

Manufacturer and product licence holder
Metoject 50 mg/ml is manufactured by medac Gesellschaft für klinische Spezialpräparate mbH, Theaterstr. 6, 22880 Wedel, Germany.
Procured from the EU by product licence holder Star Pharmaceuticals Ltd, 5 Sandridge Close, Harrow, Middlesex HA1 1XD. Repackaged by Servipharm Ltd.

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Metoject is trademark of medac Gesellschaft für klinische Spezialpräparate mbH.

Blind or partially sighted?
Is this leaflet hard to see or read?
Call 020 8423 2111 to obtain the leaflet in a format suitable for you.

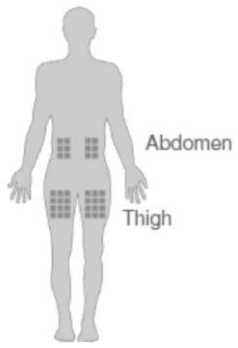
Instructions for subcutaneous use
Metoject 50 mg/ml is administered as an injection under the skin once a week only. Carefully read the instructions below before starting your injection, and always use the injection technique advised by your doctor, pharmacist or nurse.

For any problem or question, contact your doctor, pharmacist or nurse.

Preparation
Select a clean, well-lit and flat working surface.
Wash your hands carefully.
Unpack the methotrexate pre-filled syringe and read the package leaflet carefully. Remove the pre-filled syringe from the packaging at room temperature.
Before use, check the Metoject syringe for visual defects (or cracks).
In case a small air bubble is visible in the solution, this will not affect your dose nor will it harm you.

Injection site
The best sites for injection are:
- upper thighs,
- abdomen except around the navel.

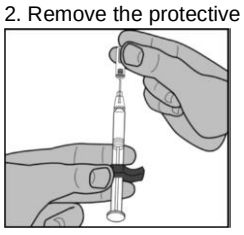
Areas for subcutaneous injection



- If someone is helping you with the injection, he/ she may also give the injection into the back of your arms, just below the shoulder.
- Change the injection site with each injection. This may reduce the risk of developing irritations at the injection site.
- Never inject into skin that is tender, bruised, red, hard, scarred or where you have stretch marks. If you have psoriasis, you should try not to inject directly into any raised, thick, red or scaly skin patches or lesions.

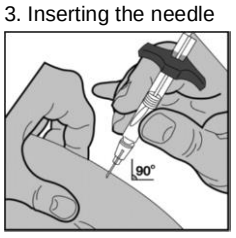
Injecting the solution
1. Choose an injection site and clean the area of and around the chosen injection site with soap and water or disinfectant.

2. Remove the protective plastic cap



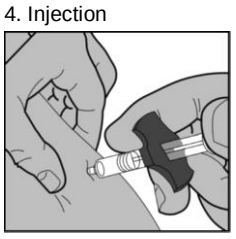
Carefully remove the grey protective plastic cap by pulling it straight off the syringe. If the cap is very stiff, turn it slightly with a pulling movement.
Important: Do not touch the needle of the pre-filled syringe!
Note: Once you have removed the cap, perform your injection without delay.

3. Inserting the needle



Using two fingers, pinch up a fold of skin and quickly insert the needle into the skin at a 90-degree angle.

4. Injection



Insert the needle fully into the fold of skin. Push the plunger down slowly and inject the liquid underneath your skin. Hold the skin securely until the injection is completed. Carefully pull the needle straight out.

5. Discard the used syringe including the needle into a sharps bin.
Do not put it in the household rubbish.

Methotrexate should not come into contact with the surface of the skin or mucosa. If this happens, you must rinse immediately with plenty of water.

If you or someone around you is injured by the needle, consult your doctor immediately and do not use this pre-filled syringe.

Disposal and other handling
The manner of handling and throwing away of the medicine and pre-filled syringe must be in accordance with local requirements. Pregnant healthcare personnel should not handle and/or administer Metoject.

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
Metoject 50 mg/ml solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
1 ml of solution contains 50 mg methotrexate
(as methotrexate disodium).

1 pre-filled syringe of 0.20 ml contains 10 mg methotrexate.
1 pre-filled syringe of 0.25 ml contains 12.5 mg methotrexate.
1 pre-filled syringe of 0.30 ml contains 15 mg methotrexate.
1 pre-filled syringe of 0.35 ml contains 17.5 mg methotrexate.
1 pre-filled syringe of 0.40 ml contains 20 mg methotrexate.
1 pre-filled syringe of 0.45 ml contains 22.5 mg methotrexate.
1 pre-filled syringe of 0.50 ml contains 25 mg methotrexate.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Solution for injection, in pre-filled syringe.
Clear, yellow-brown solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications
Metoject 50 mg/ml is indicated for the treatment of
- active rheumatoid arthritis in adult patients,
- polyarthritic forms of severe, active juvenile idiopathic arthritis, when the response to nonsteroidal anti-inflammatory drugs (NSAIDs) has been inadequate,
- severe recalcitrant disabling psoriasis, which is not adequately responsive to other forms of therapy such as phototherapy, PUVA, and retinoids, and severe psoriatic arthritis in adult patients.
- mild to moderate Crohn's disease either alone or in combination with corticosteroids in adult patients refractory or intolerant to thiopurines.

4.2 Posology and method of administration

Important warning about the dosage of Metoject 50 mg/ml (methotrexate)
In the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, psoriasis and psoriatic arthritis, and Crohn's disease, Metoject 50 mg/ml (methotrexate) **must only be used once a week**. Dosage errors in the use of Metoject 50 mg/ml (methotrexate) can result in serious adverse reactions, including death. Please read this section of the summary of product characteristics very carefully.

Metoject should only be prescribed by physicians with expertise in the use of methotrexate and a full understanding of the risks of methotrexate therapy. The administration should routinely be done by health professionals. If the clinical situation permits the treating physician can, in selected cases, delegate the subcutaneous administration to the patient her/himself. Patients must be educated and trained in the proper injection technique when self-administering methotrexate. The first injection of Metoject 50 mg/ml should be performed under direct medical supervision. Metoject 50 mg/ml is injected subcutaneously once **once weekly.**

The patient is to be explicitly informed about the fact of administration **once weekly**. It is advisable to determine a fixed, appropriate weekday as day of injection.

Methotrexate elimination is reduced in patients with a third distribution space (ascites, pleural effusions). Such patients require especially careful monitoring for toxicity, and require dose reduction or, in some cases, discontinuation of methotrexate administration (see sections 5.2 and 4.4).

Dosage in adult patients with rheumatoid arthritis
The recommended initial dose is 7.5 mg of methotrexate **once weekly**, administered subcutaneously. Depending on the individual activity of the disease and tolerability by the patient, the initial dose may be increased gradually by 2.5 mg per week. A weekly dose of 25 mg should in general not be exceeded. However, doses exceeding 20 mg/week are associated with significant increase in toxicity, especially bone marrow suppression. Response to treatment can be expected after approximately 4 – 8 weeks. Upon achieving the therapeutically desired result, the dose should be reduced gradually to the lowest possible effective maintenance dose.

Dosage in children and adolescents below 16 years with polyarthritic forms of juvenile idiopathic arthritis
The recommended dose is 10-15 mg/m^2 body surface area (BSA)/**once weekly**, administered by subcutaneous injection. In therapy-refractory cases the weekly dosage may be increased up to 20mg/m^2 body surface area/**once weekly**. However, an increased monitoring frequency is indicated if the dose is increased.

Patients with JIA should always be referred to a rheumatology specialist in the treatment of children/adolescents.

Use in children < 3 years of age is not recommended as insufficient data on efficacy and safety is available for this population. (see section 4.4).

Dosage in patients with psoriasis vulgaris and psoriatic arthritis
It is recommended that a test dose of 5 – 10 mg should be administered parenterally, one week prior to therapy to detect idiosyncratic adverse reactions. The recommended initial dose is 7.5 mg of methotrexate **once weekly**, administered subcutaneously. The dose is to be increased gradually but should not, in general, exceed a weekly dose of 25 mg of methotrexate. Doses exceeding 20 mg per week can be associated with significant increase in toxicity, especially bone marrow suppression. Response to treatment can generally be expected after approximately 2 – 6 weeks. Upon achieving the therapeutically desired result, the dose should be reduced gradually to the lowest possible effective maintenance dose.

Dosage in patients with Crohn's disease
- Induction treatment:
  25 mg/week administered subcutaneously.
  Response to treatment can be expected after approximately 8 to 12 weeks.
- Maintenance treatment:
  15 mg/week administered subcutaneously.

There is not sufficient experience in the paediatric population to recommend Metoject 50 mg/ml for the treatment of Crohn's disease in this population.

Maximum weekly dose
The dose should be increased as necessary but should in general not exceed the maximum recommended weekly dose of 25 mg. In a few exceptional cases a higher dose might be clinically justified, but should not exceed a maximum weekly dose of 30 mg of methotrexate as toxicity will markedly increase.

Patients with renal impairment
Metoject 50 mg/ml should be used with caution in patients with impaired renal function. The dose should be adjusted as follows:

Creatinine clearance (ml/min)	Dose
≥ 60	100 %
30 – 59	50 %
< 30	Metoject 50 mg/ml must not be used

See section 4.3

Patients with hepatic impairment
Methotrexate should be administered with great caution, if at all, to patients with significant current or previous liver disease, especially if due to alcohol. If bilirubin is > 5 mg/dl (85.5 µmol/l), methotrexate is contraindicated.

For a full list of contraindications, see section 4.3.

Use in elderly patients
Dose reduction should be considered in elderly patients due to reduced liver and kidney function as well as lower folate reserves which occur with increased age.

Use in patient with a third distribution space (pleural effusions, ascitis)
As the half-life of methotrexate can be prolonged to 4 times the normal length in patients who possess a third distribution space dose reduction or, in some cases, discontinuation of methotrexate administration may be required (see sections 5.2 and 4.4).

Method of administration
The medicinal product is for single use only.
Metoject 50 mg/ml is given by the subcutaneous route. See section 6.6 for instructions on subcutaneous use.

The overall duration of the treatment is decided by the physician.

Note:
If changing from oral to parenteral administration a reduction of the dose may be required due to the variable bioavailability of methotrexate after oral administration.

Folic acid supplementation may be considered according to current treatment guidelines.

4.3 Contraindications
Metoject 50 mg/ml is contraindicated in the case of
- hypersensitivity to the active substance or to any of the excipients listed in section 6.1,
- severe liver impairment (see section 4.2),
- alcohol abuse,
- severe renal impairment (creatinine clearance less than 30 ml/min., see sections 4.2 and 4.4),
- pre-existing blood dyscrasias, such as bone marrow hypoplasia, leukopenia, thrombocytopenia, or significant anaemia,
- serious, acute or chronic infections such as tuberculosis, HIV or other immunodeficiency syndromes,
- ulcers of the oral cavity and known active gastrointestinal ulcer disease,
- pregnancy and breast-feeding (see section 4.6),
- concurrent vaccination with live vaccines.

4.4 Special warnings and precautions for use
Patients must be clearly informed that the therapy has to be administered **once a week**, not every day.
Patients undergoing therapy should be subject to appropriate supervision so that signs of possible toxic effects or adverse reactions may be detected and evaluated with minimal delay. Therefore methotrexate should be only administered by, or under the supervision of physicians whose knowledge and experience includes the use of antimetabolite therapy. Because of the possibility of severe or even fatal toxic reactions, the patient should be fully informed by the physician of the risks involved and the recommended safety measures.

Recommended examinations and safety measures
Before beginning or reinstituting methotrexate therapy after a rest period
Complete blood count with differential blood count and platelets, liver enzymes, bilirubin, serum albumin, chest x-ray and renal function tests. If clinically indicated, exclude tuberculosis and hepatitis.

During therapy (at least once a month during the first six months and every three months thereafter)
An increased monitoring frequency should be considered also when the dose is increased.

1. Examination of the mouth and throat for mucosal changes.

2. Complete blood count with differential blood count and platelets. Haemopoietic suppression caused by methotrexate may occur abruptly and with apparently safe doses. Any profound drop in white-cell or platelet counts indicates immediate withdrawal of the medicinal product and appropriate supportive therapy. Patients should be advised to report all signs and symptoms suggestive of infection. Patients taking simultaneous administration of haematotoxic medicinal products (e.g. leflunomide) should be monitored closely with blood count and platelets.

3. Liver function tests: Particular attention should be given to the appearance of liver toxicity. Treatment should not be instituted or should be discontinued if any abnormality of liver function tests, or liver biopsy, is present or develops during therapy. Such abnormalities should return to normal within two weeks after which treatment may be recommenced at the discretion of the physician. There is no evidence to support use of a liver biopsy to monitor hepatic toxicity in rheumatological indications.

   For psoriasis patients the need for a liver biopsy prior to and during therapy is controversial. Further research is needed to establish whether serial liver chemistry tests or propeptide of type III collagen can detect hepatotoxicity sufficiently. The evaluation should be performed case by case and differentiate between patients with no risk factors and patients with risk factors such as excessive prior alcohol consumption, persistent elevation of liver enzymes, history of liver disease, family history of inheritable liver disease, diabetes mellitus, obesity, and history of significant exposure to hepatotoxic drugs or chemicals and prolonged methotrexate treatment or cumulative doses of 1.5 g or more.

   Check of liver-related enzymes in serum: Temporary increases in transaminases to twice or three times of the upper limit of normal have been reported by patients at a frequency of 13 – 20 %. In the case of a constant increase in liver-related enzymes, a reduction of the dose or discontinuation of therapy should be taken into consideration.

   Due to its potentially toxic effect on the liver, additional hepatotoxic medicinal products should not be taken during treatment with methotrexate *unless clearly necessary* and the consumption of alcohol should be avoided or greatly reduced (see section 4.5). Closer monitoring of liver enzymes should be exercised in patients taking other hepatotoxic medicinal products concomitantly (e.g. leflunomide). The same should be taken into account with the simultaneous administration of haematotoxic medicinal products (e.g. leflunomide).

4. Renal function should be monitored by renal function tests and urinalysis (see sections 4.2 and 4.3).
   As methotrexate is eliminated mainly by renal route, increased serum concentrations are to be expected in the case of renal impairment, which may result in severe undesirable effects.
   Where renal function may be compromised (e.g. in the elderly), monitoring should take place more frequently. This applies in particular, when medicinal products are administered concomitantly, that affect the elimination of methotrexate, cause kidney damage (e.g. non-steroidal anti-inflammatory medicinal products) or that can potentially lead to impairment of blood formation. Dehydration may also intensify the toxicity of methotrexate.

5. Assessment of respiratory system: Alertness for symptoms of lung function impairment and, if necessary lung function test. Pulmonary affection requires a quick diagnosis and discontinuation of methotrexate. Pulmonary symptoms (especially a dry, non-productive cough) or a non-specific pneumonitis occurring during methotrexate therapy may be indicative of a potentially dangerous lesion and require interruption of treatment and careful investigation. Acute or chronic interstitial pneumonitis, often associated with blood eosinophilia, may occur and deaths have been reported. Although clinically variable, the typical patient with methotrexate-induced lung disease presents with fever, cough, dyspnoea, hypoxemia, and an infiltrate on chest X-ray, infection needs to be excluded. Pulmonary affection requires a quick diagnosis and discontinuation of methotrexate therapy. This lesion can occur at all doses.
   In addition, pulmonary alveolar haemorrhage has been reported with methotrexate used in rheumatologic and related indications. This event may also be associated with vasculitis and other comorbidities. Prompt investigations should be considered when pulmonary alveolar haemorrhage is suspected to confirm the diagnosis.

6. Methotrexate may, due to its effect on the immune system, impair the response to vaccination results and affect the result of immunological tests. Particular caution is also needed in the presence of inactive, chronic infections (e.g. herpes zoster, tuberculosis, hepatitis B or C) for reasons of eventual activation. Vaccination using live vaccines must not be carried out under methotrexate therapy.

Malignant lymphomas may occur in patients receiving low dose methotrexate, in which case therapy must be discontinued. Failure of the lymphoma to show signs of spontaneous regression requires the initiation of cytotoxic therapy.

Concomitant administration of folate antagonists such as trimethoprim/ sulphamethoxazole has been reported to cause an acute megaloblastic pancytopenia in rare instances.

Radiation-induced dermatitis and sunburn can reappear under methotrexate therapy (recall-reaction). Psoriatic lesions can exacerbate during UV-irradiation and simultaneous administration of methotrexate.

Methotrexate elimination is reduced in patients with a third distribution space (ascites, pleural effusions). Such patients require especially careful monitoring for toxicity, and require dose reduction or, in some cases, discontinuation of methotrexate administration. Pleural effusions and ascites should be drained prior to initiation of methotrexate treatment (see section 5.2).

Diarrhoea and ulcerative stomatitis can be toxic effects and require interruption of therapy, otherwise haemorrhagic enteritis and death from intestinal perforation may occur.

Vitamin preparations or other products containing folic acid, folinic acid or their derivatives may decrease the effectiveness of methotrexate.

For the treatment of psoriasis, methotrexate should be restricted to severe recalcitrant, disabling psoriasis which is not adequately responsive to other forms of therapy, but only when the diagnosis has been established by biopsy and/or after dermatological consultation.

Encephalopathy / leukoencephalopathy have been reported in oncologic patients receiving methotrexate therapy and cannot be excluded for methotrexate therapy in non-oncologic indications.

Fertility and reproduction
Fertility
Methotrexate has been reported to cause oligospermia, menstrual dysfunction and amenorrhoea in humans, during and for a short period after cessation of therapy, and to cause impaired fertility, affecting spermatogenesis and oogenesis during the period of its administration – effects that appear to be reversible on discontinuing therapy.

Teratogenicity – Reproductive risk
Methotrexate causes embryotoxicity, abortion and foetal defects in humans. Therefore, the possible risks of effects on reproduction, pregnancy loss and congenital malformations should be discussed with female patients of childbearing potential (see section 4.6). The absence of pregnancy must be confirmed before Metoject is used.
If women of a sexually mature age are treated, effective contraception must be performed during treatment and for at least six months after.
For contraception advice for men see section 4.6.

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially "sodium free".

Paediatric population
Use in children < 3 years of age is not recommended as insufficient data on efficacy and safety are available for this population (see section 4.2).

4.5 Interaction with other medicinal products and other forms of interaction
Nitrous oxide
The use of nitrous oxide potentiates the effect of methotrexate on folate metabolism, yielding increased toxicity such as severe, unpredictable myelosuppression and stomatitis. Whilst this effect can be reduced by administering calcium folinate, the concomitant use of nitrous oxide and methotrexate should be avoided.

Alcohol, hepatotoxic medicinal products, haematotoxic medicinal products
The probability of methotrexate exhibiting a hepatotoxic effect is increased by regular alcohol consumption and when other hepatotoxic medicinal products are taken at the same time (see section 4.4).

Patients taking other hepatotoxic medicinal products concomitantly (e.g. leflunomide) should be monitored with special care. The same should be taken into account with the simultaneous administration of haematotoxic medicinal products (e.g. leflunomide, azathioprine, retinoids, sulfasalazine). The incidence of pancytopenia and hepatotoxicity can be increased when leflunomide is combined with methotrexate.

Combined treatment with methotrexate and retinoids like acitretin or etretinate increases the risk of hepatotoxicity.

Oral antibiotics
Oral antibiotics like tetracyclines, chloramphenicol, and non-absorbable broad-spectrum antibiotics can interfere with the enterohepatic circulation, by inhibition of the intestinal flora or suppression of the bacterial metabolism.

Antibiotics
Antibiotics, like penicillines, glycopeptides, sulfonamides, ciprofloxacin and cefalotin can, in individual cases, reduce the renal clearance of methotrexate, so that increased serum concentrations of methotrexate with simultaneous haematological and gastro-intestinal toxicity may occur.

Medicinal products with high plasma protein binding
Methotrexate is plasma protein bound and may be displaced by other protein bound medicinal products such as salicylates, hypoglycaemics, diuretics, sulphonamides, diphenylhydantoins, tetracyclines, chloramphenicol and p-aminobenzoic acid, and the acidic anti-inflammatory agents, which can lead to increased toxicity when used concurrently.

Probenecid, weak organic acids, pyrazoles and non-steroidal anti-inflammatory agents
Probenecid, weak organic acids such as loop diuretics, and pyrazoles (phenylbutazone) can reduce the elimination of methotrexate and higher serum concentrations may be assumed inducing higher haematological toxicity. There is also a possibility of increased toxicity when low dose methotrexate and non-steroidal anti-inflammatory medicinal products or salicylates are combined.

Medicinal products with adverse reactions on the bone marrow
In the case of medication with medicinal products which may have adverse reactions on the bone marrow (e.g. sulphonamides, trimethoprim-sulphamethoxazole, chloramphenicol, pyrimethamine); attention should be paid to the possibility of pronounced impairment of blood formation.

Medicinal products which cause folate deficiency
The concomitant administration of products which cause folate deficiency (e.g. sulphonamides, trimethoprim-sulphamethoxazole) can lead to increased methotrexate toxicity. Particular care is therefore advisable in the presence of existing folic acid deficiency.

Products containing folic acid or folinic acid
Vitamin preparations or other products containing folic acid, folinic acid or their derivatives may decrease the effectiveness of methotrexate.

Other antirheumatic medicinal products
An increase in the toxic effects of methotrexate is, in general, not to be expected when Metoject 50 mg/ml is administered simultaneously with other antirheumatic medicinal products (e.g. gold compounds, penicillamine, hydroxychloroquine, sulfasalazine, azathioprine, ciclosporin).

Sulfasalazine
Although the combination of methotrexate and sulfasalazine can cause an increase in efficacy of methotrexate and as a result more undesirable effects due to the inhibition of folic acid synthesis through sulfasalazine, such undesirable effects have only been observed in rare individual cases in the course of several studies.

Mercaptopurine
Methotrexate increases the plasma levels of mercaptopurine.
The combination of methotrexate and mercaptopurine may therefore require dose adjustment.

Proton-pump inhibitors
A concomitant administration of proton-pump inhibitors like omeprazole or pantoprazole can lead to interactions: Concomitant administration of methotrexate and omeprazole has led to delayed renal elimination of methotrexate. In combination with pantoprazole inhibited renal elimination of the metabolite 7-hydroxymethotrexate with myalgia and shivering was reported in one case.

Theophylline
Methotrexate may decrease the clearance of theophylline; theophylline levels should be monitored when used concurrently with methotrexate.

Caffeine- or theophylline-containing beverages
An excessive consumption of caffeine- or theophylline-containing beverages (coffee, caffeine-containing soft drinks, black tea) should be avoided during methotrexate therapy.

4.6 Fertility, pregnancy and lactation
Women of childbearing potential/Contraception in females
Women must not get pregnant during methotrexate therapy, and effective contraception must be used during treatment with methotrexate and at least 6 months thereafter (see section 4.4).

Prior to initiating therapy, women of childbearing potential must be informed of the risk of malformations associated with methotrexate and any existing pregnancy must be excluded with certainty by taking appropriate measures, e.g. a pregnancy test. During treatment pregnancy tests should be repeated as clinically required (e.g. after any gap of contraception). Female patients of reproductive potential must be counselled regarding pregnancy prevention and planning.

Contraception in males
It is not known if methotrexate is present in semen. Methotrexate has been shown to be genotoxic in animal studies, such that the risk of genotoxic effects on sperm cells cannot completely be excluded.

Limited clinical evidence does not indicate an increased risk of malformations or miscarriage following paternal exposure to low dose methotrexate (less than 30 mg/week). For higher doses, there is insufficient data to estimate the risks of malformations or miscarriage following paternal exposure.

As precautionary measures, sexually active male patients or their female partners are recommended to use reliable contraception during treatment of the male patient and for at least 6 months after cessation of methotrexate. Men should not donate semen during therapy or for 6 months following discontinuation of methotrexate.

Pregnancy
Methotrexate is contraindicated during pregnancy in non-oncological indications (see section 4.3). If pregnancy occurs during treatment with methotrexate and up to six months thereafter, medical advice should be given regarding the risk of harmful effects on the child associated with treatment and ultrasonography examinations should be performed to confirm normal foetal development.
In animal studies, methotrexate has shown reproductive toxicity, especially during the first trimester (see section 5.3). Methotrexate has been shown to be teratogenic to humans; it has been reported to cause foetal death, miscarriages and/or congenital abnormalities (e.g. craniofacial, cardiovascular, central nervous system and extremity-related).
Methotrexate is a powerful human teratogen, with an increased risk of spontaneous abortions, intrauterine growth restriction and congenital malformations in case of exposure during pregnancy.
- Spontaneous abortions have been reported in 42.5% of pregnant women exposed to low-dose methotrexate treatment (less than 30 mg/week), compared to a reported rate of 22.5% in disease-matched patients treated with drugs other than methotrexate.
- Major birth defects occurred in 6.6% of live births in women exposed to low-dose methotrexate treatment (less than 30 mg/ week) during pregnancy, compared to approximately 4% of live births in disease-matched patients treated with drugs other than methotrexate.

Insufficient data is available for methotrexate exposure during pregnancy higher than 30 mg/week, but higher rates of spontaneous abortions and congenital malformations are expected.
When methotrexate was discontinued prior to conception, normal pregnancies have been reported.

Breast-feeding
Methotrexate is excreted in human milk. Because of the potential for serious adverse reactions in breast-fed infants, Metoject 50 mg/ml is contraindicated during breast-feeding. Therefore breast-feeding must be discontinued prior to and throughout administration.

Fertility
Methotrexate affects spermatogenesis and oogenesis and may decrease fertility. In humans, methotrexate has been reported to cause oligospermia, menstrual dysfunction and amenorrhoea. These effects appear to be reversible after discontinuation of therapy in most cases.

4.7 Effects on ability to drive and use machines
Central nervous symptoms such as tiredness and dizziness can occur during treatment, Metoject 50 mg/ml has minor or moderate influence on the ability to drive and use machines.

4.8 Undesirable effects
Summary of the safety profile
Most serious adverse reactions of methotrexate include bone marrow suppression, pulmonary toxicity, hepatotoxicity, renal toxicity, neurotoxicity, thromboembolic events, anaphylactic shock and Stevens-Johnson syndrome.

Most frequently (very common) observed adverse reactions of methotrexate include gastrointestinal disorders e.g. stomatitis, dyspepsia, abdominal pain, nausea, loss of appetite and abnormal liver function tests e.g. increased ALAT, ASAT, bilirubin, alkaline phosphatase. Other frequently (common) occurring adverse reactions are leukopenia, anaemia, thrombopenia, headache, tiredness, drowsiness, pneumonia, interstitial alveolitis/pneumonitis often associated with eosinophilia, oral ulcers, diarrhoea, exanthema, erythema and pruritus.

Tabulated list of adverse reactions
The most relevant undesirable effects are suppression of the haematopoietic system and gastrointestinal disorders.

The following headings are used to organise the undesirable effects in order of frequency:
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)

Infections and infestations
Uncommon: Pharyngitis.
Rare: Infection (incl. reactivation of inactive chronic infection), sepsis, conjunctivitis.

Neoplasms benign, malignant and unspecified (including cysts and polyps)
Very rare: Lymphoma (see "description" below).

Blood and lymphatic system disorders
Common: Leukopenia, anaemia, thrombopenia.
Uncommon: Pancytopenia.
Very rare: Agranulocytosis, severe courses of bone marrow depression, lymphoproliferative disorders (see "description" below).
Not known: Eosinophilia.

Immune system disorders
Rare: Allergic reactions, anaphylactic shock, hypogammaglobulinaemia.

Metabolism and nutrition disorders
Uncommon: Precipitation of diabetes mellitus.

Psychiatric disorders
Uncommon: Depression, confusion.
Rare: Mood alterations.

Nervous system disorders
Common: Headache, tiredness, drowsiness.
Uncommon: Dizziness.
Very rare: Pain, muscular asthenia or paraesthesia/hypoaesthesia, changes in sense of taste (metallic taste), convulsions, meningism, acute aseptic meningitis, paralysis.
Not known: Encephalopathy/leukoencephalopathy.

Eye disorders
Rare: Visual disturbances.
Very rare: Impaired vision, retinopathy.

Cardiac disorders
Rare: Pericarditis, pericardial effusion, pericardial tamponade.

Vascular disorders
Rare: Hypotension, thromboembolic events.

Respiratory, thoracic and mediastinal disorders
Common: Pneumonia, interstitial alveolitis/pneumonitis often associated with eosinophilia. Symptoms indicating potentially severe lung injury (interstitial pneumonitis) are: dry, not productive cough, short of breath and fever.
Rare: Pulmonary fibrosis, *Pneumocystis jirovecii* pneumonia, shortness of breath and bronchial asthma, pleural effusion.
Not known: Epistaxis, pulmonary alveolar haemorrhage.

Gastrointestinal disorders
Very common: Stomatitis, dyspepsia, nausea, loss of appetite, abdominal pain.
Common: Oral ulcers, diarrhoea.
Uncommon: Gastrointestinal ulcers and bleeding, enteritis, vomiting, pancreatitis.
Rare: Gingivitis.
Very rare: Haematemesis, haematorrhea, toxic megacolon.

Hepatobiliary disorders (see section 4.4)
Very common: Abnormal liver function tests (increased ALAT, ASAT, alkaline phosphatase and bilirubin).
Uncommon: Cirrhosis, fibrosis and fatty degeneration of the liver, decrease in serum albumin.
Rare: Acute hepatitis.
Very rare: Hepatic failure.

Skin and subcutaneous tissue disorders
Common: Exanthema, erythema, pruritus.
Uncommon: Photosensitisation, loss of hair, increase in rheumatic nodules, skin ulcer, herpes zoster, vasculitis, herpetiform eruptions of the skin, urticaria.
Rare: Increased pigmentation, acne, petechiae, ecchymosis, allergic vasculitis.
Very rare: Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), increased pigmentary changes of the nails, acute paronychia, furunculosis, telangiectasia.
Not known: Skin exfoliation / dermatitis exfoliative.

Musculoskeletal and connective tissue disorders
Uncommon: Arthralgia, myalgia, osteoporosis.
Rare: Stress fracture.
Not known: Osteonecrosis of jaw (secondary to lymphoproliferative disorders).

Renal and urinary disorders
Uncommon: Inflammation and ulceration of the urinary bladder, renal impairment, disturbed micturition.
Rare: Renal failure, oliguria, anuria, electrolyte disturbances.
Not known: Proteinuria.

Reproductive system and breast disorders
Uncommon: Inflammation and ulceration of the vagina.
Very rare: Loss of libido, impotence, gynaecomastia, oligospermia, impaired menstruation, vaginal discharge.

General disorders and administration site conditions
Rare: Fever, wound-healing impairment.
Very rare: Local damage (formation of sterile abscess, lipodystrophy) of injection site following intramuscular or subcutaneous administration.
Not known: Asthenia, injection site necrosis, oedema.

Description of selected adverse reactions
The appearance and degree of severity of undesirable effects depends on the dose level and the frequency of administration. However, as severe undesirable effects can occur even at lower doses, it is indispensable that patients are monitored regularly by the doctor at short intervals.

Lymphoma/Lymphoproliferative disorders: there have been reports of individual cases of lymphoma and other lymphoproliferative disorders which subsided in a number of cases once treatment with methotrexate had been discontinued.

Subcutaneous application of methotrexate is locally well tolerated. Only mild local skin reactions (such as burning sensations, erythema, swelling, discolouration, pruritus, severe itching, pain) were observed, decreasing during therapy.

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 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.

4.9 Overdose
a) Symptoms of overdose
Toxicity of methotrexate mainly affects the haematopoietic system.

b) Treatment measures in the case of overdose
Calcium folinate is the specific antidote for neutralising the toxic undesirable effects of methotrexate.

In cases of accidental overdose, a dose of calcium folinate equal to or higher than the offending dose of methotrexate should be administered intravenously or intramuscularly within one hour and dosing continued until the serum levels of methotrexate are below 10^{-7} mol/l.

In cases of massive overdose, hydration and urinary alkalisation may be necessary to prevent precipitation of methotrexate and/or its metabolites in the renal tubules. Neither haemodialysis nor peritoneal dialysis has been shown to improve methotrexate elimination. Effective clearance of methotrexate has been reported with acute, intermittent haemodialysis using a high flux dialyser.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Folic acid analogues, ATC code: L01BA01
Antirheumatic medicinal product for the treatment of chronic, inflammatory rheumatic diseases and polyarthritic forms of juvenile idiopathic arthritis. Immunomodulating and anti-inflammatory agent for the treatment of Crohn's disease.

Mechanism of action
Methotrexate is a folic acid antagonist which belongs to the class of cytotoxic agents known as antimetabolites. It acts by the competitive inhibition of the enzyme dihydrofolate reductase and thus inhibits DNA synthesis. It has not yet been clarified, as to whether the efficacy of methotrexate, in the management of psoriasis, psoriasis arthritis, chronic polyarthritis and Crohn's disease, is due to an anti-inflammatory or immunosuppressive effect and to which extent a methotrexate-induced increase in extracellular adenosine concentration at inflamed sites contributes to these effects.

International clinical guidelines reflect the use of methotrexate as a second choice for Crohn's disease patients that are intolerant or have failed to respond to first-line immunomodulating agents as azathioprine (AZA) or 6-mercaptopurine (6-MP).

The adverse events observed in the studies performed with methotrexate for Crohn's disease at cumulative doses have not shown a different safety profile of methotrexate than the profile it is already known. Therefore, similar cautions must be taken with the use of methotrexate for the treatment of Crohn's disease as in other rheumatic and non-rheumatic indications of methotrexate (see sections 4.4 and 4.6).

5.2 Pharmacokinetic properties

Absorption
Following oral administration, methotrexate is absorbed from the gastrointestinal tract. In case of low-dosed administration (dosages between 7.5 mg/m² and 80 mg/m² body surface area), the mean bioavailability is approx. 70 %, but considerable interindividual and intraindividual deviations are possible (25 – 100 %). Maximum serum concentrations are achieved after 1 – 2 hours.

Bioavailability of subcutaneous injection is nearly 100 %.

Distribution
Approximately 50 % of methotrexate is bound to serum proteins. Upon being distributed into body tissues, high concentrations in the form of polyglutamates are found in the liver, kidneys and spleen in particular, which can be retained for weeks or months. When administered in small doses, methotrexate passes into the cerebrospinal fluid in minimal amounts. The terminal half-life is on average 6 – 7 hours and demonstrates considerable variation (3 – 17 hours). The half-life can be prolonged to 4 times the normal length in patients who possess a third distribution space (pleural effusion, ascites).

Biotransformation
Approx. 10 % of the administered methotrexate dose is metabolised intrahepatically. The principle metabolite is 7-hydroxymethotrexate.

Elimination
Excretion takes places, mainly in unchanged form, primarily renal via glomerular filtration and active secretion in the proximal tubulus. Approx. 5 – 20 % methotrexate and 1 – 5 % 7-hydroxymethotrexate are eliminated biliary. There is pronounced enterohepatic circulation.

In the case of renal impairment, elimination is delayed significantly. Impaired elimination with regard to hepatic impairment is not known.

5.3 Preclinical safety data
Animal studies show that methotrexate impairs fertility, is embryo- and foetotoxic and teratogenic. Methotrexate is mutagenic *in vivo* and *in vitro*. As conventional carcinogenicity studies have not been performed and data from chronic toxicity studies in rodents are inconsistent, methotrexate is considered **not classifiable** as to its carcinogenicity to humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Sodium chloride
Sodium hydroxide for pH adjustment
Water for injections

6.2 Incompatibilities
In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf-life
2 years.

6.4 Special precautions for storage
Store below 25 °C.
Keep the pre-filled syringes in the outer carton in order to protect from light.

6.5 Nature and contents of container
Nature of container:
A pre-filled colourless glass syringe (type I) of 1 ml capacity, filled with a clear, yellow-brown solution. It is embedded with an injection needle with a plunger stopper of rubber and plastic rods inserted on the stopper to form the syringe. Also contains alcohol pads.

Pack sizes:
The following pack sizes are available:
Pre-filled syringes containing 0.20 ml, 0.25 ml, 0.30 ml, 0.35 ml, 0.40 ml, 0.45 ml and 0.50 ml of solution.

They are available in a packsize of 4 syringes and 1 syringe with embedded SC needle. Also contains alcohol pads in the package.
All pack sizes are available with graduation marks

6.6 Special precautions for disposal and other handling
The manner of handling and disposal must be consistent with that of other cytotoxic preparations in accordance with local requirements.
Pregnant health care personnel should not handle and/or administer Metoject 50 mg/ml.

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

For single use only.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

In some regions Metoject 50 mg/ml may be marketed with a safety system to prevent needle stick injury and reuse of the needle.

Instructions for subcutaneous use of Metoject 50 mg/ml without safety system
The best places for the injection are:
- upper thighs,
- abdomen except around the navel.

1. Clean the area around the chosen injection site with soap and water or disinfectant..
2. Pull the protective plastic cap straight off.
3. Build a skin fold by gently squeezing the area at the injection site.
4. The fold must be held pinched until the syringe is removed from the skin after the injection.
5. Push the needle fully into the skin at a 90-degree angle.
6. Push the plunger down slowly and inject the liquid underneath the skin. Remove the syringe from the skin at the same 90-degree angle.

7. MARKETING AUTHORISATION HOLDER
Procured from the EU by product licence holder Star Pharmaceuticals Ltd, 5 Sandridge Close, Harrow, Middlesex HA1 1XD. Repackaged by Servipharm Ltd.

8. MARKETING AUTHORISATION NUMBER
PL 20636/2364

9. DATE OF REVISION OF THE TEXT
05.08.21[25-SPC]

PATIENT INFORMATION LEAFLET

2364
05.08.21[25]

Methotrexate® 50 mg/ml solution for injection

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 or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. WHAT METHOTREXATE 50 MG/ML IS AND WHAT IT IS USED FOR

Methotrexate contains methotrexate as active substance.

Methotrexate is a substance with the following properties:
- it interferes with the growth of certain cells in the body that reproduce quickly
- it reduces the activity of the immune system (the body's own defence mechanism)
- it has anti-inflammatory effects

Methotrexate 50 mg/ml is indicated for the treatment of
- active rheumatoid arthritis in adult patients.
- polyarthritic forms of severe, active juvenile idiopathic arthritis, when the response to nonsteroidal anti-inflammatory drugs (NSAIDs) has been inadequate.
- severe recalcitrant disabling psoriasis, which is not adequately responsive to other forms of therapy such as phototherapy, PUVA, and retinoids, and severe psoriatic arthritis in adult patients.
- mild to moderate Crohn's disease in adult patients when adequate treatment with other medicines is not possible.

Rheumatoid arthritis (RA) is a chronic collagen disease, characterised by inflammation of the synovial membranes (joint membranes). These membranes produce a fluid which acts as a lubricant for many joints. The inflammation causes thickening of the membrane and swelling of the joint.

Juvenile arthritis concerns children and adolescents less than 16 years. Polyarthritic forms are indicated if 5 or more joints are affected within the first 6 months of the disease.

Psoriatic arthritis is a kind of arthritis with psoriatic lesions of the skin and nails, especially at the joints of fingers and toes.

Psoriasis is a common chronic skin disease, characterised by red patches covered by thick, dry, silvery, adherent scales.

Methotrexate 50 mg/ml modifies and slows down the progression of the disease.

Crohn's disease is a type of inflammatory bowel disease that may affect any part of the gastrointestinal tract causing symptoms such as abdominal pain, diarrhoea, vomiting or weight loss.

2. WHAT YOU NEED TO KNOW BEFORE YOU USE METHOTREXATE 50 MG/ML

Do not use Methotrexate 50 mg/ml:
- if you are allergic to methotrexate or any of the other ingredients of this medicine (listed in section 6).
- if you suffer from severe liver or kidney diseases or blood diseases,
- if you regularly drink large amounts of alcohol,
- if you suffer from a severe infection, e.g. tuberculosis, HIV or other immunodeficiency syndromes,
- if you suffer from ulcers in the mouth, stomach ulcer or intestinal ulcer,
- if you are pregnant or breast-feeding (see section "Pregnancy, breast-feeding and fertility"),
- if you receive vaccinations with live vaccines at the same time.

Warnings and precautions
Talk to your doctor or pharmacist before using Methotrexate 50 mg/ml if:
- you are elderly or if you feel generally unwell and weak.
- your liver function is impaired.
- you suffer from dehydration (water loss).

Special precautionary measures for treatment with Methotrexate 50 mg/ml
Methotrexate temporarily affects sperm and egg production, which is reversible in most cases. Methotrexate can cause miscarriage and severe birth defects. You must avoid becoming pregnant when using methotrexate and for at least six months after treatment has stopped. See also section "Pregnancy, breast-feeding and fertility".

Recommended follow-up examinations and safety measures
Even when Methotrexate 50 mg/ml is administered in low doses, severe side effects can occur. In order to detect them in time, check-ups and laboratory tests have to be carried out by your doctor.

Before therapy
Before starting the treatment, blood samples will be taken in order to check that you have enough blood cells, and tests will be carried out to check your liver function, serum albumin (a protein in the blood) and kidney function. Your doctor will also check if you suffer from tuberculosis (infectious disease in combination with little nodules in the affected tissue) and a chest X-ray will be taken.

During therapy
You will have the following tests at least once a month during the first six months and at least every three months thereafter:
- Examination of the mouth and throat for alterations of the mucosa
- Blood tests
- Check of liver function
- Check of kidney function
- Check of respiratory system and if necessary lung function test

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.

Methotrexate may affect your immune system and vaccination results. It may also affect the result of immunological tests. Inactive, chronic infections (e.g. herpes zoster [shingles], tuberculosis, hepatitis B or C) may flare up. During therapy with Methotrexate 50 mg/ml you must not be vaccinated with live vaccines.

Radiation-induced dermatitis and sun-burn can reappear under methotrexate therapy (recall-reaction). Psoriatic lesions can exacerbate during UV-irradiation and simultaneous administration of methotrexate. Enlarged lymph nodes (lymphoma) may occur and therapy must then be stopped.

Diarrhoea can be a toxic effect of Methotrexate 50 mg/ml and requires an interruption of therapy. If you suffer from diarrhoea please speak to your doctor.

Certain brain disorders (encephalopathy/leukoencephalopathy) have been reported in cancer patients receiving methotrexate. Such side effects cannot be excluded when methotrexate is used to treat other diseases.

Other medicines and Methotrexate 50 mg/ml
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Please note that this also applies to medicines that you will take in the future.

The effect of the treatment may be affected if Methotrexate 50 mg/ml is administered at the same time as certain other medicines:
- **Antibiotics** such as: tetracyclines, chloramphenicol, and non-absorbable broad-spectrum antibiotics, penicillines, glycopeptides, sulphonamides, ciprofloxacin and cefalotin (medicines to prevent/fight certain infections)
- **Non-steroidal anti-inflammatory** drugs or **salicylates** (medicines against pain and/or inflammation such as acetylsalicylic acid, diclofenac and ibuprofen or pyrazole)
- **Probenecid** (medicine against gout)
- Weak organic acids like loop **diuretics** ("water tablets")
- Medicines which may have adverse effects on the **bone marrow**, e.g. trimethoprim-sulphamethoxazole (an antibiotic) and pyrimethamine
- Other **medicines used to treat rheumatoid arthritis** such as leflunomide, sulfasalazine and azathioprine.
- Mercaptopurine (a **cytostatic** medicine).
- Retinoids (medicine against **psoriasis** and other dermatological diseases).
- Theophylline (medicine against **bronchial asthma** and other lung diseases).
- Some medicines against **stomach trouble** such as omeprazole and pantoprazole.
- Hypoglycaemics (medicines that are used to **lower the blood sugar**).

Vitamins containing **folic acid** may impair the effect of your treatment and should only be taken when advised by your doctor.

Vaccination with live vaccine must be avoided.

Methotrexate 50 mg/ml with food, drink and alcohol
Alcohol as well as large amounts of coffee, caffeine-containing soft drinks and black tea should be avoided during treatment with Methotrexate 50 mg/ml.

Pregnancy, breast-feeding and fertility

Pregnancy
Do not use Methotrexate 50 mg/ml during pregnancy or if you are trying to become pregnant. 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. Therefore, it is very important that methotrexate is not given to pregnant patients or patients planning to become pregnant. In women of child-bearing age, any possibility of pregnancy must be excluded with appropriate measures, e.g. pregnancy test before starting treatment.

You must avoid becoming pregnant whilst taking methotrexate and for at least 6 months after treatment is stopped by using reliable contraception throughout this time (see also section "Warnings and precautions").

If you do become pregnant during treatment or suspect you might be pregnant, speak to your doctor as soon as possible. You should be offered advice regarding the risk of harmful effects on the child through treatment.

If you wish to become pregnant you should consult your doctor, who may refer you for specialist advice before the planned start of treatment.

Breast-feeding
Stop breast-feeding prior to and during treatment with Methotrexate 50 mg/ml.

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. Methotrexate may be genotoxic. This means that the medicine may cause genetic mutation. Methotrexate can affect sperm production with the potential to cause birth defects. Therefore, you should avoid fathering a child or to donate semen whilst taking methotrexate and for at least 6 months after treatment is stopped.

Driving and using machines
Treatment with Methotrexate 50 mg/ml may cause adverse reactions affecting the central nervous system, e.g. tiredness and dizziness. Thus the ability to drive a vehicle and/or to operate machines may, in certain cases, be compromised. If you feel tired or drowsy you should not drive or use machines.

Methotrexate 50 mg/ml contains sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially "sodium-free".

3. HOW TO USE METHOTREXATE 50 MG/ML

Important warning about the dose of Metoject 50 mg/ml (methotrexate):
Use Metoject 50 mg/ml **only once a week** for the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, psoriasis and psoriatic arthritis, and Crohn's disease. Using too much of Metoject 50 mg/ml (methotrexate) 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.

Always use this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Your doctor decides on the dose, which is adjusted individually. Usually it takes 4 – 8 weeks before there is any effect of the treatment.

Methotrexate 50 mg/ml is administered by or under the supervision of a physician or healthcare staff as an injection under the skin (subcutaneous injection) **once a week only**. Together with your doctor you decide on a suitable weekday each week on which you receive your injection.

Use in children and adolescents
The doctor decides on the appropriate dose in children and adolescents with polyarthritic forms of juvenile idiopathic arthritis.
Methotrexate is not recommended in children less than 3 years of age due to insufficient experience in this age group.

Method and duration of administration
Methotrexate is injected subcutaneously **once weekly!**
The duration of the treatment is determined by the treating physician. Treatment of rheumatoid arthritis, juvenile idiopathic arthritis, psoriasis vulgaris, psoriatic arthritis and Crohn's disease with Methotrexate is a long-term treatment.

At the start of your treatment, Methotrexate may be injected by medical staff. However, your doctor may decide that you can learn how to inject Methotrexate under the skin yourself. You will receive appropriate training for you to do this. Under no circumstances should you attempt to inject yourself, unless you have been trained to do so.
Please refer to the instructions for use at the end of the leaflet.

The manner of handling and disposal must be consistent with that of other cytostatic preparations in accordance with local requirements. Pregnant health care personnel should not handle and/or administer Methotrexate 50 mg/ml.

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 than you should
If you use more Methotrexate than you should, talk to your doctor immediately.

If you forget to use Methotrexate
Do not take a double dose to make up for a forgotten dose.

If you stop using Methotrexate
If you stop using Methotrexate, talk to your doctor immediately.

If you have the impression that the effect of Methotrexate 50 mg/ml is too strong or too weak, you should talk to your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, this medicine can cause side effects, although not everybody gets them.
The frequency as well as the degree of severity of the side effects depends on the dosage level and the frequency of administration. As severe side effects may occur even at low dosage, it is important that you are monitored regularly by your doctor. Your doctor will do **tests to check for abnormalities** developing in the blood (such as low white blood cells, low platelets, and lymphoma) and changes in the kidneys and the liver.

Tell your doctor immediately if you experience any of the following symptoms, as these may indicate a serious, potentially life-threatening side effect, which require urgent specific treatment:
- **persistent dry, non-productive cough, shortness of breath and fever;** these may be signs of an inflammation of the lungs (common)
- **spitting or coughing blood;** these might be signs of bleeding from the lungs (not known)
- **symptoms of liver damage such as yellowing of the skin and whites of the eyes**; methotrexate can cause chronic liver damage (liver cirrhosis), formation of scar tissue in the liver (liver fibrosis), fatty degeneration of the liver [all uncommon], inflammation of the liver (acute hepatitis) [rare] and liver failure [very rare]
- **allergy symptoms such as skin rash including red itchy skin, swelling of the hands, feet, ankles, face, lips, mouth or throat (which may cause difficulty in swallowing or breathing) and feeling you are going to faint;** these may be signs of severe allergic reactions or an anaphylactic shock [rare]
- **symptoms of kidney damage such as swelling of the hands, ankles or feet or changes in frequency of urination or decrease (oliguria) or absence of urine (anuria);** these may be signs of kidney failure [rare]
- **symptoms of infections, e.g. fever, chills, achiness, sore throat;** methotrexate can make you more susceptible to infections. Severe infections like a certain type of pneumonia (*Pneumocystis jirovecii pneumonia*) or blood poisoning (sepsis) may occur [rare]
- **symptoms such as weakness of one side of the body (stroke) or pain, swelling, redness and unusual warmth in one of your legs (deep vein thrombosis); This may happen when a dislodged blood clot causes a blockage of a blood vessel** (thromboembolic event) [rare]
- **fever and serious deterioration of your general condition, or sudden fever accompanied by a sore throat or mouth, or urinary problems**; methotrexate can cause a sharp fall in certain white blood cells (agranulocytosis) and severe bone marrow suppression [very rare]
- **unexpected bleeding, e.g. bleeding gums, blood in the urine, vomiting blood or bruising,** these can be signs of a severely reduced number of blood platelets caused by severe courses of bone marrow depression [very rare]
- **symptoms such as severe headache often in combination with fever, neck stiffness, feeling sick, vomiting, disorientation and sensitivity to light** may indicate an inflammation of the membranes of the brain (acute aseptic meningitis) [very rare]
- certain brain disorders (encephalopathy/leukoencephalopathy) have been reported in cancer patients receiving methotrexate. Such side effects cannot be excluded when methotrexate therapy is used to treat other diseases. Signs of this kind of brain disorders may be **altered mental state, movement disorders (ataxia), visual disturbances or disturbances of memory** [not known]
- **severe skin rash or blistering of the skin (this can also affect your mouth, eyes and genitals**); these may be signs of conditions called Stevens Johnson syndrome or burned skin syndrome (toxic epidermal necrolysis/Lyell's syndrome) [very rare]

In the following, please find the other side effects that may occur:

Very common: may affect more than 1 in 10 people
- Inflammation of the mouth lining, indigestion, feeling sick, loss of appetite, abdominal pain.
- Abnormal liver function test (ASAT, ALAT, bilirubin, alkaline phosphatase).

Common: may affect up to 1 in 10 people
- Mouth ulcers, diarrhoea.
- Rash, reddening of the skin, itching.
- Headache, tiredness, drowsiness.
- Reduced blood cell formation with decrease in white and/or red blood cells and/or platelets.

Uncommon: may affect up to 1 in 100 people
- Throat inflammation.
- Inflammation of the bowels, vomiting, inflammation of pancreas, black or tarry stools, gastrointestinal ulcers and bleeding.
- Increased sensitivity to light, loss of hair, increased number of rheumatic nodules, skin ulcers, shingles, inflammation of blood vessels, herpes-like skin rash, hives.
- Onset of diabetes mellitus.
- Dizziness, confusion, depression.
- Decrease in serum albumin.
- Decrease in the number of all blood cells and platelets.
- Inflammation and ulcer of the urinary bladder or vagina, reduced kidney function, disturbed urination.
- Joint pain, muscle pain, reduction of bone mass.

Rare: may affect up to 1 in 1,000 people
- Inflammation of gum tissue.
- Increased skin pigmentation, acne, blue spots on the skin due to vessel bleeding (ecchymosis, petechiae), allergic inflammation of blood vessels.
- Decreased number of anti-bodies in the blood.
- Infection (incl. reactivation of inactive chronic infection), red eyes (conjunctivitis).
- Mood swings (mood alterations).
- Visual disturbances.
- Inflammation of the sac around the heart, accumulation of fluid in the sac around the heart, obstruction of cardiac filling due to fluid in the sac around the heart.
- Low blood pressure.
- Formation of scar tissue in the lung (pulmonary fibrosis), shortness of breath and bronchial asthma, accumulation of fluid in the sac around the lung.
- Stress fracture.
- Electrolyte disturbances.
- Fever, wound-healing impairment.

Very rare: may affect up to 1 in 10,000 people
- Acute toxic dilatation of the gut (toxic megacolon).
- Increased pigmentation of the nails, inflammation of the cuticles (acute paronychia), deep infection of hair follicles (furunculosis), visible enlargement of small blood vessels.
- Local damage (formation of sterile abscess, changes in the fatty tissue) of injection site.
  Pain, loss of strength or sensation of numbness or tingling/having less sensitivity to stimulation than normal, changes in taste (metallic taste), convulsions, paralysis, meningism.
- Impaired vision, non-inflammatory eye disorder (retinopathy).
- Loss of sexual drive, impotence, male breast enlargement, defective sperm formation (oligospermia), menstrual disorder, vaginal discharge.
- Enlargement of lymphatic nodes (lymphoma).
- Lymphoproliferative disorders (excessive growth of white blood cells).

Not known: frequency cannot be estimated from the available data
- Increased number of certain white blood cells.
- Nosebleed.
- Proteins in urine.
- Feeling of weakness.
- Bone damage in the jaw (secondary to excessive growth of white blood cells).
- Tissue destruction at injection site.
- Redness and shedding of skin.
- Swelling.

Subcutaneous application of methotrexate is locally well tolerated. Only mild local skin reactions were observed, decreasing during therapy.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the Yellow Card Scheme Website: 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 50 MG/ML
- Keep out of the sight and reach of children.
- Do not store above 25 °C.
- Keep the pre-filled syringes in outer carton in order to protect from light.
- Do not use after the expiry date stated on the packaging. The expiry date refers to the last day of that month.
- If your pre-filled syringe shows any signs of deterioration, consult your doctor or pharmacist who will tell you what to do.
- Medicines should not be disposed via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. The measures will help to protect the environment

6. CONTENTS OF THE PACK AND OTHER INFORATION
What Methotrexate 50 mg/ml contains
The active substance is methotrexate. 1 ml of solution contains methotrexate disodium corresponding to 50 mg methotrexate.

1 pre-filled syringe of 0.20 ml contains 10 mg methotrexate.
1 pre-filled syringe of 0.25 ml contains 12.5 mg methotrexate.
1 pre-filled syringe of 0.30 ml contains 15 mg methotrexate.
1 pre-filled syringe of 0.35 ml contains 17.5 mg methotrexate.
1 pre-filled syringe of 0.40 ml contains 20 mg methotrexate.
1 pre-filled syringe of 0.45 ml contains 22.5 mg methotrexate.
1 pre-filled syringe of 0.50 ml contains 25 mg methotrexate.

The other ingredients are sodium chloride, sodium hydroxide, water for injections.

What Methotrexate 50 mg/ml looks like and contents of the pack
A pre-filled colourless glass syringe of 1 ml capacity, filled with a clear, yellow-brown solution. It is embedded with an injection needle with a plunger stopper of rubber and plastic rods inserted on the stopper to form the syringe. Also contains alcohol pads.

The following pack sizes are available:
- Pre-filled syringes containing 0.20 ml, 0.25 ml, 0.30 ml, 0.35 ml, 0.40 ml, 0.45 ml and 0.50 ml of solution.
- They are available in a packsize of 4 syringes and 1 syringe with embedded SC needle. Also contains alcohol pads in the package.

Manufacturer and product licence holder
Methotrexate 50 mg/ml is manufactured by medac Gesellschaft für klinische Spezialpräparate mbH, Theaterstr. 6, 22880 Wedel, Germany. Procured from the EU by product licence holder Star Pharmaceuticals Ltd, 5 Sandridge Close, Harrow, Middlesex HA1 1XD. Repackaged by Servipharm Ltd.

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Blind or partially sighted?
Is this leaflet hard to see or read?
Call 020 8423 2111 to obtain the leaflet in a format suitable for you.

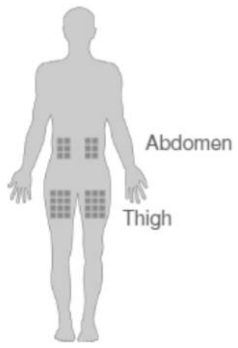
Instructions for subcutaneous use
Methotrexate 50 mg/ml is administered as an injection under the skin once a week only. Carefully read the instructions below before starting your injection, and always use the injection technique advised by your doctor, pharmacist or nurse.

For any problem or question, contact your doctor, pharmacist or nurse.

Preparation
Select a clean, well-lit and flat working surface.
Wash your hands carefully.
Unpack the methotrexate pre-filled syringe and read the package leaflet carefully. Remove the pre-filled syringe from the packaging at room temperature.
Before use, check the Methotrexate syringe for visual defects (or cracks). In case a small air bubble is visible in the solution, this will not affect your dose nor will it harm you.

Injection site
The best sites for injection are:
- upper thighs,
- abdomen except around the navel.

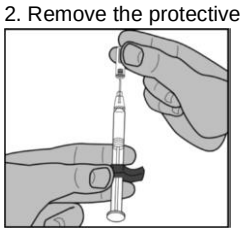
Areas for subcutaneous injection



- If someone is helping you with the injection, he/ she may also give the injection into the back of your arms, just below the shoulder.
- Change the injection site with each injection. This may reduce the risk of developing irritations at the injection site.
- Never inject into skin that is tender, bruised, red, hard, scarred or where you have stretch marks. If you have psoriasis, you should try not to inject directly into any raised, thick, red or scaly skin patches or lesions.

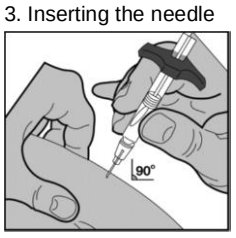
Injecting the solution
1. Choose an injection site and clean the area of and around the chosen injection site with soap and water or disinfectant.

2. Remove the protective plastic cap



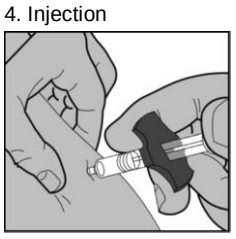
Carefully remove the grey protective plastic cap by pulling it straight off the syringe. If the cap is very stiff, turn it slightly with a pulling movement.
Important: Do not touch the needle of the pre-filled syringe!
Note: Once you have removed the cap, perform your injection without delay.

3. Inserting the needle



Using two fingers, pinch up a fold of skin and quickly insert the needle into the skin at a 90-degree angle.

4. Injection



Insert the needle fully into the fold of skin. Push the plunger down slowly and inject the liquid underneath your skin. Hold the skin securely until the injection is completed. Carefully pull the needle straight out.

5. Discard the used syringe including the needle into a sharps bin.
Do not put it in the household rubbish.

Methotrexate should not come into contact with the surface of the skin or mucosa. If this happens, you must rinse immediately with plenty of water.

If you or someone around you is injured by the needle, consult your doctor immediately and do not use this pre-filled syringe.

Disposal and other handling
The manner of handling and throwing away of the medicine and pre-filled syringe must be in accordance with local requirements. Pregnant healthcare personnel should not handle and/or administer Methotrexate.

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
Methotrexate 50 mg/ml solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
1 ml of solution contains 50 mg methotrexate
(as methotrexate disodium).

1 pre-filled syringe of 0.20 ml contains 10 mg methotrexate.
1 pre-filled syringe of 0.25 ml contains 12.5 mg methotrexate.
1 pre-filled syringe of 0.30 ml contains 15 mg methotrexate.
1 pre-filled syringe of 0.35 ml contains 17.5 mg methotrexate.
1 pre-filled syringe of 0.40 ml contains 20 mg methotrexate.
1 pre-filled syringe of 0.45 ml contains 22.5 mg methotrexate.
1 pre-filled syringe of 0.50 ml contains 25 mg methotrexate.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Solution for injection, in pre-filled syringe.
Clear, yellow-brown solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications
Methotrexate 50 mg/ml is indicated for the treatment of
- active rheumatoid arthritis in adult patients,
- polyarthritic forms of severe, active juvenile idiopathic arthritis, when the response to nonsteroidal anti-inflammatory drugs (NSAIDs) has been inadequate,
- severe recalcitrant disabling psoriasis, which is not adequately responsive to other forms of therapy such as phototherapy, PUVA, and retinoids, and severe psoriatic arthritis in adult patients.
- mild to moderate Crohn's disease either alone or in combination with corticosteroids in adult patients refractory or intolerant to thiopurines.

4.2 Posology and method of administration

Important warning about the dosage of Metoject 50 mg/ml (methotrexate)
In the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, psoriasis and psoriatic arthritis, and Crohn's disease, Metoject 50 mg/ml (methotrexate) **must only be used once a week**. Dosage errors in the use of Metoject 50 mg/ml (methotrexate) can result in serious adverse reactions, including death. Please read this section of the summary of product characteristics very carefully.

Methotrexate should only be prescribed by physicians with expertise in the use of methotrexate and a full understanding of the risks of methotrexate therapy. The administration should routinely be done by health professionals. If the clinical situation permits the treating physician can, in selected cases, delegate the subcutaneous administration to the patient her/himself. Patients must be educated and trained in the proper injection technique when self-administering methotrexate. The first injection of Methotrexate 50 mg/ml should be performed under direct medical supervision. Methotrexate 50 mg/ml is injected subcutaneously once **once weekly.**

The patient is to be explicitly informed about the fact of administration **once weekly**. It is advisable to determine a fixed, appropriate weekday as day of injection.

Methotrexate elimination is reduced in patients with a third distribution space (ascites, pleural effusions). Such patients require especially careful monitoring for toxicity, and require dose reduction or, in some cases, discontinuation of methotrexate administration (see sections 5.2 and 4.4).

Dosage in adult patients with rheumatoid arthritis
The recommended initial dose is 7.5 mg of methotrexate **once weekly**, administered subcutaneously. Depending on the individual activity of the disease and tolerability by the patient, the initial dose may be increased gradually by 2.5 mg per week. A weekly dose of 25 mg should in general not be exceeded. However, doses exceeding 20 mg/week are associated with significant increase in toxicity, especially bone marrow suppression. Response to treatment can be expected after approximately 4 – 8 weeks. Upon achieving the therapeutically desired result, the dose should be reduced gradually to the lowest possible effective maintenance dose.

Dosage in children and adolescents below 16 years with polyarthritic forms of juvenile idiopathic arthritis
The recommended dose is 10-15 mg/m^2 body surface area (BSA)/**once weekly**, administered by subcutaneous injection. In therapy-refractory cases the weekly dosage may be increased up to 20mg/m^2 body surface area/**once weekly**. However, an increased monitoring frequency is indicated if the dose is increased.

Patients with JIA should always be referred to a rheumatology specialist in the treatment of children/adolescents.

Use in children < 3 years of age is not recommended as insufficient data on efficacy and safety is available for this population. (see section 4.4).

Dosage in patients with psoriasis vulgaris and psoriatic arthritis
It is recommended that a test dose of 5 – 10 mg should be administered parenterally, one week prior to therapy to detect idiosyncratic adverse reactions. The recommended initial dose is 7.5 mg of methotrexate **once weekly**, administered subcutaneously. The dose is to be increased gradually but should not, in general, exceed a weekly dose of 25 mg of methotrexate. Doses exceeding 20 mg per week can be associated with significant increase in toxicity, especially bone marrow suppression. Response to treatment can generally be expected after approximately 2 – 6 weeks. Upon achieving the therapeutically desired result, the dose should be reduced gradually to the lowest possible effective maintenance dose.

Dosage in patients with Crohn's disease
- Induction treatment:
  25 mg/week administered subcutaneously.
  Response to treatment can be expected after approximately 8 to 12 weeks.
- Maintenance treatment:
  15 mg/week administered subcutaneously.

There is not sufficient experience in the paediatric population to recommend Methotrexate 50 mg/ml for the treatment of Crohn's disease in this population.

Maximum weekly dose
The dose should be increased as necessary but should in general not exceed the maximum recommended weekly dose of 25 mg. In a few exceptional cases a higher dose might be clinically justified, but should not exceed a maximum weekly dose of 30 mg of methotrexate as toxicity will markedly increase.

Patients with renal impairment
Methotrexate 50 mg/ml should be used with caution in patients with impaired renal function. The dose should be adjusted as follows:

Creatinine clearance (ml/min)	Dose
≥ 60	100 %
30 – 59	50 %
< 30	Methotrexate 50 mg/ml must not be used

See section 4.3

Patients with hepatic impairment
Methotrexate should be administered with great caution, if at all, to patients with significant current or previous liver disease, especially if due to alcohol. If bilirubin is > 5 mg/dl (85.5 µmol/l), methotrexate is contraindicated.

For a full list of contraindications, see section 4.3.

Use in elderly patients
Dose reduction should be considered in elderly patients due to reduced liver and kidney function as well as lower folate reserves which occur with increased age.

Use in patient with a third distribution space (pleural effusions, ascitis)
As the half-life of methotrexate can be prolonged to 4 times the normal length in patients who possess a third distribution space dose reduction or, in some cases, discontinuation of methotrexate administration may be required (see sections 5.2 and 4.4).

Method of administration
The medicinal product is for single use only.
Methotrexate 50 mg/ml is given by the subcutaneous route. See section 6.6 for instructions on subcutaneous use.

The overall duration of the treatment is decided by the physician.

Note:
If changing from oral to parenteral administration a reduction of the dose may be required due to the variable bioavailability of methotrexate after oral administration.

Folic acid supplementation may be considered according to current treatment guidelines.

4.3 Contraindications
Methotrexate 50 mg/ml is contraindicated in the case of
- hypersensitivity to the active substance or to any of the excipients listed in section 6.1,
- severe liver impairment (see section 4.2),
- alcohol abuse,
- severe renal impairment (creatinine clearance less than 30 ml/min., see sections 4.2 and 4.4),
- pre-existing blood dyscrasias, such as bone marrow hypoplasia, leukopenia, thrombocytopenia, or significant anaemia,
- serious, acute or chronic infections such as tuberculosis, HIV or other immunodeficiency syndromes,
- ulcers of the oral cavity and known active gastrointestinal ulcer disease,
- pregnancy and breast-feeding (see section 4.6),
- concurrent vaccination with live vaccines.

4.4 Special warnings and precautions for use
Patients must be clearly informed that the therapy has to be administered **once a week**, not every day.
Patients undergoing therapy should be subject to appropriate supervision so that signs of possible toxic effects or adverse reactions may be detected and evaluated with minimal delay. Therefore methotrexate should be only administered by, or under the supervision of physicians whose knowledge and experience includes the use of antimetabolite therapy. Because of the possibility of severe or even fatal toxic reactions, the patient should be fully informed by the physician of the risks involved and the recommended safety measures.

Recommended examinations and safety measures
Before beginning or reinstituting methotrexate therapy after a rest period
Complete blood count with differential blood count and platelets, liver enzymes, bilirubin, serum albumin, chest x-ray and renal function tests. If clinically indicated, exclude tuberculosis and hepatitis.

During therapy (at least once a month during the first six months and every three months thereafter)
An increased monitoring frequency should be considered also when the dose is increased.

1. Examination of the mouth and throat for mucosal changes.

2. Complete blood count with differential blood count and platelets. Haemopoietic suppression caused by methotrexate may occur abruptly and with apparently safe doses. Any profound drop in white-cell or platelet counts indicates immediate withdrawal of the medicinal product and appropriate supportive therapy. Patients should be advised to report all signs and symptoms suggestive of infection. Patients taking simultaneous administration of haematotoxic medicinal products (e.g. leflunomide) should be monitored closely with blood count and platelets.

3. Liver function tests: Particular attention should be given to the appearance of liver toxicity. Treatment should not be instituted or should be discontinued if any abnormality of liver function tests, or liver biopsy, is present or develops during therapy. Such abnormalities should return to normal within two weeks after which treatment may be recommenced at the discretion of the physician. There is no evidence to support use of a liver biopsy to monitor hepatic toxicity in rheumatological indications.

   For psoriasis patients the need for a liver biopsy prior to and during therapy is controversial. Further research is needed to establish whether serial liver chemistry tests or propeptide of type III collagen can detect hepatotoxicity sufficiently. The evaluation should be performed case by case and differentiate between patients with no risk factors and patients with risk factors such as excessive prior alcohol consumption, persistent elevation of liver enzymes, history of liver disease, family history of inheritable liver disease, diabetes mellitus, obesity, and history of significant exposure to hepatotoxic drugs or chemicals and prolonged methotrexate treatment or cumulative doses of 1.5 g or more.

   Check of liver-related enzymes in serum: Temporary increases in transaminases to twice or three times of the upper limit of normal have been reported by patients at a frequency of 13 – 20 %. In the case of a constant increase in liver-related enzymes, a reduction of the dose or discontinuation of therapy should be taken into consideration.

   Due to its potentially toxic effect on the liver, additional hepatotoxic medicinal products should not be taken during treatment with methotrexate *unless clearly necessary* and the consumption of alcohol should be avoided or greatly reduced (see section 4.5). Closer monitoring of liver enzymes should be exercised in patients taking other hepatotoxic medicinal products concomitantly (e.g. leflunomide). The same should be taken into account with the simultaneous administration of haematotoxic medicinal products (e.g. leflunomide).

4. Renal function should be monitored by renal function tests and urinalysis (see sections 4.2 and 4.3).
   As methotrexate is eliminated mainly by renal route, increased serum concentrations are to be expected in the case of renal impairment, which may result in severe undesirable effects.
   Where renal function may be compromised (e.g. in the elderly), monitoring should take place more frequently. This applies in particular, when medicinal products are administered concomitantly, that affect the elimination of methotrexate, cause kidney damage (e.g. non-steroidal anti-inflammatory medicinal products) or that can potentially lead to impairment of blood formation. Dehydration may also intensify the toxicity of methotrexate.

5. Assessment of respiratory system: Alertness for symptoms of lung function impairment and, if necessary lung function test. Pulmonary affection requires a quick diagnosis and discontinuation of methotrexate. Pulmonary symptoms (especially a dry, non-productive cough) or a non-specific pneumonitis occurring during methotrexate therapy may be indicative of a potentially dangerous lesion and require interruption of treatment and careful investigation. Acute or chronic interstitial pneumonitis, often associated with blood eosinophilia, may occur and deaths have been reported. Although clinically variable, the typical patient with methotrexate-induced lung disease presents with fever, cough, dyspnoea, hypoxemia, and an infiltrate on chest X-ray, infection needs to be excluded. Pulmonary affection requires a quick diagnosis and discontinuation of methotrexate therapy. This lesion can occur at all doses.
   In addition, pulmonary alveolar haemorrhage has been reported with methotrexate used in rheumatologic and related indications. This event may also be associated with vasculitis and other comorbidities. Prompt investigations should be considered when pulmonary alveolar haemorrhage is suspected to confirm the diagnosis.

6. Methotrexate may, due to its effect on the immune system, impair the response to vaccination results and affect the result of immunological tests. Particular caution is also needed in the presence of inactive, chronic infections (e.g. herpes zoster, tuberculosis, hepatitis B or C) for reasons of eventual activation. Vaccination using live vaccines must not be carried out under methotrexate therapy.

Malignant lymphomas may occur in patients receiving low dose methotrexate, in which case therapy must be discontinued. Failure of the lymphoma to show signs of spontaneous regression requires the initiation of cytotoxic therapy.

Concomitant administration of folate antagonists such as trimethoprim/ sulphamethoxazole has been reported to cause an acute megaloblastic pancytopenia in rare instances.

Radiation-induced dermatitis and sunburn can reappear under methotrexate therapy (recall-reaction). Psoriatic lesions can exacerbate during UV-irradiation and simultaneous administration of methotrexate.

Methotrexate elimination is reduced in patients with a third distribution space (ascites, pleural effusions). Such patients require especially careful monitoring for toxicity, and require dose reduction or, in some cases, discontinuation of methotrexate administration. Pleural effusions and ascites should be drained prior to initiation of methotrexate treatment (see section 5.2).

Diarrhoea and ulcerative stomatitis can be toxic effects and require interruption of therapy, otherwise haemorrhagic enteritis and death from intestinal perforation may occur.

Vitamin preparations or other products containing folic acid, folinic acid or their derivatives may decrease the effectiveness of methotrexate.

For the treatment of psoriasis, methotrexate should be restricted to severe recalcitrant, disabling psoriasis which is not adequately responsive to other forms of therapy, but only when the diagnosis has been established by biopsy and/or after dermatological consultation.

Encephalopathy / leukoencephalopathy have been reported in oncologic patients receiving methotrexate therapy and cannot be excluded for methotrexate therapy in non-oncologic indications.

Fertility and reproduction
Fertility
Methotrexate has been reported to cause oligospermia, menstrual dysfunction and amenorrhoea in humans, during and for a short period after cessation of therapy, and to cause impaired fertility, affecting spermatogenesis and oogenesis during the period of its administration – effects that appear to be reversible on discontinuing therapy.

Teratogenicity – Reproductive risk
Methotrexate causes embryotoxicity, abortion and foetal defects in humans. Therefore, the possible risks of effects on reproduction, pregnancy loss and congenital malformations should be discussed with female patients of childbearing potential (see section 4.6). The absence of pregnancy must be confirmed before Methotrexate is used. If women of a sexually mature age are treated, effective contraception must be performed during treatment and for at least six months after. For contraception advice for men see section 4.6.

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially "sodium free".

Paediatric population
Use in children < 3 years of age is not recommended as insufficient data on efficacy and safety are available for this population (see section 4.2).

4.5 Interaction with other medicinal products and other forms of interaction
Nitrous oxide
The use of nitrous oxide potentiates the effect of methotrexate on folate metabolism, yielding increased toxicity such as severe, unpredictable myelosuppression and stomatitis. Whilst this effect can be reduced by administering calcium folinate, the concomitant use of nitrous oxide and methotrexate should be avoided.

Alcohol, hepatotoxic medicinal products, haematotoxic medicinal products
The probability of methotrexate exhibiting a hepatotoxic effect is increased by regular alcohol consumption and when other hepatotoxic medicinal products are taken at the same time (see section 4.4).

Patients taking other hepatotoxic medicinal products concomitantly (e.g. leflunomide) should be monitored with special care. The same should be taken into account with the simultaneous administration of haematotoxic medicinal products (e.g. leflunomide, azathioprine, retinoids, sulfasalazine). The incidence of pancytopenia and hepatotoxicity can be increased when leflunomide is combined with methotrexate.

Combined treatment with methotrexate and retinoids like acitretin or etretinate increases the risk of hepatotoxicity.

Oral antibiotics
Oral antibiotics like tetracyclines, chloramphenicol, and non-absorbable broad-spectrum antibiotics can interfere with the enterohepatic circulation, by inhibition of the intestinal flora or suppression of the bacterial metabolism.

Antibiotics
Antibiotics, like penicillines, glycopeptides, sulfonamides, ciprofloxacin and cefalotin can, in individual cases, reduce the renal clearance of methotrexate, so that increased serum concentrations of methotrexate with simultaneous haematological and gastro-intestinal toxicity may occur.

Medicinal products with high plasma protein binding
Methotrexate is plasma protein bound and may be displaced by other protein bound medicinal products such as salicylates, hypoglycaemics, diuretics, sulphonamides, diphenylhydantoins, tetracyclines, chloramphenicol and p-aminobenzoic acid, and the acidic anti-inflammatory agents, which can lead to increased toxicity when used concurrently.

Probenecid, weak organic acids, pyrazoles and non-steroidal anti-inflammatory agents
Probenecid, weak organic acids such as loop diuretics, and pyrazoles (phenylbutazone) can reduce the elimination of methotrexate and higher serum concentrations may be assumed inducing higher haematological toxicity. There is also a possibility of increased toxicity when low dose methotrexate and non-steroidal anti-inflammatory medicinal products or salicylates are combined.

Medicinal products with adverse reactions on the bone marrow
In the case of medication with medicinal products which may have adverse reactions on the bone marrow (e.g. sulphonamides, trimethoprim-sulphamethoxazole, chloramphenicol, pyrimethamine); attention should be paid to the possibility of pronounced impairment of blood formation.

Medicinal products which cause folate deficiency
The concomitant administration of products which cause folate deficiency (e.g. sulphonamides, trimethoprim-sulphamethoxazole) can lead to increased methotrexate toxicity. Particular care is therefore advisable in the presence of existing folic acid deficiency.

Products containing folic acid or folinic acid
Vitamin preparations or other products containing folic acid, folinic acid or their derivatives may decrease the effectiveness of methotrexate.

Other antirheumatic medicinal products
An increase in the toxic effects of methotrexate is, in general, not to be expected when Methotrexate 50 mg/ml is administered simultaneously
with other antirheumatic medicinal products (e.g. gold compounds, penicillamine, hydroxychloroquine, sulfasalazine, azathioprine, ciclosporin).

Sulfasalazine
Although the combination of methotrexate and sulfasalazine can cause an increase in efficacy of methotrexate and as a result more undesirable effects due to the inhibition of folic acid synthesis through sulfasalazine, such undesirable effects have only been observed in rare individual cases in the course of several studies.

Mercaptopurine
Methotrexate increases the plasma levels of mercaptopurine.
The combination of methotrexate and mercaptopurine may therefore require dose adjustment.

Proton-pump inhibitors
A concomitant administration of proton-pump inhibitors like omeprazole or pantoprazole can lead to interactions: Concomitant administration of methotrexate and omeprazole has led to delayed renal elimination of methotrexate. In combination with pantoprazole inhibited renal elimination of the metabolite 7-hydroxymethotrexate with myalgia and shivering was reported in one case.

Theophylline
Methotrexate may decrease the clearance of theophylline; theophylline levels should be monitored when used concurrently with methotrexate.

Caffeine- or theophylline-containing beverages
An excessive consumption of caffeine- or theophylline-containing beverages (coffee, caffeine-containing soft drinks, black tea) should be avoided during methotrexate therapy.

4.6 Fertility, pregnancy and lactation
Women of childbearing potential/Contraception in females
Women must not get pregnant during methotrexate therapy, and effective contraception must be used during treatment with methotrexate and at least 6 months thereafter (see section 4.4).

Prior to initiating therapy, women of childbearing potential must be informed of the risk of malformations associated with methotrexate and any existing pregnancy must be excluded with certainty by taking appropriate measures, e.g. a pregnancy test. During treatment pregnancy tests should be repeated as clinically required (e.g. after any gap of contraception). Female patients of reproductive potential must be counselled regarding pregnancy prevention and planning.

Contraception in males
It is not known if methotrexate is present in semen. Methotrexate has been shown to be genotoxic in animal studies, such that the risk of genotoxic effects on sperm cells cannot completely be excluded.

Limited clinical evidence does not indicate an increased risk of malformations or miscarriage following paternal exposure to low dose methotrexate (less than 30 mg/week). For higher doses, there is insufficient data to estimate the risks of malformations or miscarriage following paternal exposure.

As precautionary measures, sexually active male patients or their female partners are recommended to use reliable contraception during treatment of the male patient and for at least 6 months after cessation of methotrexate. Men should not donate semen during therapy or for 6 months following discontinuation of methotrexate.

Pregnancy
Methotrexate is contraindicated during pregnancy in non-oncological indications (see section 4.3). If pregnancy occurs during treatment with methotrexate and up to six months thereafter, medical advice should be given regarding the risk of harmful effects on the child associated with treatment and ultrasonography examinations should be performed to confirm normal foetal development.
In animal studies, methotrexate has shown reproductive toxicity, especially during the first trimester (see section 5.3). Methotrexate has been shown to be teratogenic to humans; it has been reported to cause foetal death, miscarriages and/or congenital abnormalities (e.g. craniofacial, cardiovascular, central nervous system and extremity-related).
Methotrexate is a powerful human teratogen, with an increased risk of spontaneous abortions, intrauterine growth restriction and congenital malformations in case of exposure during pregnancy.
- Spontaneous abortions have been reported in 42.5% of pregnant women exposed to low-dose methotrexate treatment (less than 30 mg/week), compared to a reported rate of 22.5% in disease-matched patients treated with drugs other than methotrexate.
- Major birth defects occurred in 6.6% of live births in women exposed to low-dose methotrexate treatment (less than 30 mg/ week) during pregnancy, compared to approximately 4% of live births in disease-matched patients treated with drugs other than methotrexate.

Insufficient data is available for methotrexate exposure during pregnancy higher than 30 mg/week, but higher rates of spontaneous abortions and congenital malformations are expected.
When methotrexate was discontinued prior to conception, normal pregnancies have been reported.

Breast-feeding
Methotrexate is excreted in human milk. Because of the potential for serious adverse reactions in breast-fed infants, Methotrexate 50 mg/ml is contraindicated during breast-feeding. Therefore breast-feeding must be discontinued prior to and throughout administration.

Fertility
Methotrexate affects spermatogenesis and oogenesis and may decrease fertility. In humans, methotrexate has been reported to cause oligospermia, menstrual dysfunction and amenorrhoea. These effects appear to be reversible after discontinuation of therapy in most cases.

4.7 Effects on ability to drive and use machines
Central nervous symptoms such as tiredness and dizziness can occur during treatment, Methotrexate 50 mg/ml has minor or moderate influence on the ability to drive and use machines.

4.8 Undesirable effects
Summary of the safety profile
Most serious adverse reactions of methotrexate include bone marrow suppression, pulmonary toxicity, hepatotoxicity, renal toxicity, neurotoxicity, thromboembolic events, anaphylactic shock and Stevens-Johnson syndrome.

Most frequently (very common) observed adverse reactions of methotrexate include gastrointestinal disorders e.g. stomatitis, dyspepsia, abdominal pain, nausea, loss of appetite and abnormal liver function tests e.g. increased ALAT, ASAT, bilirubin, alkaline phosphatase. Other frequently (common) occurring adverse reactions are leukopenia, anaemia, thrombopenia, headache, tiredness, drowsiness, pneumonia, interstitial alveolitis/pneumonitis often associated with eosinophilia, oral ulcers, diarrhoea, exanthema, erythema and pruritus.

Tabulated list of adverse reactions
The most relevant undesirable effects are suppression of the haematopoietic system and gastrointestinal disorders.

The following headings are used to organise the undesirable effects in order of frequency:
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)

Infections and infestations
Uncommon: Pharyngitis.
Rare: Infection (incl. reactivation of inactive chronic infection), sepsis, conjunctivitis.

Neoplasms benign, malignant and unspecified (including cysts and polyps)
Very rare: Lymphoma (see "description" below).

Blood and lymphatic system disorders
Common: Leukopenia, anaemia, thrombopenia.
Uncommon: Pancytopenia.
Very rare: Agranulocytosis, severe courses of bone marrow depression, lymphoproliferative disorders (see "description" below).
Not known: Eosinophilia.

Immune system disorders
Rare: Allergic reactions, anaphylactic shock, hypogammaglobulinaemia.

Metabolism and nutrition disorders
Uncommon: Precipitation of diabetes mellitus.

Psychiatric disorders
Uncommon: Depression, confusion.
Rare: Mood alterations.

Nervous system disorders
Common: Headache, tiredness, drowsiness.
Uncommon: Dizziness.
Very rare: Pain, muscular asthenia or paraesthesia/hypoaesthesia, changes in sense of taste (metallic taste), convulsions, meningism, acute aseptic meningitis, paralysis.
Not known: Encephalopathy/leukoencephalopathy.

Eye disorders
Rare: Visual disturbances.
Very rare: Impaired vision, retinopathy.

Cardiac disorders
Rare: Pericarditis, pericardial effusion, pericardial tamponade.

Vascular disorders
Rare: Hypotension, thromboembolic events.

Respiratory, thoracic and mediastinal disorders
Common: Pneumonia, interstitial alveolitis/pneumonitis often associated with eosinophilia. Symptoms indicating potentially severe lung injury (interstitial pneumonitis) are: dry, not productive cough, short of breath and fever.
Rare: Pulmonary fibrosis, *Pneumocystis jirovecii* pneumonia, shortness of breath and bronchial asthma, pleural effusion.
Not known: Epistaxis, pulmonary alveolar haemorrhage.

Gastrointestinal disorders
Very common: Stomatitis, dyspepsia, nausea, loss of appetite, abdominal pain.
Common: Oral ulcers, diarrhoea.
Uncommon: Gastrointestinal ulcers and bleeding, enteritis, vomiting, pancreatitis.
Rare: Gingivitis.
Very rare: Haematemesis, haematorrhea, toxic megacolon.

Hepatobiliary disorders (see section 4.4)
Very common: Abnormal liver function tests (increased ALAT, ASAT, alkaline phosphatase and bilirubin).
Uncommon: Cirrhosis, fibrosis and fatty degeneration of the liver, decrease in serum albumin.
Rare: Acute hepatitis.
Very rare: Hepatic failure.

Skin and subcutaneous tissue disorders
Common: Exanthema, erythema, pruritus.
Uncommon: Photosensitisation, loss of hair, increase in rheumatic nodules, skin ulcer, herpes zoster, vasculitis, herpetiform eruptions of the skin, urticaria.
Rare: Increased pigmentation, acne, petechiae, ecchymosis, allergic vasculitis.
Very rare: Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), increased pigmentary changes of the nails, acute paronychia, furunculosis, telangiectasia.
Not known: Skin exfoliation / dermatitis exfoliative.

Musculoskeletal and connective tissue disorders
Uncommon: Arthralgia, myalgia, osteoporosis.
Rare: Stress fracture.
Not known: Osteonecrosis of jaw (secondary to lymphoproliferative disorders).

Renal and urinary disorders
Uncommon: Inflammation and ulceration of the urinary bladder, renal impairment, disturbed micturition.
Rare: Renal failure, oliguria, anuria, electrolyte disturbances.
Not known: Proteinuria.

Reproductive system and breast disorders
Uncommon: Inflammation and ulceration of the vagina.
Very rare: Loss of libido, impotence, gynaecomastia, oligospermia, impaired menstruation, vaginal discharge.

General disorders and administration site conditions
Rare: Fever, wound-healing impairment.
Very rare: Local damage (formation of sterile abscess, lipodystrophy) of injection site following intramuscular or subcutaneous administration.
Not known: Asthenia, injection site necrosis, oedema.

Description of selected adverse reactions
The appearance and degree of severity of undesirable effects depends on the dose level and the frequency of administration. However, as severe undesirable effects can occur even at lower doses, it is indispensable that patients are monitored regularly by the doctor at short intervals.

Lymphoma/Lymphoproliferative disorders: there have been reports of individual cases of lymphoma and other lymphoproliferative disorders which subsided in a number of cases once treatment with methotrexate had been discontinued.

Subcutaneous application of methotrexate is locally well tolerated. Only mild local skin reactions (such as burning sensations, erythema, swelling, discolouration, pruritus, severe itching, pain) were observed, decreasing during therapy.

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 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.

4.9 Overdose
a) Symptoms of overdose
Toxicity of methotrexate mainly affects the haematopoietic system.

b) Treatment measures in the case of overdose
Calcium folinate is the specific antidote for neutralising the toxic undesirable effects of methotrexate.

In cases of accidental overdose, a dose of calcium folinate equal to or higher than the offending dose of methotrexate should be administered intravenously or intramuscularly within one hour and dosing continued until the serum levels of methotrexate are below 10^{-7} mol/l.

In cases of massive overdose, hydration and urinary alkalisation may be necessary to prevent precipitation of methotrexate and/or its metabolites in the renal tubules. Neither haemodialysis nor peritoneal dialysis has been shown to improve methotrexate elimination. Effective clearance of methotrexate has been reported with acute, intermittent haemodialysis using a high flux dialyser.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Folic acid analogues, ATC code: L01BA01
Antirheumatic medicinal product for the treatment of chronic, inflammatory rheumatic diseases and polyarthritic forms of juvenile idiopathic arthritis. Immunomodulating and anti-inflammatory agent for the treatment of Crohn's disease.

Mechanism of action
Methotrexate is a folic acid antagonist which belongs to the class of cytotoxic agents known as antimetabolites. It acts by the competitive inhibition of the enzyme dihydrofolate reductase and thus inhibits DNA synthesis. It has not yet been clarified, as to whether the efficacy of methotrexate, in the management of psoriasis, psoriasis arthritis, chronic polyarthritis and Crohn's disease, is due to an anti-inflammatory or immunosuppressive effect and to which extent a methotrexate-induced increase in extracellular adenosine concentration at inflamed sites contributes to these effects.

International clinical guidelines reflect the use of methotrexate as a second choice for Crohn's disease patients that are intolerant or have failed to respond to first-line immunomodulating agents as azathioprine (AZA) or 6-mercaptopurine (6-MP).

The adverse events observed in the studies performed with methotrexate for Crohn's disease at cumulative doses have not shown a different safety profile of methotrexate than the profile it is already known. Therefore, similar cautions must be taken with the use of methotrexate for the treatment of Crohn's disease as in other rheumatic and non-rheumatic indications of methotrexate (see sections 4.4 and 4.6).

5.2 Pharmacokinetic properties

Absorption
Following oral administration, methotrexate is absorbed from the gastrointestinal tract. In case of low-dosed administration (dosages between 7.5 mg/m² and 80 mg/m² body surface area), the mean bioavailability is approx. 70 %, but considerable interindividual and intraindividual deviations are possible (25 – 100 %). Maximum serum concentrations are achieved after 1 – 2 hours.

Bioavailability of subcutaneous injection is nearly 100 %.

Distribution
Approximately 50 % of methotrexate is bound to serum proteins. Upon being distributed into body tissues, high concentrations in the form of polyglutamates are found in the liver, kidneys and spleen in particular, which can be retained for weeks or months. When administered in small doses, methotrexate passes into the cerebrospinal fluid in minimal amounts. The terminal half-life is on average 6 – 7 hours and demonstrates considerable variation (3 – 17 hours). The half-life can be prolonged to 4 times the normal length in patients who possess a third distribution space (pleural effusion, ascites).

Biotransformation
Approx. 10 % of the administered methotrexate dose is metabolised intrahepatically. The principle metabolite is 7-hydroxymethotrexate.

Elimination
Excretion takes places, mainly in unchanged form, primarily renal via glomerular filtration and active secretion in the proximal tubulus. Approx. 5 – 20 % methotrexate and 1 – 5 % 7-hydroxymethotrexate are eliminated biliary. There is pronounced enterohepatic circulation.

In the case of renal impairment, elimination is delayed significantly. Impaired elimination with regard to hepatic impairment is not known.

5.3 Preclinical safety data
Animal studies show that methotrexate impairs fertility, is embryo- and foetotoxic and teratogenic. Methotrexate is mutagenic *in vivo* and *in vitro*. As conventional carcinogenicity studies have not been performed and data from chronic toxicity studies in rodents are inconsistent, methotrexate is considered **not classifiable** as to its carcinogenicity to humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Sodium chloride
Sodium hydroxide for pH adjustment
Water for injections

6.2 Incompatibilities
In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf-life
2 years.

6.4 Special precautions for storage
Store below 25 °C.
Keep the pre-filled syringes in the outer carton in order to protect from light.

6.5 Nature and contents of container
Nature of container:
A pre-filled colourless glass syringe (type I) of 1 ml capacity, filled with a clear, yellow-brown solution. It is embedded with an injection needle with a plunger stopper of rubber and plastic rods inserted on the stopper to form the syringe. Also contains alcohol pads.

Pack sizes:
The following pack sizes are available:
Pre-filled syringes containing 0.20 ml, 0.25 ml, 0.30 ml, 0.35 ml, 0.40 ml, 0.45 ml and 0.50 ml of solution.

They are available in a packsize of 4 syringes and 1 syringe with embedded SC needle. Also contains alcohol pads in the package.
All pack sizes are available with graduation marks

6.6 Special precautions for disposal and other handling
The manner of handling and disposal must be consistent with that of other cytotoxic preparations in accordance with local requirements. Pregnant health care personnel should not handle and/or administer Methotrexate 50 mg/ml.

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

For single use only.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

In some regions Methotrexate 50 mg/ml may be marketed with a safety system to prevent needle stick injury and reuse of the needle.

Instructions for subcutaneous use of Methotrexate 50 mg/ml without safety system
The best places for the injection are:
- upper thighs,
- abdomen except around the navel.

1. Clean the area around the chosen injection site with soap and water or disinfectant..
2. Pull the protective plastic cap straight off.
3. Build a skin fold by gently squeezing the area at the injection site.
4. The fold must be held pinched until the syringe is removed from the skin after the injection.
5. Push the needle fully into the skin at a 90-degree angle.
6. Push the plunger down slowly and inject the liquid underneath the skin. Remove the syringe from the skin at the same 90-degree angle.

7. MARKETING AUTHORISATION HOLDER
Procured from the EU by product licence holder Star Pharmaceuticals Ltd, 5 Sandridge Close, Harrow, Middlesex HA1 1XD. Repackaged by Servipharm Ltd.

8. MARKETING AUTHORISATION NUMBER
PL 20636/2364

9. DATE OF REVISION OF THE TEXT
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