Package leaflet: Information for the user

Metotab 2.5 mg tablet
Metotab 7.5 mg tablet
Metotab 10 mg tablet

methotrexate

Read all of this leaflet carefully before you start taking 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 Metotab is and what it is used for

Metotab is indicated for the treatment of
- severe, active rheumatoid arthritis in adult patients.
- severe and generalised psoriasis vulgaris, especially of the plaque type, in adult patients.

Rheumatoid arthritis (RA) is a chronic autoimmune disease, characterised by joint inflammation, leading to swelling of joints, difficulties in moving and pain.

Psoriasis vulgaris is a chronic autoimmune disease of the skin, characterised by patches of red, thickened, dry skin, often covered by silvery scales.

Metotab affects and slows down the course of the disease.

2. What you need to know before you take Metotab

Important warning about the dose of Metotab (methotrexate):
Take Metotab **only once a week** for the treatment of rheumatoid arthritis and psoriasis.
Taking too much of Metotab (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.

Do not take Metotab
- if you are allergic to methotrexate or any of the other ingredients of this medicine (listed in section 6).
- if you have a severe liver or kidney disease or blood disease.
- if you drink large quantities of alcohol.
- if you have a severe infection, e.g. tuberculosis or HIV or other immunodeficiency syndrome.

- if you have ulcers in your mouth, stomach or intestine.
- if you are pregnant or breast-feeding (see section "Pregnancy, breast-feeding and fertility").
- if you are to be vaccinated with live vaccines at the same time.

Warnings and precautions
Talk to your doctor or pharmacist before taking Metotab
- if you are elderly or in generally poor condition.
- if your liver or kidney function is impaired.
- if you are dehydrated.
- if you have diabetes mellitus and are being treated with insulin.

Special precautionary measures for treatment with Metotab
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 6 months after treatment has stopped if you are a woman. If you are a man you should avoid fathering a child if you are being given methotrexate at the time and for at least 3 months after the end of your treatment. See also section "Pregnancy, breast-feeding and fertility".

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

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

During the treatment
Your doctor may perform the following examinations:

- Examination of the oral cavity and the pharynx for changes in the mucous membrane such as inflammation or ulceration.
- Blood tests/blood count with number of blood cells and measurement of serum methotrexate levels.
- Blood test to monitor liver function.
- Imaging tests to monitor liver condition.
- Small sample of tissue taken from the liver in order to examine it more closely.
- Blood test to monitor kidney function.
- Respiratory tract monitoring and, if necessary, lung function test.

It is very important that you appear for these scheduled examinations.
If the results of any of these tests are conspicuous, your doctor will adjust your treatment accordingly.

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

Other precautions

- Contact your doctor if you develop a persistent cough or breathlessness.

- 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 some vaccines may not work properly when using methotrexate. If you suffer from inactive or chronic infections (such as herpes zoster [shingles], tuberculosis, hepatitis B or C) it may happen that these infections flare up or worsen under treatment with methotrexate.

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

- If you have previously had skin problems after radiation therapy (radiation-induced dermatitis) and burns to the skin after sun exposure, these symptoms can come back during methotrexate therapy (re-reaction). Skin changes caused by psoriasis may worsen during treatment with methotrexate and simultaneous UV radiation.

- Enlarged lymph nodes (lymphoma) may occur and if this is the case, therapy must be stopped.

- Diarrhoea can be a possible side effect of Metotab and requires an interruption of therapy. If you suffer from diarrhoea please speak to your doctor.

- Stop taking Metotab and contact your doctor immediately in the event of any swelling, e.g. of the face, tongue and/or throat and/or difficulty swallowing or hives accompanied by breathing difficulties (allergic shock).

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

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

Other medicines and Metotab
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

The effect of the treatment may be affected if Metotab is taken at the same time as certain other medicines:

- **Antibiotics** such as: tetracyclines, chloramphenicol, non-absorbable broad-spectrum antibiotics, penicillins, 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).
- Metamizole (synonyms novaminsulfon and dipyrone) (medicine against severe pain and /or fever).
- **Probenecid** (a medicine against gout).
- Weak organic acids like loop **diuretics** (“water tablets”)

- Medicines which may have adverse effects on the **bone marrow** such as trimethoprim-sulphamethoxazole (an antibiotic) and pyrimethamine.
- Other **medicines used to treat rheumatoid arthritis** such as leflunomide, sulphasalazine and azathioprine.
- Cyclosporine (for suppressing the immune system).
- Mercaptopurine (a medicine used in the treatment of blood cancer).
- Retinoids (medicine against **psoriasis** and other dermatological diseases).
- Theophylline (a medicine against **bronchial asthma** and other lung diseases).
- Certain medicines against **stomach trouble** such as omeprazole and pantoprazole.
- Hypoglycaemics (medicines that are used to **lower the blood sugar**).

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

Vaccination with live vaccines must be avoided while you are being treated with Metotab.

Metotab with food, drink and alcohol
- Alcohol should be avoided during treatment with this medicine.
- Excessive consumption of coffee, drinks containing caffeine and black tea should be avoided during treatment with Metotab.

Pregnancy, breast-feeding and fertility

Pregnancy
Do not use Metotab 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. a pregnancy test before starting treatment.
You must avoid becoming pregnant while 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
Breast-feeding should be discontinued prior to and during treatment with Metotab.

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 while taking methotrexate and for at least 3 months after treatment is stopped.

Driving and using machines
Side effects affecting the central nervous system such as tiredness and dizziness can occur during treatment with Metotab. This can in some cases adversely affect the ability to drive a vehicle or use machines. If you feel tired or dizzy, do not drive or use machines.

Metotab contains lactose monohydrate
Metotab contains lactose monohydrate. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

3. How to take Metotab

Recommended dose

Dose in rheumatoid arthritis and psoriasis

Take Metotab **only once a week**. You and your doctor will together decide on a suitable day of the week for taking it.

The tablets should be swallowed whole with a drink of water while sitting upright or standing. The score line is not intended for breaking the tablet.

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

Your doctor will decide the dose, which is adapted individually to you. Usually it takes 4−8 weeks before the treatment has any effect on rheumatoid arthritis and 2−6 weeks for psoriasis vulgaris. The duration of the treatment will be decided by your doctor.

If you have the impression that the effect of Metotab is too strong or too weak, talk to your doctor or pharmacist.

If you take more Metotab than you should
Follow your doctor's dose recommendations. Do not change the dose yourself.

Contact your doctor immediately if you suspect that you have taken more Metotab than you should. He will decide on the appropriate treatment depending on the size of the overdose.

If you forget to take Metotab
Do not take a double dose to make up for a forgotten tablet. Ask your doctor for advice. Take the dose prescribed by your doctor as soon as possible and each week thereafter.

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 dose and how often Metotab is administered. As severe side effects can occur even at low doses, 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, lymphoma) and changes in the kidneys and the liver.

The most relevant side effects are effects on the formation of blood cells and the gastrointestinal tract.

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, breathlessness and fever**; these may be signs of 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/paralysis of one side of the body (stroke) or pain, swelling, redness and unusual warmth in one of your legs (deep vein thrombosis);** these symptoms can be associated with a dislodged blood clot blocking 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 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 all 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 values (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 decreased numbers of white blood cells, decreased numbers of red blood cells, decreased numbers of platelets.

Uncommon: may affect up to 1 in 100 people
- Throat inflammation.
- Inflammation of the bowels, vomiting, inflammation of pancreas, black and tarry stool, gastrointestinal ulcers and bleeding.

- Sunburn-like reactions due to increased sensitivity of the skin to sunlight, loss of hair, increased number of rheumatic nodules, skin ulcer, shingles (herpes zoster), inflammation of blood vessels, herpes-like skin rash, hives.
- Onset of diabetes mellitus.
- Dizziness, impaired capacity to think (cognitive dysfunction), 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
- Poor absorption of nutrients, inflammation of gum tissue.
- Increased skin pigmentation, acne, blue spots 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.
- 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 lung sacs.
- Fracture induced by stress or fatigue of the bone (stress fracture).
- Electrolyte disturbances.
- Fever, wound-healing impairment.

Very rare: may affect up to 1 in 10,000 people
- Sudden severe 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.
- Pain, decreased muscle 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), impaired oogenesis, impaired spermatogenesis, sterility, 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 white blood cells.
- Nosebleed.
- Proteins in urine.
- Feeling of weakness.
- Bone damage in the jaw (secondary to excessive growth of white blood cells).
- Redness and shedding of skin.
- Swelling.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Metotab

Keep this medicine out of the sight and reach of children.

Do not store above 25 °C. Do not use Metotab after the expiry date which is stated on the carton after "EXP". The expiry date refers to the last day of that month. Keep the blister in the outer carton in order to protect from light.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Metotab contains
- The active substance is methotrexate: 2.5, 7.5 and 10 mg methotrexate, respectively (as methotrexate disodium).
- The other ingredients are lactose monohydrate, pregelatinised starch, magnesium stearate.

What Metotab looks like and contents of the pack
Yellow, slightly speckled, round, biconvex tablets. The 10 mg tablets have a score line which is for identification only.

PVC/PVDC/aluminium blister, containing 10, 30, 50 or 100 tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

[To be completed nationally]

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

Austria, Sweden:
Metotab

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