Package leaflet: Information for the user

Methotrexate 10 mg Tablets
methotrexate

"Take methotrexate tablet once a week"

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 Methotrexate Tablets are and what they are used for

Methotrexate Tablets contain the active ingredient methotrexate. Methotrexate is an antimetabolite and immunosuppressant (medicine which affects the reproduction of the body's cells and reduces the activity of the immune system).

Methotrexate is used to treat:
- active rheumatoid arthritis in adults,
- severe psoriasis, especially plaque-type, in patients who have tried other treatments but their illness has not improved,
- active psoriatic arthritis, in adult patients

acute lymphoblastic leukaemia (ALL) in adults, adolescents and children aged 3 years and over
Your doctor will be able to explain how Methotrexate Tablets might help in your particular condition.

2. What you need to know before you take Methotrexate Tablets

Do not take Methotrexate Tablets if you
- if you are allergic to methotrexate or any of the other ingredients of this medicine (listed in section 6)
- if you have a severe kidney impairment (or your doctor classes the impairment as severe)
- if you have a liver impairment
- if you have blood disorders such as bone marrow hypoplasia, leukopenia, thrombocytopenia or significant anaemia
- if you drink alcohol excessively

- if you have a weakened immune system
- if you are suffering from a serious infection such as tuberculosis or HIV
- if you have ulcers in the stomach or in the intestines
- if you have an inflammation of the mucous membrane of the mouth or mouth ulcers
- if you are breast-feeding and additionally, for non-oncologic indications (for non-cancer treatment) if you are pregnant (see section "Pregnancy, breast-feeding and fertility")
- if you have had a live vaccine recently or are about to have one

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

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

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

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

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

Warnings and precautions

Important warning about the dose of Methotrexate Tablets (methotrexate):
Take Methotrexate Tablets **only once a week** for the treatment of rheumatic or skin diseases (RA and psoriasis or psoriatic arthritis)
Taking too much of Methotrexate Tablets (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.

Talk to your doctor or pharmacist before taking Methotrexate Tablets:
- if you have diabetes mellitus treated with insulin
- if you are suffering from inactive, chronic infections (e.g. tuberculosis, hepatitis B or C, shingles [herpes zoster]) as they may flare up

- if you have ever had any liver or kidney disease
- if you have problems with your lung function
- if you are particularly overweight
- if you have an abnormal build-up of fluid in the abdomen (ascites) or around the lungs (pleural effusions)
- if you are dried out (dehydrated) or suffer from conditions that result in dehydration (vomiting, diarrhoea, constipation, inflammation of the mucous membrane of the mouth)

If you had skin problems after radiotherapy (radiation dermatitis) or sunburn, these reactions can recur after methotrexate therapy (recall reaction).

Enlarged lymph nodes (lymphoma) may occur in patients receiving low dose methotrexate and if this is the case, therapy must be stopped.

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.

Diarrhoea can be a possible side effect of Methotrexate Tablets 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.

Psoriasis skin changes can become worse during treatment with methotrexate if you are under UV light.

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

Recommended follow-up examinations and precautions
Severe side effects can occur even when methotrexate is used at low doses. Your doctor must carry out investigations and laboratory tests in order to detect these effects as early as possible.

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).

Children and adolescents, elderly
Children and adolescents treated with methotrexate should haveparticularly carefulmedical monitoring, in order to detect important side effects quickly.
This medicine is not recommended in children under 3 years of age as there is insufficient experience in this age group

Other medicines and Methotrexate Tablets
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription and herbal or natural medicinal products.
Remember to inform your doctor about the treatment with Methotrexate Tablets if you are

prescribed another medicine during treatment.

It is particularly important to tell your doctor if you are using the following medicines:
- other medicines for rheumatoid arthritis or psoriasis, such as leflunomide, azathioprine (also used to prevent rejection after an organ transplant), sulfasalazine (also used for ulcerative colitis)
- ciclosporin (for supressing the immune system)
- non-steroidal anti-inflammatory drugs or salicylates (medicines against pain and/or inflammation such as acetylsalicylic acid, diclofenac and ibuprofen or pyrazole)
- live vaccines
- diuretics, that reduce fluid retention
- medicines for lowering blood sugar levels such as metformin
- retinoids (for the treatment of psoriasis and other skin diseases)
- antiepileptic medicines (prevention of seizures)
- barbiturates (sleeping medicines)
- sedatives
- oral contraceptives
- probenecid (for gout)
- antibiotics
- pyrimethamine (for the prevention and treatment of malaria)
- vitamin preparations containing folic acid
- proton pump inhibitors (for the treatment of heartburn, ulcers and some other stomach complaints)
- theophylline (for breathing problems)
- mercaptopurine (for the treatment of certain types of leukaemia).
- cancer treatments (such as doxorubicin and procarbazine during high-dose methotrexate therapy)

Methotrexate Tablets with food, drink and alcohol
This medicine can be taken with or without food. When you have taken your dose, drink some water and swallow it to ensure you have taken your full dose and there is no methotrexate left in your mouth. You should not drink alcohol during treatment with Methotrexate Tablets and should avoid drinking excessive amounts of coffee, caffeinated drinks and black leaf tea. Ensure that you drink a lot of fluids during treatment with Methotrexate Tablets because dehydration (the reduction of body water) can increase the side effects of methotrexate.

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

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

For non-oncological indications, in women of child-bearing age the possibility of a pregnancy must be ruled out, e.g. by pregnancy tests, before treatment is started.
Do not use Methotrexate Tablets if you are trying to become pregnant. You must avoid becoming pregnant during treatment with methotrexate and for at least 6 months after the end of treatment. Therefore, you must ensure that you are taking effective contraception for the whole of this period (see also section "Warnings and precautions").

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

Breast-feeding
Do not breastfeed during treatment, because methotrexate passes into breast milk. If your attending doctor considers treatment with methotrexate absolutely necessary during the lactation period, you must stop breast-feeding.

Fertility

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

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

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

Driving and using machines

Caution: This medicine can affect your capacity to react and your ability to drive.

Side effects affecting the central nervous system such as tiredness or dizziness can occur during treatment with Methotrexate Tablets. In some cases the ability to drive or use machines may be affected. If you feel tired or dizzy, you should not drive a vehicle or use machines.

Methotrexate Tablets contains lactose
Methotrexate Tablets contains lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. How to take Methotrexate Tablets

Methotrexate Tablets should be prescribed only by doctors who are familiar with the properties of the medicine and how it works.

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

Taking Methotrexate Tablets incorrectly can result in severe side effects and even death.

The duration of the treatment is determined by the treating physician. Treatment of rheumatoid arthritis, severe psoriasis and severe psoriatic arthritis with Methotrexate Tablets is a long-term treatment.

Recommended dose

Your doctor will decide what dose of Methotrexate Tablets you should take according to the condition you are being treated for, how severe it is and your general health. Keep to the dose exactly and follow your doctor's instructions exactly on when to take the medicine.

Dose in rheumatic and skin diseases (RA and psoriasis or psoriatic arthritis)
Take Methotrexate Tablets **only once a week**.
Decide with your doctor the most suitable day of the week to take the medicine.

*Dosage in adult rheumatoid arthritis:*The usual initial dose is 7.5 mg - 15 mg **orally, once weekly**.

*Dosage for psoriasis and psoriatic arthritis:*The usual initial dose is 7.5 mg - 15 mg **orally, once weekly**.
The doctor may increase the dose if the used dose is not effective but tolerated well.
Your doctor may adjust the dose to suit you according to your response to treatment and side effects.

*Dose in acute lymphoblastic leukaemia (ALL)*Your doctor will tell you what dose you should take for your condition and when you should take the dose. Keep to this dose exactly. To be taken **orally, once weekly.**

Use in children and adolescents
The doctor will calculate the dose required from the child's body surface area (m2), and the dose is expressed as mg/m2.

Elderly
Because of the reduced liver and kidney function and the lower folate reserves in elderly patients, a relatively low dosage should be chosen for them.

For 10 mg tablets: The score line is only there to help you break the tablet if you have difficulty swallowing it whole.

Safe handling of Methotrexate Tablets
Proper procedures for safe handling of cytotoxic agents should be administered. Disposable gloves should be used when handling methotrexate tablets. Pregnant women should avoid handling methotrexate tablets, if possible.

If you take more Methotrexate Tablets than you should
Follow your doctor's dose recommendations. Never change the dose on your own. If you suspect that you (or someone else) have (has) taken too much Methotrexate Tablets, tell your doctor immediately or contact nearest hospital casualty department. The doctor will decide whether any treatment is needed.

An overdose of methotrexate can cause serious reactions. The symptoms of an overdose caninclude bleeding, an unusual feeling of weakness, ulcers in the mouth, feeling sick, vomiting, black or bloody stools, coughing up blood or vomiting blood with a coffee grounds appearance and a reduced urine. See also section 4.

Take the medicine pack with you when you visit your doctor or the hospital. The antidote in the event of an overdose is calcium folinate
If you forget to take Methotrexate Tablets
Never take a double dose to make up for a forgotten dose but continue with the prescribed dose. Ask your doctor for advice.

If you stop taking Methotrexate Tablets
Do not interrupt or stop the treatment with Methotrexate Tablets without first discussing this with your doctor. If you suspect you have a severe side effect, talk to your doctor immediately.

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

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Tell your doctor immediately if you suddenly get wheeziness, difficulty in breathing, swelling of the eyelids, face or lips, rash or itching (especially affecting your whole body).

Contact your doctor immediately if you develop any of the side effects listed below:

- breathing problems (these include a general feeling of illness, dry, irritating cough, shortness of breath, difficulty in breathing, chest pain or fever)
- spitting or coughing blood*
- serious peeling or blistering of the skin
- unusual bleeding (including vomiting blood), bruising or nose bleeds
- nausea, vomiting, abdominal discomfort or severe diarrhoea
- mouth ulcers
- black or tarry stools
- blood in the urine or stool
- small red spots on the skin
- fever, sore throat, flu-like symptoms
- yellow colouring of the skin (jaundice) or dark urine
- pain or difficulties in passing urine
- thirst and/or frequent urination
- seizures (convulsions)
- unconsciousness
- blurred or restricted vision
- severe fatigue.

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

The following side effects have also been reported:

Very common (may affect more than 1 in 10 people):
- loss of appetite, feeling sick (nausea), vomiting, abdominal pain, indigestion, inflammation and ulcers of the mouth and throat
- blood test showing raised liver enzymes.

Common (may affect up to 1 in 10 people):
- infections
- reduced blood cell formation with a decrease in white and/or red blood cells and/or platelets (leucocytopenia, anaemia, thrombocytopenia)
- headache, tiredness, lightheadedness
- inflammation of the lungs (pneumonia) with dry cough, shortness of breath and fever
- diarrhoea
- skin rash, skin redness and itching.

Uncommon (may affect up to 1 in 100 people):
- lymphoma (lump in neck, groin or armpits with associated backache, weight loss or night sweats)
- severe allergic reactions
- diabetes
- depression
- dizziness, confusion, seizures

- lung damage
- ulcers and bleeding in the digestive tract
- liver diseases, reduced content of blood proteins
- nettle rash, skin reaction in strong light, brown discoloration of the skin, hair loss, increased number of rheumatic nodules, shingles, painful psoriasis, slow wound healing
- joint or muscle pain, osteoporosis (reduction in bone strength)
- kidney disease, inflammation or ulcers of the bladder (possibly also with blood in the urine), painful urination
- inflammation and ulcers of the vagina.

Rare (may affect up to 1 in 1,000 people):
- a blood disorder characterised by the appearance of very large red blood cells (megaloblastic anaemia)
- mood swings
- weakness in movements, also only limited to the left or right side of the body
- severe visual disorders
- inflammation of the heart sac, accumulation of fluid in the heart sac
- low blood pressure, blood clots
- tonsillitis, stopping breathing, asthma
- inflammation of the pancreas, inflammation of the digestive tract, bloody stools, inflamed gums, indigestion
- acute hepatitis (inflammation of the liver)
- discoloration of the nails,acne, red or purple spots due to bleeding from blood vessels
- worsening of psoriasis during treatment with UV therapy
- skin lesions resembling sunburn or dermatitis after radiotherapy
- bone fractures
- kidney failure, reduction or lack of urine production, abnormal levels of electrolytes in blood
- impaired sperm formation, menstrual disorders.

Very rare (may affect up to 1 in 10,000 people):
- viral, fungal or bacterial systemic infections,
- serious disorder of bone marrow (anaemia), swollen glands
- lymphoproliferative disorders (excessive growth of white blood cells)
- insomnia
- pain, muscle weakness, changes in the sense of taste (metallic taste), inflammation of the membrane lining the brain resulting in paralysis or vomiting, sensation of numbness or
- tingling/having less sensitivity to stimulation than normal impaired movement of the muscles used for speech production, difficulty in speaking, impairment of language, feeling sleepy or tired, feeling confused, having unusual sensations in the head, brain swelling, ringing in ears
- red eyes, damage to the retina of the eye
- accumulation of fluid in the lung, lung infections
- vomiting blood, severe complications in the digestive tract
- liver failure
- fingernail infections, detachment of the nail from the nail bed, boils, widening of small blood vessels, damage to the blood vessels of the skin, allergic inflammation of blood vessels
- protein in the urine
- loss of sex drive, erection problems, vaginal discharge, infertility, enlargement of the breasts in men (gynaecomastia)
- fever

Not known (frequency cannot be estimated from the available data)
- pathological change of the white matter of the brain (leukoencephalopathy)

- haemorrhages
- bleeding from the lungs*
- redness and shedding of skin

- bone damage in the jaw (secondary to excessive growth of white blood cells).
- swelling

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

Methotrexate can reduce the number of white blood cells and therefore weaken your immune defences. If you notice any symptoms of an infection such as fever or a marked worsening in your general state of health or fever with local signs of an infection such as sore throat/inflammation of the throat or mouth or problems passing water, see your doctor immediately. A blood test will be done to check for reduction in the white blood cells (agranulocytosis). It is important to tell your doctor about all the medicines you take.

Methotrexate can cause serious (sometimes life-threatening) side effects. Your doctor will therefore do tests to check for any changes in your blood (such as a low white blood cell count, a low blood platelet count, lymphomas), kidneys or liver.

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

Ireland
HPRA Pharmacovigilance Earlsfort Terrace,
IRL - Dublin 2;
Tel: +353 1 6764971;
Fax: +353 1 6762517.
Website: www.hpra.ie;
E-mail: medsafety@hpra.ie

5. How to store Methotrexate Tablets

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

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

Storage
This medicine does not require any special temperature storage conditions.
Blister: Store in the original package in order to protect from light.

Disposal
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 to protect the environment.

6. Contents of the pack and other information

What Methotrexate Tablets contain
The active substance is methotrexate.

Each tablet contains 10 milligrams (mg) of methotrexate.

The other ingredients are anhydrous calcium hydrogen phosphate, lactose monohydrate, sodium starch glycolate (Type A), cellulose, microcrystalline, talc and magnesium stearate (E470b).

What Methotrexate Tablets look like and contents of the pack
Methotrexate 10 mg Tablets are yellow coloured, capsule shaped, biconvex uncoated tablet with length of 10.00 mm ± 0.20 mm and breadth 5.00 mm ± 0.20 mm, with central breakline on one side and plain on other side.

Tablets are packed in blister (containing amber coloured PVC film and aluminium blister foil).

Pack sizes:
Blister pack: 10 tablets; 12 tablets, 15 tablets, 20 tablets, 24 tablets; 25 tablets, 28 tablets; 30 tablets; 50 tablets; 100 tablets

PVC/Alu perforated unit dose blister in pack-sizes of 10x1, 12x1, 15x1, 20x1, 24x1, 25x1, 28x1, 30x1, 50x1 & 100x1 tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder
Accord Healthcare Ireland Limited
Euro House
Euro Business Park
Little Island
Cork T45 K857
Ireland

Manufacturer
Accord Healthcare B.V.,
Winthontlaan 200,
3526 KV Utrecht,
The Netherlands

Accord Healthcare Polska Sp.z o.o.,
ul. Lutomierska 50,95-200 Pabianice,
Poland

This leaflet was last revised