Package leaflet: Information for the user

Methotrexate 2.5 mg Tablets
Methotrexate 10 mg Tablets
methotrexate

Do not exceed the weekly dose of this medicine due to toxicity hazards.

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, pharmacist or nurse. 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,
- severe psoriasis, especially plaque-type, in patients who have tried other treatments but their illness has not improved,
- severe psoriatic arthritis.

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 are allergic (hypersensitive) to methotrexate, or any of the other ingredients of this medicine (listed in section 6);
- if you are pregnant or breast-feeding (see section "Pregnancy, breast-feeding and fertility");
- if you have significant liver disease (your doctor decides the severity of your disease);
- if you have significant kidney disease (your doctor decides the severity of your disease);
- if you have or have had a bone marrow disease or serious blood disorders;

- if you have severe acute or chronic infections or immunodeficiency syndrome;
- if you suffer from alcoholism.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before taking Methotrexate Tablets if you suffer from or have suffered in the past from any of the following conditions;
- have or have had any liver or kidney disease;
- are using any medicines or vitamin products (see section "Other medicines and Methotrexate Tablets");
- have ulcerations in your stomach or bowel (peptic ulcer or ulcerative colitis);
- are in poor general condition;
- have received any vaccinations recently or are you due to have any;
- have any symptoms or signs of infection;
- Diabetes mellitus treated with insulin.

Methotrexate temporarily affects sperm and egg production. You and your partner should avoid conception (becoming pregnant or fathering children) if currently receiving methotrexate and for at least six months after your treatment with methotrexate has stopped. See section "Pregnancy, breast-feeding and fertility".

Before treatment is started your doctor may carry out blood tests, and also to check how well your kidneys and liver are working. You may also have a chest X-ray. Further tests may also be done during and after treatment. Do not miss appointments for blood tests.

Children and adolescents
Methotrexate Tablets are not recommended in children and adolescents for rheumatoid arthritis and psoriasis.

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.

Some medicines can affect the way Methotrexate Tablets work, or Methotrexate Tablets can reduce the effectiveness of other medicines taken at the same time. These include:
- aspirin or similar medicines (known as salicylates);
- certain antibiotics (such as chloramphenicol, penicillin, sulphonamides, co-trimoxazole, trimethoprim and tetracyclines);
- diuretics, triamterene (water tablets);
- phenytoin (medicine often used to treat epilepsy);
- probenicid(medicine used to treat gout);
- folic acid (vitamin preparations);
- omeprazole or pantoprazole (medicine used to stop the production of stomach acid);
- agents that may be harmful to kidneys and liver [e.g. sulfasalazine and leflunomide (medicines for rheumatic disease), vitamin A and its derivatives, alcohol];
- anticancer agents (e.g. cisplatin, mercaptopurine);
- non-steroidal anti-inflammatory medicines (medicines taken for pain relief) e. g. ibuprofen and pyrazols;
- medicines taken to help control rheumatism e. g. azathioprine;
- theophylline (medicine used to treat respiratory diseases);
- cyclosporine (an agent that can suppress or prevent the immune response).

Tell your physician about use of Methotrexate Tablets during your next visits.

Methotrexate Tablets with food and alcohol
Alcohol should be avoided while taking methotrexate.

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

Pregnancy
Do **not** use Methotrexate during pregnancy or if you are trying to become pregnant. Methotrexate can cause birth defects, harm unborn babies or cause miscarriages and so it is very important that it is not given to pregnant patients or patients planning to become pregnant. Therefore, 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 whilst taking methotrexate and for at least 6 months after treatment is stopped. Therefore you must ensure reliable contraception during this whole period (see section "Warnings and precautions").

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 wish to become pregnant you should consult a genetic information centre before the planned start of treatment, because methotrexate may be genotoxic, which means that the medicine may cause genetic mutation.

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
Methotrexate may be genotoxic. This means that the medicine may cause genetic mutation. Methotrexate can affect sperm and egg production with the potential to cause birth defects. Therefore, you must avoid fathering a child whilst taking methotrexate and for at least **6** months after treatment is stopped. Since treatment with methotrexate may lead to infertility, it might be advisable for male patients to look into the possibility of **sperm preservation** before starting treatment (see section "Warnings and precautions").

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

Driving and using machines
You can feel fatigue and dizziness during Methotrexate Tablets treatment. Do not drive or use machines if you have such symptoms.

Methotrexate Tablets contain lactose

Methotrexate Tablets contain lactose. 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 Methotrexate Tablets

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

- Take Methotrexate Tablets once a week.
- Patients with rheumatoid arthritis or psoriasis will usually take their tablets orally **once a week** on the same day each week.
- Do not take tablets more often than your doctor has told you to.
- **Daily administration can lead to serious toxic effects.**
- Take the tablets with a glass of water whilst sitting upright or standing.

Recommended dose
Rheumatoid arthritis
The recommended dose is 7.5 mg - 15 mg **orally, once weekly**.

Psoriasis
The recommended dose is 7.5 mg - 15 mg **orally, once weekly**.

This should be adjusted according to your response to treatment and side effects.

Use in children
Not recommended for use in children.

If you take more Methotrexate Tablets than you should
If you take (or someone else has taken) more of the medicine than you should, a physician or nearest hospital casualty department must be contacted immediately.

An overdose of methotrexate can lead to severe toxic reactions. Overdose symptoms may include easy bruising or bleeding, unusual weakness, mouth sores, nausea, vomiting, black or bloody stools, coughing up blood or vomit that looks like coffee grounds, and decreased urinating. See also section 4.

Take your medicine package with you if you go to a doctor or hospital.

If you forget to take Methotrexate Tablets
If you forget to take a dose, take it as soon as you remember if this is within two days. However, if you have missed a dose by more than two days, please contact your doctor for advice. **Do not take a double dose to make up for a missed dose.**

If you stop taking Methotrexate Tablets
Do not stop taking Methotrexate Tablets unless your doctor tells you to. Should you need to stop taking Methotrexate Tablets, your doctor will have decided which is the best method for you.

If you have any further questions on how to take 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.

In general, the incidence and severity of adverse reactions of methotrexate are related to dose and frequency of administration. Most adverse reactions are reversible if detected early.

<u>If you notice any of the following, please contact your doctor immediately:</u>

- Unusual bleeding (including vomiting blood) or bruising

- severe diarrhoea
- ulcers in mouth
- an allergic reaction such as skin rash or swelling of your lips or tongue -
- fever
- yellowing of the skin (jaundice)
- pain or difficulty in passing urine
- thirst and/or frequent urination
- chest pain
- a dry cough and/or pain or difficulty in breathing or shortness of breath
- blurred or decreased vision.

Most of the effects listed below will only be seen in patients who are receiving high doses of methotrexate to treat cancer. They are not seen as often and are not as severe at the doses used in the treatment of psoriasis or rheumatoid arthritis.

Common (may affect up to 1 in 10 people)
- leukopenia (decrease number of white blood cells)*,
- nausea,
- vomiting,
- diarrhoea
- unusual fatigue,
- headache,
- dizziness,
- loss of appetite,
- erythematous rashes,
- stomatitis (soreness of the mouth and lips),
- increase of liver transaminases (enzymes)*,
- decreased resistance to infections,
- Tingling or numbness in the hands or feet
- alopecia.

Uncommon (may affect up to 1 in 100 people)
- bone marrow depression manifested by thrombocytopenia and other abnormalities developing in the blood*,
- formation of excess fibrous connective tissue in an organ (fibrosis),
- inflammation of the lungs, which can cause shortness of breath and difficulty breathing,
- itchy skin,
- anemia,
- nosebleed,
- skin condition that causes painful blisters and sores of the skin and mucous membranes, especially in the mouth (Stevens-Johnson syndrome)
- serious illness with blistering of the skin (Toxic epidermal necrolysis),
- anaphylactic reactions,
- kidney dysfunction,
- a cancer of the lymph nodes (or tissues),
- vaginal ulceration.

* Only detected by your doctor.

Rare (may affect up to 1 in 1,000 people)
- depression,

- confusion,
- hemiparesis (impairment of motor function affecting only one side of the body),
- diabetes mellitus,
- hypotension,
- thromboembolism,
- dyspnoea,
- gastrointestinal ulceration and bleeding,
- liver damage (hepatic toxicity, periportal fibrosis, hepatic cirrhosis, acute hepatitis),
- skin reactions (acne, skin depigmentation, urticaria, photosensitivity, erythema multiforme, burning in skin psoriatic lesions, skin ulcers),
- herpes zoster,
- decreased bone mineral density a type of bone disease (osteoporosis),
- increase in rheumatic nodules,
- pain in joint or muscles,
- menstrual disorders,
- impotence,
- decrease of libido.
- fatal whole-body inflammation (sepsis),

Very rare (may affect up to 1 in 10,000 people)
- immune deficiency (hypogammaglobulinaemia),
- irritation,
- difficulty in speaking (dysarthria),
- sleepiness, tiredness (lethargy),
- visual disturbance,
- redness and irritation of the thin membrane that covers the eye (conjunctivitis),
- fluid in the sac around the heart. May cause cardiac tamponade which is a life threatening condition where the heart is unable to pump correctly due to the external pressure. May require medical intervention to drain the fluid and remove the pressure,
- inflammation of blood vessels, often with skin rash (vasculitis),
- infection of lungs,
- dry cough,
- loss of sex drive,
- low sperm count,
- vaginal bleeding.

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
HPRA Pharmacovigilance
Earlsfort Terrace
IRL - Dublin 2
Tel: +353 1 6764971
Fax: +353 1 6762517
Website: www.hpra.ie
e-mail: medsafety@hpra.ie
by reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Methotrexate Tablets

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

This medicinal product does not require any special temperature storage conditions.

Keep the blister in the outer carton in order to protect from light.

Store in original container in order to protect from light.

Do not use Methotrexate Tablets after the expiry date which is stated on the label after EXP. The expiry date refers to last day of that month.

Do not throw 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.

2.5 mg tablets: each tablet contains methotrexate 2.5 mg.

10 mg tablets: each tablet contains methotrexate 10 mg.

The other ingredients in 2.5 mg tablets and 10 mg tablets are: anhydrous calcium hydrogen phosphate, lactose monohydrate, sodium starch glycolate, microcrystalline cellulose, talc, magnesium stearate.

What Methotrexate Tablets look like and contents of the pack

Methotrexate 2.5 mg Tablets are yellow, circular, biconvex uncoated tablets with dimension of 4.50 mm ± 0.2 mm plain on both sides.
Methotrexate 2.5 mg Tablets are available in HDPE bottles containing 25 or 100 tablets and Blister pack containing 10, 24, 25, 28 30, 50 or 100 tablets.

Methotrexate 10 mg Tablets are yellow coloured, capsule shaped, biconvex uncoated tablet with length of 10 mm ± 0.2 mm and breadth 5 mm ± 0.2 mm, with central breakline on one side and plain on other side.
Methotrexate 10 mg Tablets are available in HDPE bottles containing 25 or 100 tablets and Blister pack containing 10, 25, 30, 50 or 100 tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder

Cipla (EU) Limited
Hillbrow House, Hillbrow Road,
Esher, Surrey, KT10 9NW,
United Kingdom.

Manufacturer

Cipla (EU) Limited,
20 Balderton Street,

London W1K 6TL,
United Kingdom.

S&D Pharma CZ
spol. s.r.o, Theodor 28
Pchery (Pharmos a.s. facility), 27308
Czech Republic.

Cipla Europe NV,
Uitbreidingstraat 80,
2600 Antwerp,
Belgium

This medicinal product is authorised in the Member States of the EEA under the following names:

United kingdom	Methotrexate 2.5 mg/10 mg Tablets
Ireland	Methotrexate 2.5 mg/10 mg Tablets
Malta	Methotrexate 2.5 mg/10 mg Tablets
Croatia	Metotreksat Cipla 2,5 mg/10 mg tablete
Czech Republic	Methotrexat Cipla 2,5 mg/10 mg tablety
Denmark	Methotrexate Cipla
Greece	Methotrexate Cipla 2.5 mg/10 mg δισκία
Norway	Methotrexate Cipla
Poland	Methotrexat Cipla
Spain	Metotrexato 2,5 mg/10 mg comprimidos
Sweden	Methotrexate Cipla

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