Package Leaflet: Information For The User

Methotrexate 100 mg/ml concentrate for solution for infusion
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 or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their sign of illness are the same as yours.
- 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. See section 4.

What is in this leaflet:

1. What Methotrexate is and what it is used for

Methotrexate contains the active substance methotrexate. Methotrexate is a cytostatic that inhibits cell growth. Methotrexate has its greatest effect on cells which increase frequently like cancer cells, bone marrow cells and skin cells.

Methotrexate is used in the treatment of the following types of cancer:
- acute lymphocytic leukaemia,
- non-Hodgkin's lymphomas,
- osteogenic sarcoma,
- adjuvant and in advance disease of breast cancer,
- metastatic or recurrent head and neck cancer,
- choriocarcinoma and similar trophoblastic diseases,
- advanced cancer of urinary bladder.

2. What you need to know before you take Methotrexate

Do not use Methotrexate
- If you are allergic (hypersensitive) to methotrexate or any of the other ingredients of this medicine (listed in section 6).
- If you have severe liver or kidney disease.
- If you have increased alcohol consumption.
- If you have disorders of the blood-forming system.
- If you have severe or existing infection such as tuberculosis and HIV.
- If you have ulcers in the mouth and throat or ulcers in the stomach and gut.
- If you are breast-feeding (see section Pregnancy, breast-feeding and fertility).

You should not be given live vaccines during treatment with Methotrexate.

Warnings and precautions
- Methotrexate can cause serious and sometimes life-threatening undesirable effects. Your doctor will talk to you about the advantage and risks of the treatment and what the early signs and symptoms of undesirable effects are.

- Your skin or eyes can be extremely sensitive to sunlight or other forms of light during the treatment with Methotrexate. Therefore sunlight and solarium should be avoided.
- Methotrexate can cause decrease in cells responsible for providing immunity, carrying oxygen, and those responsible for normal blood clotting, thereby increasing chances of you getting the infections (e.g pneumonia) or increased bleedings.
- Acute bleeding from the lungs in patients with underlying rheumatologic disease has been reported with methotrexate.
- 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".

Talk to your doctor, pharmacist or nurse before taking Methotrexate
- If you are to undergo radiotherapy at the same time as the Methotrexate treatment. The risk of tissue and bone damage can increase with simultaneous treatment.
- If you are having treatment in your spine (intrathecally) or in a vein (intravenously) this can cause a potentially life-threatening inflammation in the brain.
  Methotrexate 100 mg/ml must not be administered in your spine (intrathecally).
- If you have a medical condition that means that fluid is retained in your body, for example in the lungs or in the stomach.
- If you have impaired kidney function.
- If you have impaired liver function.
- If you have an infection.
- If you need to be vaccinated. Methotrexate can reduce the effect of the vaccines.
- If you have insulin dependent diabetes, **Methotrexate** treatment should be carefully monitored.

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).

Recommended follow-up examinations and precautions:
Even when methotrexate is used at low doses, serious side effects can occur. In order to recognise these in good time, your doctor must carry out check-ups and laboratory tests.

Before the start of treatment:
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.

Other medicines and Methotrexate
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, Methotrexate affects or is affected by certain other medicinal products against:
- Pain and inflammation (so called NSAIDs and salicylates)
- Cancer (cisplatin, cytarabine, mercaptopurine)
- Infections (ciprofloxacin and antibiotics such as penicillins, tetracycline and chloramphenicol)
- Asthma (theophylline)
- Vitamin preparations containing folic acid or substances like folic acid
- Rheumatism (leflunomide)
- High blood pressure (furosemide)
- Gout (probenicide)
- Radiotherapy
- Stomach ulcers, heartburn, reflux (such as omeprazole, pantoprazole, lansoprazole)
- Epilepsy (phenytoin)

- Psoriasis or severe acne (retinoids, such as acitretin ot isotretinoin)
- Rheumatoid arthritis or bowel disease (sulfasalazine)
- Rejection after an organ transplant (azathioprine)
- If you need to be vaccinated with a live vaccination

Methotrexate with food, drink and alcohol
During treatment with Methotrexate, you should not drink any alcohol and you should avoid excessive consumption of coffee, soft drinks containing caffeine and black tea. Also make sure you drink plenty of liquids during treatment with Methotrexate because dehydartion (reduction in body water) can increase the toxicity of Methotrexate.

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

For non-oncological indications, in women of child-bearing age the possibility of a pregnancy must be ruled out, e.g. by pregnancy tests, before treatment is started.

Do not use Methotrexate if you are trying to become pregnant. You must avoid becoming pregnant during treatment with methotrexate and for at least 6 months after the end of treatment. Therefore, you must ensure that you are taking effective contraception for the whole of this period (see also section "Warnings and precautions").

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

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

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").

Breast-feeding
Methotrexate is excreted in breast milk in such quantities that there are risks of affecting the baby. Breast-feeding should therefore be suspended prior to treatment with Methotrexate.

Driving and using machines
Undesirable effects such as tiredness and dizziness may occur. If you feel tired or dizzy do not drive and do not use machines.

Methotrexate contains sodium

This medicine contains 194 mg sodium (main component of table salt) in maximum recommended daily dose. This is equivalent to 9.7% of the recommended maximum daily dietary intake of sodium for an adult.

3. How to take Methotrexate

Methotrexate is given to you by healthcare professionals.

The dose you receive and how often you receive the dose, depend on the disease you are being treated for your state of health and your age, weight and body surface. Methotrexate can be given in a muscle (intramuscularly), in a vein (intravenously), or in an artery (intra-arterially).

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

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Methotrexate can have undesirable effects which may be dangerous or life-threatening. During the treatment you should be alert to signs of undesirable effects and report them to your doctor.

Contact a doctor immediately if you notice any of the following undesirable effects. You may need immediate medical care.

- Unexplained breathlessness, dry cough or wheezing (symptoms of lung problems).
- Sudden itching, skin rash (urticaria), swollen hands, feet, ankles, face, lips, mouth or throat (which can make it hard to breathe and swallow). It can also feel as if you are going to faint (symptoms of a severe allergic reaction).
- Vomiting, diarrhoea or stomatitis and peptic ulcers (Symptoms of effect on gastrointestinal track).
- Yellowing of the skin or eyes, dark coloured urine (symptoms of effect on the liver)
- Fever, shivering, aching body and sore throat (symptoms of infection).
- Unexpected bleeding (for example bleeding gums, dark urine, blood in the urine or vomit) or unexpected bruising, black, tar-like faeces – this can be due to a reduced coagulation capacity or bleeding from the stomach or gut).
- Skin rashes with flaking or blistering and effects on mucous membranes e.g. in the nose (symptoms of Stevens-Johnsons syndrome, toxic epidermal necrolysis and erythema multiforme).
- Abnormal behaviour, transient blindness and generalised seizures (Symptoms of effect on central nervous system).
- Paralysis (paresis).

A list of undesirable effects that have been reported in treatment with Methotrexate is set out below according to how common they are.

Very common (may affect more than 1 in 10 people):
- Loss of appetite, nausea, vomiting, abdominal pain, impaired digestion, dyspepsia
- Inflammation and ulceration in mouth and throat
- Increase in level of liver enzyme

Common (may affect up to 1 in 10 people):
- Herpes zoster
- Effects on the blood e.g. anaemia, leukopenia, thrombocytopenia
- Diarrhoea
- Dry cough, shortness of breath, chest pain, fever
- Rashes, redness and itching
- Headache, Tiredness, drowsiness

Uncommon (may affect up to 1 in 100 people)

- Pancytopenia, agranulocytosis
- Inflammation of blood vessels
- Anaphylactoid reactions and allergic vasculitis
- Vertigo, confusion, depression
- Convulsions, encephalopathy
- Lymphoma (tumour in lymph tissue)
- Pulmonary fibrosis
- Bleeds and ulcers in the stomach and intestinal tract
- Inflammation of pancreas
- Diabetic complications
- Reduced level of albumin
- Enhanced pigmentation of the skin
- Loss of hair, painful lesions of scaly patches caused by psoriasis
- Increase of rheumatic nodules (lumps of tissues)
- Effects on skin and mucous membrane, sometimes serious (Stevens-Johnsons syndrome, toxic epidermal necrolysis)
- Skin becoming hypersensitive to sunlight, urticaria
- Brittle bones (osteoporosis), arthralgia, myalgia
- Liver fibrosis and cirrhosis, fatty liver
- Inflammation and ulceration of urinary bladder, haematuria, dysuria
- Inflammation and ulceration of vagina

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

- Pericarditis, pericarditis effusion and tamponade
- Megaloblastic anaemia
- Mood swings
- Paresis
- Effects on speech including dysarthria and aphasia
- Myelopathy
- Visual disturbance, blurred vision
- Thrombosis (cerebral, deep vein and retinal vein)
- Low blood pressure
- Diabetes
- Pharyngitis apnoea , bronchial asthma, gingivitis
- Inflammation in the small intestine
- Blood in the faeces
- Malabsorption
- Acne, sores on the skin, pigment changes of the nails, bruises
- Fractures
- Renal failure, oliguria, azotaemia and anuria
- Hyperuricemia
- Elevated serum creatinine and urea level
- Liver damage.
- Abnormal development of mammary glands

Very rare (may affect up to1 in 10,000 people)

- Infections, sepsis opportunistic infections
- Severe failure of the bone marrow, anaemia due to the fact that the bone marrow cannot produce blood cells (aplastic anaemia) Lymphadenopathy, lymphoproliferative disorder (excessive growth of white blood cells), eosinophilia, neutropenia and hypogammaglobulinaemia
- Immunosuppression
- Insomnia
- Impaired intellectual functions such as thinking, remembering and reasoning
- Joint and/or muscle pain, lack of strength

- Myasthenia (muscle weakness)
- Meningism (paralysis, vomiting), acute aseptic meningitis
- Abnormal sensations, changes in sense of taste (metallic taste)
- Conjunctivitis, retinopathy, loss of vision, puffy eye
- Inflammation eye follicles epiphora and photophobia
- Tumour lysis syndrome
- Allergic vasculitis, hidradentis
- Problem with lung function, shortness of breath, pneumonia
- Infections of lungs
- Pleural effusion
- Dilation of colon (Toxic megacolon), blood in vomit
- Reactivation of chronic hepatitis, acute liver degeneration, herpes simplex hepatitis, liver insufficiency
- Painful swelling of skin around nail
- Expansion of small blood vessels in the skin (paronychia)
- Proteinuria
- Loss of libido impotence
- Menstrual disorder
- Discharge from the vagina
- Infertility
- Fever, impaired wound healing

Not known (frequency cannot be estimated from the available data):
- Bleeding, blood outside of vessels
- Psychosis
- Accumulation of fluid in brain and lungs
- Metabolic disorder
- Skin necrosis, exfoliative dermatitis
- Bone damage in the jaw (secondary to excessive growth of white blood cells)
- Redness and shedding of skin

Methotrexate must not be given in the spine as it may cause very serious side effects.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any side effects not listed in this leaflet. You can also report side effects directly via
HPRA Pharmacovigilance
Website: www.hpra.ie

By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Methotrexate

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

Do not use this medicine after the expiry date which is stated on the label/carton after EXP. The expiry date refers to the last day of the month.

Do not store above 30°C.

Vial after first opening – Use immediately after opening.

After dilution
Chemical and physical stability of the diluted solution have been demonstrated in glucose solution (5%) and sodium chloride solution (0.9%) at concentrations of 5mg/ml and 20mg/ml for 36 hours at

20-25°C and 35 days at 2-8°C. Diluted product is stable in both diluents at both concentrations for 36 hours at 20-25°C and 35 days at 2-8°C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and condition prior to use are the responsibility of the user and would not longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled validated aseptic condition.

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

6. Contents of the pack and other information

What Methotrexate contains

- The active substance is methotrexate.

- 1 ml solution contains 100 mg methotrexate

The other ingredients are sodium hydroxide and water for injection.

What Methotrexate looks like and contents of the pack

The medicinal product is a clear yellow solution.
Package size:
1 vial in carton for 5 ml, 10 ml and 50 ml pack size
5 vials in a carton for 5 ml, 10 ml & 50 ml pack size

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 medicine is authorised in the Member States of the European Economic Area and in the United Kingdom (Northern Ireland) under the following names:

Name of the Member State	Name of the medicine
Sweden	Metotrexat Accord 100 mg/ml Koncentrat till infusionsvätska, lösning
Austria	Methotrexat Accord 100 mg/ml Konzentrat zur Herstellung einer Infusionslösung
Belgium	Methotrexate Accord Healthcare 100 mg/ml Concentraat voor oplossing voor infusie

Cyprus	Methotrexate Accord 100 mg/ml, Concentrate for Solution for Infusion
Czech Republic	Methotrexat Accord 100 mg/ml Koncentrát pro infuzní roztok
Germany	Methotrexat Accord 100 mg/ml Konzentrat zur Herstellung einer Infusionslösung
Denmark	Methotrexat Accord
Spain	METOTREXATO ACCORD 100 mg/ml Concentrado para solución para perfusión
Finland	Methotrexat Accord 100 mg/ml Infuusiokonsentraatti, liuosta varten
France	METHOTREXATE ACCORD 100 mg/ml, Solution à diluer pour perfusion
Hungary	Methotrexat Accord 100 mg/ml koncentrátum oldatos infúzióhoz
Ireland	Methotrexate 100 mg/ml Concentrate for Solution for Infusion
Lithuania	Methotrexate Accord 100 mg/ml koncentratas infuziniam tirpalui
Malta	Methotrexate 100 mg/ml Concentrate for Solution for Infusion
The Netherlands	Methotrexaat Accord 100 mg/ml, Concentraat voor oplossing voor intraveneuze infusie
Norway	Metotreksat Accord
Portugal	Methotrexat Accord
Slovak Republic	Methotrexat Accord 100 mg/ml Koncentrát na infúzny roztok
United Kingdom (Northern Ireland)	Methotrexate 100 mg/ml Concentrate for Solution for Infusion
Italy	Metotrexato Accord
Estonia	Methotrexate Accord
Poland	Metotreksat Accord

This leaflet was last revised in10/2023.

The following information is intended for medical or healthcare professional only

WARNINGS
The **dose must be adjusted carefully** depending on the body surface area if methotrexate is used for the treatment of **tumour diseases.**
Fatal cases of intoxication have been reported after administration of **incorrect calculated** doses.
Health care professionals and patients should be fully informed about toxic effects.

Instruction on how to prepare, handle and dispose of Methotrexate 100 mg/ml concentrate for solution for infusion
The solution should be visually inspected prior to use. Only clear solution practically free from particles should be used.

Methotrexate injection may be further diluted with an appropriate preservative-free medium such as glucose solution (5%) or sodium chloride solution (0.9%). Chemical and physical stability of the diluted solution have been demonstrated in glucose solution (5%) and sodium chloride solution (0.9%) at concentrations of 5mg/ml and 20mg/ml for 36 hours at 20-25°C and 35 days at 2-8°C. Diluted product is stable in both diluents at both concentrations for 36 hours at 20-25°C and 35 days at 2-8°C. For microbial point of view, the product should be used immediately. If not used immediately, in-use storage times and condition prior to use are the responsibility of the user and would not longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled validated aseptic condition.

With respect to the handling the following general recommendations should be considered: The product should be used and administered only by trained personnel; the mixing of the solution should take place in designated areas, designed to protect personnel and the environment (e.g safety cabins); protective clothing should be worn (including gloves, eye protection, and masks if necessary).

Pregnant healthcare personnel should not handle and/or administer Methotrexate.

Methotrexate should not come into contact with the skin or mucosa. In the event of contamination, the affected area must be irrigated immediately with copious quantities of water for at least ten minutes.

For single use only. Any unused solution should be discarded. Waste should be disposed of carefully in suitable separate containers, clearly labelled as to their contents (as the patient's body fluids and excreta may also contain appreciable amounts of antineoplastic agents and it has been suggested that they, and material such as bed linen contaminated with them, should also be treated as hazardous waste). Any unused product or waste should be disposed of in accordance with local requirements by incineration

Adequate procedures should be in place for accidental contamination due to spillage; staff exposure to antineoplastic agents should be recorded and monitored.