advertising & communication services ltd.	Artwork No.	-		Colours Used
	Customer	Accord	■	Pantone Black
	Description	Methotrexate		
	Market	IE		
	Language	English		
	Size	300 x 300 mm PIL		
	Min. Font Size	9		
	Version No.	11 (Page 1 of 2)		
	Date	13_11_13 (Methotrexate (ACC-IE) PIL)		

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Package Leaflet: Information For The User

Methotrexate 25 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 or nurse.
- 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 symptoms are the same as yours.
- If you get any side effects, talk to your doctor, or pharamcist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Methotrexate 25 mg/ml is and what it is used for

Methotrexate 25 mg/ml 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 25 mg/ml is used in the treatment of the following types of cancer:
- acute lymphocytic leukaemia,
- prophylaxis of meningeal 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 25 mg/ml

Do not use Methotrexate 25 mg/ml
- If you are allergic to methotrexate or any of the other ingredients of this medicine (listed in section 6).
- 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 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 pregnant or breastfeeding (see section Pregnancy, breast-feeding and fertility).
- If you have increased alcohol consumption.

You should not be given live vaccines during treatment with Methotrexate 25 mg/ml.

Warnings and precautions
- Methotrexate can cause serious and sometimes life-threatening undesirable effects. Your doctor will talk to you about the advantages and risks of the treatment and what the early signs and symptoms of undesirable effects are.
- Methotrexate has been reported to cause foetal death and/or congenital malformations. Pregnancy should be avoided if you or your partner is being treated with Methotrexate (see Pregnancy and breast-feeding and fertility).
- Your skin or eyes can be extremely sensitive to sunlight or other forms of light during the treatment with Methotrexate 25 mg/ml. Therefore sunlight and solarium should be avoided.
- Methotrexate may 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.

Talk to your doctor, pharmacist or nurse before taking Methotrexate 25 mg/ml
- 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.
- If you have symptoms connected to a medical condition that means that fluid is retained in your body, for example in the lungs or in the abdomen.
- 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.

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 25 mg/ml
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 (antibiotics such as penicillins, tetracycline, ciprofloxacin 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, lanzoprazol
- Epilepsy (phenytoin)
- Psoriasis or severe acne (retinoids, such as acitretin or isotretinoin)
- Reumatiod arthitis or bowel disease (sulphsalazine)
- Rejection after an organ transplant (azathioprine)
- If you need to be vaccinated with a live vaccination

Methotrexate 25 mg/ml with food, drink and alcohol
During treatment with Methotrexate 25 mg/ml, 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 25 mg/ml because dehydration (reduction in body water) can increase the toxicity of Methotrexate 25 mg/ml.

Pregnancy, breast-feeding and fertility
If you are pregnant or breast-feeding or think you may be pregnant or are planning to have a baby, tell your doctor for advice before taking this medicine.
Methotrexate has been reported to cause foetal death and/or congenital malformations. Therefore do not use Methotrexate 25 mg/ml during pregnancy except with an explicit prescription from a doctor. Tell your doctor immediately if you think you are pregnant. Pregnancy should be avoided if you or your partner is being treated with Methotrexate, as treatment with Methotrexate of both male and female can affect the foetus. How long you and your partner should wait before you/your partner try to get pregnant after completing treatment is not known. The recommendations vary from three months to one year. Methotrexate is excreted breast milk in such quantities that there are risks of affecting the baby. Breast-feeding should therefore be suspended during 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 25 mg/ml contains 345.59 mg (15.033 mmol) of sodium per maximum daily dose (1800 mg).
To be taken into consideration by patients on a controlled sodium diet.

3. How to take Methotrexate 25 mg/ml

Methotrexate 25 mg/ml 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 25 mg/ml can be given in a muscle (intramuscularly), in a vein (intravenously), in an artery (intra-arterially) or in the spine (intrathecally).
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 25 mg/ml 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 <u>immediately</u> 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).

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 25 mg/ml solution for injection
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%).

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).

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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 upto 1 in 10 people):
- Herpes zoster
- Effects on the blood e.g. anaemia, leukocytopenia, thrombocytopenia
- Headache, Tiredness, drowsiness
- Dry cough, shortness of breath, chest pain, fever
- Diarrhoea
- Rashes, redness and itching

Uncommon (may affect upto 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
- Liver fibrosis and cirrhosis, fatty liver
- Diabetic complications
- Reduced levels of albumin
- Skin becoming hypersensitive to sunlight, urticaria
- Hair loss, herpes zoster, 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)
- Inflammation and ulceration of urinary bladder, haematuria, dysuria
- Inflammation and ulceration of vagina
- Brittle bones (osteoporosis), arthralgia, myalgia

Rare (may affect upto 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
- Pharyngitis apnoea, bronchial asthma
- Gingivitis
- Inflammation in the small intestine
- Blood in the faeces
- Malabsorption
- Liver damage
- 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
- Abnormal development of mammary glands
- Raised blood sugar levels (diabetes mellitus)

Very rare (may affect upto 1 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, eosinophilia and neutropenia .
- Immunosuppression
- Hypogammaglobulinaemia
- Insomnia
- impaired intellectual functions such as thinking, remembering and reasoning
- Joint and/or muscle pain, lack of strength
- Myasthenia (muscle weakness)
- Abnormal sensations, changes in sense of taste (metallic taste)
- Meningism (Paralysis, vomiting), acute aseptic meningitis
- Conjunctivitis, retinopathy, loss of vision, puffy eye
- Inflammation eye follicles epiphora and photophobia
- Tumour lysis syndrome
- Problem with lung function, shortness of breath, pneumonia
- Infections of lungs
- Pleural effusion
- Dilation of colon (Toxic megacolon)
- 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)
- Allergic vasculitis, hidradentis
- 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

If you receive Methotrexate 25 mg/ml in the spine the following undesirable effects are common (*may affect upto 1 in 100 people*):
- Headache
- Fever
- Inflammation in the so-called arachnoid membrane in the brain and spinal cord which can cause backache, stiffness in the neck, vomiting, fever and impaired general state of health this can occur within a couple of hours after you have received the Methotrexate injection but usually disappears within a few days
- Hemiplegia or total paralysis, weakness in one or all extremities and cramp attacks (usually occurring after repeated Methotrexate injected into the spinal cord)
- Effect on the nervous system which may start with confusion, irritation and tiredness. This gets worse over time and leads to dementia (increasing loss of memory, disorientation and confusion), speech difficulties, coordination and balance difficulties, increased muscle stiffness, cramps and coma. This state can occur several months or years after the start of treatment with Methotrexate injected into the spinal cord. The condition can be life-threatening; it chiefly occurs if you have large quantities of Methotrexate injected into the spinal cord in combination with radiotherapy to the head and/or Methotrexate in some other form.

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 (see contact details below). By reporting side effects you can help provide more information on the safety of this medicine.
Pharmacovigilance Section
Irish Medicines Board
Kevin O'Malley House
Earlsfort Centre, Earlsfort Terrace, IRL - Dublin 2
Tel: +353 1 6764971, Fax: +353 1 6762517
Website: www.imb.ie, e-mail: imbpharmacovigilance@imb.ie

5. How to store Methotrexate 25 mg/ml

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.
Store below 25°C.
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 25 mg/ml contains
- The active substance is methotrexate. 1 ml solution contains 25 mg methotrexate.
- The other ingredients are sodium chloride, sodium hydroxide/ hydrochloric acid (to adjust the pH) and water for injection.

What Methotrexate 25 mg/ml looks like and contents of the pack
The medicinal product is a clear yellow solution.
Package size:
1 vial in carton for 2 ml, 20 ml and 40 ml pack size
10 vials per packs for 20 ml and 40 ml.
Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Accord Healthcare Limited
Sage House, 319, Pinner Road, North Harrow
Middlesex HA1 4HF, United Kingdom

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

Name of the Member State	Name of the medicinal product
Sweden	Metotrexat Accord 25 mg/ml injektionsvätska, lösning
Austria	Methotrexat Accord 25 mg/ml Injektionslösung
Belgium	Methotrexate Accord Healthcare 25 mg/ml Oplossing voor injectie/ Solution injectable/ Injektionslösung
Cyprus	Methotrexate Accord 25 mg/ml, ενέσιμο διάλυμα
Czech Republic	Methotrexat Accord 25 mg/ml injekční roztok
Germany	Methotrexat Accord 25 mg/ml Injektionslösung
Denmark	Methotrexat Accord
Spain	METOTREXATO ACCORD 25 mg/ml solución inyectable
Finland	Methotrexat Accord 25 mg/ml injektioneste, liuos
France	METHOTREXATE ACCORD 25 mg/ml, solution injectable
Hungary	Methotrexat Accord 25 mg/ml oldatos injekció
Ireland	Methotrexate 25 mg/ml solution for injection
Lithuania	Methotrexate Accord 25 mg/ml injekcinis tirpalas
Malta	Methotrexate 25 mg/ml solution for injection
The Netherlands	Methotrexaat Accord 25 mg/ml, oplossing voor injectie
Norway	Methotrexate Accord 25 mg/ml Injeksjonsvæske, oppløsning
Portugal	Methotrexat Accord
Slovak Republic	Methotrexat Accord 25 mg/ml Injekčný roztok
United Kingdom	Methotrexate 25 mg/ml solution for injection

This leaflet was last revised in 10/2013

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.