PACKAGE LEAFLET: INFORMATION FOR THE USER

<invented name> 25 mg/ml solution for injection in pre-filled syringe
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.
- 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 <invented name> is and what it is used for
2. What you need to know before you use <invented name>
3. How to use <invented name>
4. Possible side effects
5. How to store <invented name>
6. Contents of the pack and other information

1. WHAT <INVENTED NAME> IS AND WHAT IT IS USED FOR

<invented name> is a medicine with the following properties:
- it interferes with the growth of certain cells in the body that reproduce quickly (anti-tumour agent),
- it reduces undesired reactions of the body's own defence mechanism (immunosuppressant), and
- it has anti-inflammatory effects.

<invented name> is used for the treatment of:
- active rheumatoid arthritis (RA) in adult patients.
- polyarthritic forms (when five or more joints are involved) of severe, active juvenile idiopathic arthritis (JIA) when the response to so-called non-steroidal anti-inflammatory drugs (NSAIDs) has been inadequate
- severe forms of psoriasis, which cannot be sufficiently treated with conventional therapy such as phototherapy, PUVA, and retinoids, and severe psoriasis affecting the joints (psoriatic arthritis).

2. WHAT YOU NEED TO KNOW BEFORE YOU USE <INVENTED NAME>

Do not use <invented name>
- if you are allergic to methotrexate, or any of the other ingredients of this medicine (listed in section 6).
- if you have significant kidney disease (your doctor decides the severity of your disease).
- if you have significant liver disease (your doctor decides the severity of your

disease) .
- if you have disorders of the blood-forming system.
- if you have increased alcohol consumption.
- if you have an impaired immune system.
- if you have severe or existing infections.
- if you have gastrointestinal ulcers.
- if you are pregnant or breast-feeding (see section “Pregnancy, breast-feeding and fertility”).

You should not be given live vaccines during treatment with <invented name>.

Warnings and precautions
Talk to your doctor or pharmacist before using <invented name>
- if you have diabetes mellitus treated with insulin.
- if you have inactive, prolonged infections (e.g. tuberculosis, hepatitis B or C, shingles [herpes zoster]).
- if you have or have had any liver or kidney disease.
- if you have problems with your lung function.
- if you are severely overweight.
- if you have abnormal accumulation of liquid in the abdomen, in the cavity between the lungs and chest wall (ascites, pleural effusions).
- if you are dehydrated or suffer from conditions leading to dehydration (vomiting, diarrhoea, stomatitis).

If you experienced problems with your skin after radiation therapy (radiation induced dermatitis) and sun-burn, these conditions can reappear under methotrexate therapy (recall-reaction).

Special precautionary measures during treatment of <invented name>:
<invented name> should only be prescribed by doctors with sufficient experience in the <invented name> treatment of the disease concerned.

Methotrexate temporarily affects sperm and egg production. You and your partner must 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 also section “Pregnancy, breast-feeding and male fertility”).

Skin changes caused by psoriasis can worsen during treatment with <invented name> if exposure to UV irradiation occurs at the same time.

Recommended examinations:
Even if <invented name> is administered at low doses, severe side effects can occur. In order to diagnose them early, regular monitoring by the doctor at short-term intervals is necessary.
Before treatment is started your doctor may carry out blood tests, and also 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.
If the results of any of these tests are abnormal, treatment will only be resumed when all readings are back to normal.

Use in children, adolescents and elderly
Dosage instructions depend on patients body weight.
Use in children below 3 years of age is not recommended due to the insufficient experience in this age group.

Children and the elderly should be kept under particularly close medical surveillance during treatment with <invented name>, in order to identify possible side effects as early as possible.

Dosage for elderly patients should be relatively low due to age-related reduced liver and kidney function and low folate reserves.

Other medicines and <invented name>
Please tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This includes medicines obtained without a prescription and herbal or natural medicinal products.
Remember to tell your doctor about your treatment with <invented name>, if you are prescribed another medicine while the treatment is still ongoing.

It is especially important to tell your doctor if you are using:
- other treatments for rheumatoid arthritis or psoriasis such as leflunomide, sulfasalazine (also used for ulcerative colitis), acetylsalicylic acid, phenylbutazone, or amidopyrine
- alcohol (should be avoided)
- live vaccinations
- azathioprine (used to prevent rejection after an organ transplantation)
- retinoids (used to treat skin disorders)
- anticonvulsant drugs (used to prevent fits)
- cancer treatments
- barbiturates (sleeping injection)
- tranquillisers
- oral contraceptives
- probenecid (used to treat gout)
- antibiotics
- pyrimethamine (used to prevent and treat malaria)
- vitamin preparations, which contain folic acid
- proton-pump inhibitors (used to treat severe heartburn or ulcers)
- theophylline (used to treat asthma)

<invented name> with drink and alcohol
During treatment with this medicine you should avoid any alcohol consumption as well as excessive consumption of coffee, caffeine-containing beverages, or black tea. Also make sure you drink plenty of liquids during treatment with <invented name> because dehydration (reduction in body water) can increase the toxicity of <invented name>.

Pregnancy, breast-feeding and fertility

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before this medicine is administered.

Pregnancy
Do not use <invented name> 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 also section "Do not use <invented name>").

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 your doctor, who may refer you for specialist advice, before the planned start of treatment, because methotrexate may be genotoxic, which means that the medicine may cause genetic mutation.

Breast-feeding
Do not breast-feed during treatment, because methotrexate passes into breast milk. If your attending doctor considers treatment with methotrexate as absolutely necessary during the lactation period, you must stop breast-feeding (see also section "Do not use <invented name>").

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 also section "Warnings and precautions").

Driving and using machines
Tiredness and dizziness can occur during treatment. If affected, you should not drive or operate machinery.

<invented name> contains sodium.
This medicinal product contains less than 1 mmol sodium (23 mg) per pre-filled syringe, i.e. essentially 'sodium-free'.

3. HOW TO USE <INVENTED NAME>

This medicine should only be prescribed by physicians, who are familiar with the various characteristics of the medicinal product and its mode of action.

Important warning concerning methotrexate dosage

For the treatment of rheumatic diseases or diseases of the skin, you must only use <invented name> once weekly.
Faulty dosing may lead to serious side effects including fatal courses. Please read section “3. How to use <invented name>” of this package leaflet very carefully.

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

The usual dosage is:

Dosage in patients with rheumatoid arthritis
The recommended starting dose for methotrexate is 7.5 mg **once a week.** <invented name> is given in a single application as injection under the skin or into a muscle (see section “Method and duration of administration”).
In case of inadequate action and if tolerated well, <invented name> doses may be gradually increased by 2.5 mg per week. The mean weekly dose is 15 - 20 mg. Generally, a weekly dose of 20 mg <invented name> should not be exceeded. Upon achieving the desired therapeutic results, the dose should be reduced gradually to the lowest possible effective maintenance dose.

Dosage in adult patients with psoriasis or psoriatic arthritis
Recommended initial dose (for an average body weight of 70 kg):
It is recommended to administer a single test dose of 5 - 10 mg, in order to assess possibly damaging effects.
This dose can be administered subcutaneously (under the skin) or intramuscularly (into a muscle).
If, one week later, no blood count changes are observed, therapy is continued with a dose of approximately 7.5 mg. The dose may be gradually increased until ideal therapeutic results are obtained. Generally, a weekly dose of 30 mg should not be exceeded.
Upon achieving the desired therapeutic results, the dose should be weekly reduced to the lowest possible effective maintenance dose for the individual patient.

Patients with kidney disorders
Patients with a kidney disorder may need a reduced dose.

Dosage in children and adolescents with polyarthritic forms of juvenile idiopathic arthritis
The recommended dose is 10-15 mg/m² body surface area per week. In cases with inadequate response, the weekly dosage may be increased up to 20 mg/m² body surface area/week. However, regular check-ups should be done more often.
Use in children below 3 years of age is not recommended due to the insufficient experience in this age group.

Method and duration of administration
For subcutaneous and intramuscular use.
For single use only. This medicine has to be used immediately after opening.

Any unused solution should be discarded (see also section “How to store <invented name>”).

The duration of treatment is determined by the treating physician. <invented name> is injected once weekly! It is recommended to specify a certain day of the week as "day for injection".
Methotrexate is given as injection under the skin or into a muscle.

Treatment of rheumatoid arthritis, juvenile idiopathic arthritis, psoriasis vulgaris and psoriatic arthritis with <invented name> is a long-term treatment.

Rheumatoid arthritis
Generally, improvement of the symptoms can be expected after 4-8 weeks of treatment. Symptoms may return after <invented name> treatment is stopped.

Severe types of psoriasis vulgaris and psoriatic arthritis (psoriasis arthropathica)
Generally, response to treatment can be expected after 2 - 6 weeks. Depending on symptoms severity and on laboratory parameters, the therapy is then continued or discontinued.

At the start of your therapy, <invented name> may be injected by a doctor. However, your doctor may decide that it is right for you to learn how to inject <invented name> yourself. You will receive appropriate training for you to do this. Under no circumstances should you attempt to inject yourself unless you have been trained to do so.

If you use more <invented name> than you should
Do not change the dosage by yourself!
Use <invented name> according to the doctor's orders or according to the dosage directions stated in this package leaflet. If you use more of this 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 "Possible side effects").

Take your medicine package with you if you go to a doctor or hospital. The antidote in case of an overdose is calcium folinate.

If you forget to use <invented name>
Do not take a double dose to make up for forgotten individual doses, but continue taking the ordered dose. Ask your doctor for advice.

If you stop taking <invented name>
You should not interrupt or discontinue your treatment with <invented name>, unless you have discussed this with your doctor. If you suspect severe side effects, contact your doctor immediately for advice.

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.
Tell your doctor straight away if you get any sudden wheeziness; difficulty in breathing; swelling of the eyelids, face or lips; rash or itching (especially affecting your whole body).

Serious side effects

If you develop any of the following side effects, **contact your doctor immediately**:
- lung complaints (symptoms may be general illness; dry, irritating cough; shortness of breath, breathlessness at rest, chest pain, or fever)
- severe peeling or blistering of the skin
- unusual bleeding (including vomiting blood) or bruising
- severe diarrhoea
- ulcers in mouth
- blistering of mucous membranes
- black or tarry stools
- blood in the urine or stools
- tiny red spots on the skin
- fever
- yellowing of the skin (jaundice)
- tenderness in the upper right area of your abdomen
- pain or difficulty in passing urine
- thirst and/or frequent urination
- fits (convulsions)
- loss of consciousness
- blurred or decreased vision

The following side effects have also been reported:

Very common (may affect more than 1 in 10 people):
Inflammation of the mouth, indigestion, loss of appetite, nausea (feeling sick), vomiting, tummy pain, inflammation and ulcers in the mouth and throat, and increase in liver enzymes (can be detected by a test carried out by a doctor).

Common (may affect up to 1 in 10 people):
Changes in the number of blood cells and platelets (can be detected by a test carried out by a doctor), headache, tiredness, sleepiness, diarrhoea, measles-like rash (alone), redness, and itching.

Uncommon (may affect up to 1 in 100 people):
Spinning sensation, confusion, depression, fits, lung damage, ulcers and bleeding in the digestive tract, liver disorders (can be detected by a test carried out by a doctor), diabetes, decreased blood protein (can be detected by a test carried out by a doctor), nettle rash (alone), light sensitivity, brown skin, hair loss, increase of rheumatic nodules (lumps of tissues), shingles, painful psoriasis, joint or muscle pain, brittle bones, inflammation and ulcers in the bladder (possibly with blood in

the urine), painful urination, severe allergic reactions, inflammation and ulcers of the vagina.

Rare (may affect up to 1 in 1,000 people):
Inflammation of the lining of the heart, fluid around the heart, severely visual disturbance, mood alterations, low blood pressure, blood clots, sore throat, interruption of breathing, asthma, inflammation of the digestive tract, bloody stools, inflamed gums, abnormal digestion, changed colour of nails, acne, red or purple spots, bone fracture, kidney failure, little or no urine production, waste products in the blood, decreased number of red blood cells.

Very rare (may affect up to 1 in 10,000 people) and frequency not known (frequency cannot be estimated from the available data):
Infections, liver disorders, low level of antibodies, severe failure of the bone marrow (can be detected by a test carried out by a doctor), swollen glands, sleeplessness, pain, muscle weakness, pins and needles, breathing disorders, changes in sense of taste (metallic taste), inflammation of the lining of the brain causing paralysis or vomiting, red eyes, damage to the retina of the eye, fluid on the lungs, vomiting blood, cold sores, protein in the urine (can be detected by a test carried out by a doctor), loss of sex drive, problems having an erection, infection around a fingernail, severe complication of the digestive tract, boils, small blood vessels in the skin, fungal infections, damage to the blood vessels of the skin, lumps in the armpit or groin, slow wound healing, low sperm production, abnormal periods, vaginal discharge, infertility.

Other:
After injection into a muscle, there may be a burning sensation or damage at the injection site. After injection under the skin there may be a mild skin reaction.

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 <INVENTED NAME>

Keep out of the sight and reach of children.
Do not use this medicine after the expiry date which is stated on the label of the pre-filled syringe and the carton after “EXP”. The expiry date refers to the last day of that month.

Keep the pre-filled syringes in the outer carton in order to protect from light.
Do not store above 25°C.
Do not refrigerate or freeze.

Do not use this medicine if you notice the solution is not clear and free of particles or if the container is damaged.

This medicine and its packaging should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines and packaging no longer required. These measures will help to protect the environment.

6. CONTENTS OF THE PACK AND OTHER INFORMATION

What <invented name> contains

The active substance is methotrexate.
1 ml of solution for injection contains 25 mg methotrexate.

1 pre-filled syringe with 0.3 ml contains 7.5 mg methotrexate.
1 pre-filled syringe with 0.4 ml contains 10 mg methotrexate.
1 pre-filled syringe with 0.6 ml contains 15 mg methotrexate.
1 pre-filled syringe with 0.8 ml contains 20 mg methotrexate.
1 pre-filled syringe with 1.0 ml contains 25 mg methotrexate.

The other ingredients are: sodium chloride, sodium hydroxide (for pH adjustment) and water for injections.

What <invented name> looks like and contents of the pack
<invented name> is a clear, yellowish solution for injection available in pre-filled syringes with attached needle.

Each box contains 1pre-filled syringe with 0.3 ml, 0.4 ml, 0.6 ml, 0.8 ml or 1.0 ml solution for injection.
Not all pack sizes may be marketed.

Marketing Authorisation Holder
[to be completed nationally]

Manufacturer
[to be completed nationally]

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

DE/H/4083/001/DC

DE	Methotrexat STADA 25 mg/ml Injektionslösung in einer Fertigspritze
IE	Methotrexate Clonmel 25 mg/ml Solution for Injection in Pre-filled Syringe
NL	Methotrexaat CF 25 mg/ml, oplossing voor injectie in een voorgevulde spuit

This leaflet was last approved in {MM/YYYY}.
[to be completed nationally]

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The following information is intended for medical or healthcare professionals only:

PREPARATION GUIDE FOR:

<invented name> 25 mg/ml solution for injection in pre-filled syringe

<invented name> for the therapy of rheumatic or skin diseases must only be used once weekly.

Please refer to Summary of Product Characteristics for full prescribing and other information.

Instructions for use and handling and disposal
The solution is to be visually inspected prior to use. Only clear solutions practically free from particles should be used.

Handling and disposal must be consistent with that of other cytotoxic preparations in accordance with local requirements. Pregnant health care professionals should not handle and/or administer <invented name>.
Any contact of methotrexate with skin and mucosa is to be avoided! In case of contamination, the affected parts are to be rinsed immediately with plenty of water!

For single use only. This medicine has to be used immediately after opening.
Any unused solution should be discarded.
Any unused product or waste material should be disposed of in accordance with local requirements for cytotoxic agents.

Incompatibilities
In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

Special precautions for storage
Keep the pre-filled syringes in the outer carton in order to protect from light.
Do not store above 25°C.
Do not refrigerate or freeze.

Step-by-step instructions for subcutaneous injection:

<u>Setting up for an injection:</u>

- Open the box on a flat surface. **Read the package leaflet carefully.**
- Take one pre-filled syringe out of the box without shaking it.
- Visually inspect the solution in the syringe.

- Choose an injection site. Wipe the injection site with an alcohol pad, using a circular motion. Do not touch this area before injection. You will be instructed in detail by your doctor.

Injecting the solution:

- Remove the needle cover by firmly pulling it straight off the syringe. Be careful not to bend or twist the cover during removal to avoid damage to the needle.
- When you remove the needle cover, there may be a drop of liquid at the end of the needle. This is normal. Do not touch the needle or allow it to touch any surface. Do not touch or bump the plunger to avoid loss of fluid.
- With two fingers, form a skin fold and puncture it almost vertically. With a quick, short motion, push the needle completely into the skin fold. There is no need to aspirate prior to injection.
- Push the plunger down and inject the fluid at a slow, steady rate.

End of injection:

- Remove the needle. Be careful to keep it at the same angle as inserted.
- Dab the injection site with a swab. Do not rub as this will cause irritation at the injection site.
- To avoid any injuries, carefully put the needle cover back on the needle by gently pressing it into place.