PATIENT INFORMATION LEAFLET 2643, 2644,2645, 2646
08.10.20[11]

Metoject® PEN 7.5 mg solution for injection in pre-filled pen
Metoject® PEN 10 mg solution for injection in pre-filled pen
Metoject® PEN 12.5 mg solution for injection in pre-filled pen
Metoject® PEN 15 mg solution for injection in pre-filled pen

(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.

Your medicine is available using the above name but will be referred to as Metoject PEN throughout this leaflet. Metoject PEN is also available in other strengths than those listed above.

What is in this leaflet

1. What Metoject PEN is and what it is used for
2. What you need to know before you use Metoject PEN
3. How to use Metoject PEN
4. Possible side effects
5. How to store Metoject PEN
6. Contents of the pack and other information

1. What Metoject PEN is and what it is used for

Metoject PEN is indicated for the treatment of
- active rheumatoid arthritis in adult patients.
- polyarthritic forms of severe, active juvenile idiopathic arthritis, when the response to nonsteroidal anti-inflammatory drugs (NSAIDs) has been inadequate.
- moderate to severe psoriasis in adult patients, and severe psoriatic arthritis in adults.
- mild to moderate Crohn's disease in adult patients when adequate treatment with other medicines is not possible.

Rheumatoid arthritis (RA) is a chronic collagen disease, characterised by inflammation of the synovial membranes (joint membranes). These membranes produce a fluid which acts as a lubricant for many joints. The inflammation causes thickening of the membrane and swelling of the joint.

Juvenile arthritis concerns children and adolescents less than 16 years. Polyarthritic forms are indicated if 5 or more joints are affected within the first 6 months of the disease.

Psoriasis is a common chronic skin disease, characterised by red patches covered by thick, dry, silvery, adherent scales.

Psoriatic arthritis is a kind of arthritis with psoriatic lesions of the skin and nails, especially at the joints of fingers and toes.

Metoject PEN modifies and slows down the progression of the disease.

Crohn's disease is a type of inflammatory bowel disease that may affect any part of the gastrointestinal tract causing symptoms such as abdominal pain, diarrhoea, vomiting or weight loss.

2. What you need to know before you use Metoject PEN

Do not use Metoject PEN:
- if you are allergic to methotrexate or any of the other ingredients of this medicine (listed in section 6).
- if you suffer from liver or severe kidney diseases or blood diseases.
- if you regularly drink large amounts of alcohol.
- if you suffer from a severe infection, such as tuberculosis, HIV or other immunodeficiency syndromes.
- if you suffer from mouth ulcers, stomach ulcer or intestinal ulcer.
- if you are pregnant or breast-feeding (see section "Pregnancy, breast-feeding and fertility").
- if you receive vaccinations with live vaccines at the same time.

Warnings and precautions
Talk to your doctor or pharmacist before taking Metoject PEN if:
- you are elderly or if you feel generally unwell and weak.
- you have problems with the way your liver works.
- you suffer from dehydration (water loss).

Special precautionary measures for treatment with Metoject PEN
Methotrexate temporarily affects sperm and egg production, which is reversible in most cases. Methotrexate can cause miscarriage and severe birth defects. You must avoid becoming pregnant when using methotrexate and for at least six months after treatment has stopped.
See also section "Pregnancy, breast-feeding and fertility".

Recommended follow-up examinations and safety measures
Even when Metoject PEN is administered in low doses, severe side effects can occur. In order to detect them in time, check-ups and laboratory tests have to be carried out by your doctor.

Before therapy
Before starting the treatment, blood samples will be taken in order to check that you have enough blood cells, tests to check your liver function, serum albumin (a protein in the blood) and kidney function. Your doctor will also check if you suffer from tuberculosis (infectious disease in combination with little nodules in the affected tissue) and a chest X-ray will be taken.

During therapy
You will have the following tests at least once a month during the first six months and at least every three months thereafter:
- Examination of the mouth and throat for changes of the mucosa.
- Blood tests.
- Check of liver function.
- Check of kidney function.
- Check of respiratory system and if necessary lung function test.

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.

Methotrexate may affect your immune system and vaccination results. It may also affect the result of immunological tests. Inactive, chronic infections (such as herpes zoster [shingles], tuberculosis, hepatitis B or C) may flare up. **During therapy with Metoject PEN you must not be vaccinated with live vaccines.**

Radiation-induced dermatitis and sun-burn can reappear under methotrexate therapy (recall-reaction). Psoriatic lesions can exacerbate during UV-irradiation and simultaneous administration of methotrexate.
Enlarged lymph nodes (lymphoma) may occur and if this is the case, therapy must be stopped.

Diarrhoea can be a possible side effect of Metoject PEN 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.

Other medicines and Metoject PEN
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Please note that this also applies to medicines that you will take **in the future.**

The effect of the treatment may be affected if Metoject PEN is administered at the same time as certain other medicines:
- **Antibiotics** such as: tetracyclines, chloramphenicol, non-absorbable broad-spectrum antibiotics, penicillines, glycopeptides, sulphonamides, ciprofloxacin and cefalotin (medicines to prevent/fight certain infections).
- **Non-steroidal anti-inflammatory** drugs or **salicylates** (medicines against pain and/or inflammation such as acetylsalicylic acid, diclofenac and ibuprofen or pyrazole).
- **Probenecid** (medicine against gout).
- Weak organic acids like loop **diuretics** ("water tablets").
- Medicines, which may have adverse effects on the **bone marrow,** such as trimethoprim-sulphamethoxazole (an antibiotic) and pyrimethamine.
- Other **medicines used to treat rheumatoid arthritis** such as leflunomide, sulphasalazine and azathioprine.
- Mercaptopurine (a **cytostatic** medicine).
- Retinoids (medicine against **psoriasis** and other dermatological diseases).
- Theophylline (medicine against **bronchial asthma** and other lung diseases).
- Some medicines against **stomach trouble** such as omeprazole and pantoprazole.
- Hypoglycaemics (medicines that are used to **lower the blood sugar**).

Vitamins containing **folic acid** may impair the effect of your treatment and should only be taken when advised by your doctor.

Vaccination with live vaccine must be avoided.

Metoject PEN with food, drink and alcohol
Alcohol as well as large amounts of coffee, caffeine-containing soft drinks and black tea should be avoided during treatment with Metoject PEN.

Pregnancy, breast-feeding and fertility
Pregnancy
Do not use Metoject PEN during pregnancy or if you are trying to become pregnant. 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. Therefore, it is very important that methotrexate is not given to pregnant patients or patients planning to become pregnant. In women of child-bearing age, any possibility of pregnancy must be excluded with appropriate measures, e.g. pregnancy test before starting treatment.
You must avoid becoming pregnant whilst taking methotrexate and for at least 6 months after treatment is stopped by using reliable contraception throughout this time (see also section "Warnings and precautions").
If you do become pregnant during treatment or suspect you might be pregnant, speak to your doctor as soon as possible. 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.

Breast-feeding
Stop breast-feeding prior to and during treatment with Metoject PEN.

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. Methotrexate may be genotoxic. This means that the medicine may cause genetic mutation. Methotrexate can affect sperm production with the potential to cause birth defects. Therefore, you should avoid fathering a child or to donate semen whilst taking methotrexate and for at least 6 months after treatment is stopped.

Driving and using machines
Treatment with Metoject PEN may cause adverse reactions affecting the central nervous system, such as tiredness and dizziness. Thus the ability to drive a vehicle and/or to operate machines may, in certain cases, be compromised. If you feel tired or drowsy do not drive or use machines.

Metoject PEN contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per dose; that is to say essentially "sodium-free".

3. How to use Metoject PEN

Important warning about the dose of Metoject PEN (methotrexate):
Use Metoject PEN **only once a week** for the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, psoriasis and psoriatic arthritis, and Crohn's disease. Using too much of Metoject PEN (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.

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

Your doctor decides on the dose, which is adjusted individually to you. Usually it takes 4 – 8 weeks before there is any effect of the treatment.

Metoject PEN is administered subcutaneously (under the skin) by or under the supervision of a physician or healthcare staff as an injection **once a week only.** Together with your doctor you decide on a suitable weekday each week on which you receive your injection.

Use in children and adolescents
The doctor decides on the appropriate dose in children and adolescents with polyarthritic forms of juvenile idiopathic arthritis.
Metoject PEN is not recommended in children less than 3 years of age due to insufficient experience in this age group.

Instructions for use

Recommendations
- Carefully read the instructions below before starting your injection.
- Always use the injection technique advised by your doctor, pharmacist or nurse.

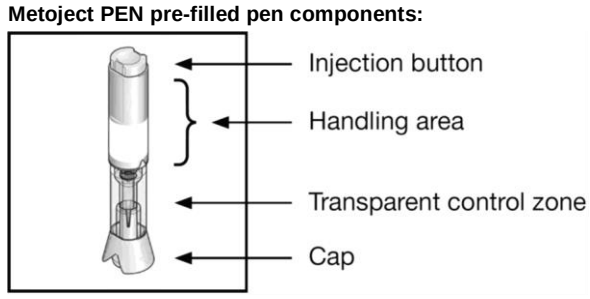
Additional information
The manner of handling and throwing away of the medicine and pre-filled pen must be in accordance with local requirements. Pregnant healthcare personnel should not handle and/or administer Metoject PEN.

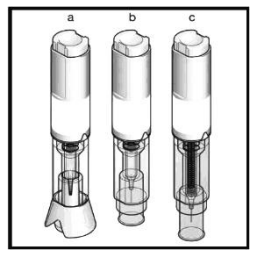
Methotrexate should not come into contact with the surface of the skin or mucosa. In the event of contamination, the affected area must be rinsed immediately with plenty of water.

What you need in order to administer your injection using the Metoject PEN pre-filled pen

You need:
- 1 Metoject PEN pre-filled pen
- 1 alcohol pad

Metoject PEN pre-filled pen components:



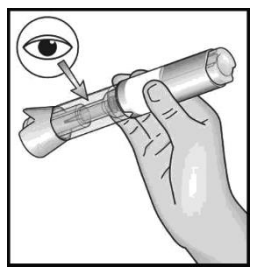


a) With cap before injection

b) After cap removal before injection

c) After injection

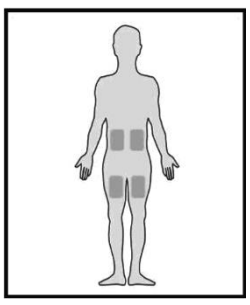
What you need to do before administering your injection:
1. Wash your hands very carefully.
2. Remove the system from its packaging.
3. Check the Metoject PEN pre-filled pen before using it:



If the Metoject PEN pre-filled pen appears to be damaged **do not use** it. Use another one and contact your doctor, pharmacist or nurse.
In case a small air bubble is visible through the transparent control zone, this will not affect your dose nor will it harm you.
If you are not able to see or to check the system correctly prior to injection, ask someone around you for assistance.

4. Set the Metoject PEN pre-filled pen on a clean flat surface (such as a table).

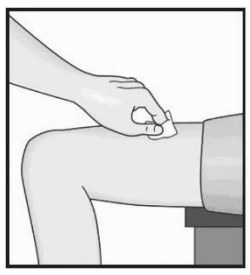
Where you should administer the injection



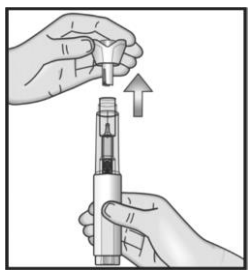
The most appropriate zones for your injection are:
- upper thighs,
- abdomen except around the navel.

- If someone around you administers the injection for you, the person may also use the top of the zone at the back of the arm, just below the shoulder.
- Change the injection area with each injection. This will minimise any reactions at the injection site.
- Never inject into areas where the skin is tender, bruised, red or hard or where you have scars or stretch marks. If you have psoriasis, you should not try to inject directly into any raised, thick, red or scaly skin patches or lesions.

How to prepare the injection



5. Clean your skin in the chosen injection zone using the enclosed alcohol pad.

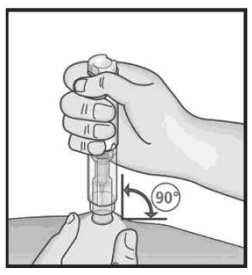


- Do not remove the cap before you are ready to administer the injection.

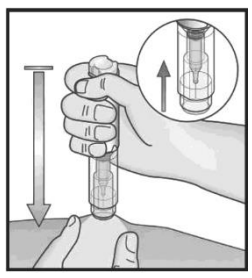
6. Hold the pen with one hand in the handling area with the cap pointing upwards. Use your other hand to gently pull the cap straight off (do not bend or twist the cap). The cap has a small needle shield that should come off with the cap automatically. If the needle shield does not come off, use another pen and contact your doctor, pharmacist or nurse.

- If you are unable to remove the cap, ask someone around you for assistance.

Note: Once you have removed the cap, perform your injection without delay.

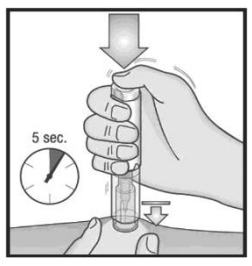


7. With your free hand, build a skin fold by gently squeezing the area of the cleaned skin at the injection site.
- The fold must be held pinched until the Metoject PEN pre-filled pen is removed from the skin after the injection.



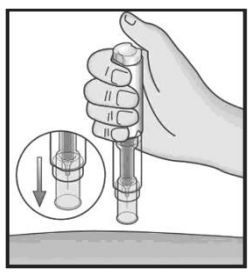
8. Position the uncapped transparent end of Metoject PEN pre-filled pen perpendicular to the fold of skin.
9. **Without pressing the button**, push the Metoject PEN pre-filled pen firmly onto your skin in order to unlock the button.
- If you are unable to push the Metoject PEN pre-filled pen to the stop-point, ask someone around you for assistance.

How to administer the injection:



10. While holding the Metoject PEN pre-filled pen firmly against the skin, **now press the button** with your thumb.
11. You will hear a click which indicates the start of the injection. Keep holding the pen against the raised skin until all of the medicine is injected. This can take up to **5 seconds.**

Note:
Do not remove the Metoject PEN pre-filled pen from the skin before the end of the injection to avoid incomplete injection.
If the injection is not triggered, release the button, make sure that the Metoject PEN pre-filled pen is pressed firmly against the skin and push hard on the button.
If you have troubles with your hearing, count 5 seconds from the moment you have pressed the button and then lift the Metoject PEN pre-filled pen from the injection site.



12. Remove the Metoject PEN pre-filled pen from the injection site, perpendicular to the skin (pull up).
13. The protective shield automatically moves into place over the needle. The protective shield is then locked and the needle is protected.
14. In case of a slight bleeding use a plaster.

Before throwing away the Metoject PEN pre-filled pen, check visually that there is no liquid left in the pen, at the bottom of the **transparent control zone.** If there is liquid left in the pen, not all of the medicine has been injected correctly and you should consult your doctor.

Note
To avoid any injury, **never insert your fingers in the opening of the protective tube** covering the needle. **Do not destroy the pen**.

Whom should you contact in case of need
- For any problem or question, contact your doctor, pharmacist or nurse.

If you or someone around you is injured by the needle, consult your doctor immediately and throw away the Metoject PEN pre-filled pen.

Method and duration of administration
Metoject PEN is injected **once weekly!**
The duration of the treatment is determined by the treating physician.
Treatment of rheumatoid arthritis, juvenile idiopathic arthritis, psoriasis vulgaris, psoriatic arthritis and Crohn's disease with Metoject PEN is a long-term treatment.

At the start of your therapy, Metoject PEN will be injected by medical staff. However, your doctor may decide that you are able to learn how to inject Metoject PEN under the skin yourself. You will then receive appropriate training.
Under no circumstances should you try to inject Metoject PEN yourself before you have received such training.

You can also find guidance on how to use Metoject PEN in the section "Instructions for use" at the end of this leaflet.
Please note that all of the contents have to be used.

The manner of handling and throwing away of the medicine and pre-filled pen must be in accordance with local requirements. Pregnant healthcare personnel should not handle and/or administer Metoject PEN.

Methotrexate should not come into contact with the surface of the skin or mucosa. In the event of contamination, the affected area must be rinsed immediately with plenty of water.

If you use more Metoject PEN than you should
If you use more Metoject PEN than you should, talk to your doctor immediately.

If you forget to use Metoject PEN
Do not take a double dose to make up for a forgotten dose.

If you stop using Metoject PEN
If you stop using Metoject PEN, talk to your doctor immediately.

If you have the impression that the effect of Metoject PEN is too strong or too weak, talk to your doctor or pharmacist.

4. Possible side effects
Like all medicines, this medicine can cause side effects, although not everybody gets them.
The frequency as well as the degree of severity of the side effects depends on the dosage level and the frequency of administration. As severe side effects may occur even at low dosage, it is important that you are monitored regularly by your doctor. Your doctor will do **tests to check for abnormalities** developing in the blood (such as low white blood cells, low platelets, lymphoma) and changes in the kidneys and the liver.

Tell your doctor immediately if you experience any of the following symptoms, as these may indicate a serious, potentially life-threatening side effect, which require urgent specific treatment:
- **persistent dry, non-productive cough, shortness of breath and fever;** these may be signs of an inflammation of the lungs [common]
- **spitting or coughing blood;** these might be signs of bleeding from the lungs [not known]
- **symptoms of liver damage such as yellowing of the skin and whites of the eyes;** methotrexate can cause chronic liver damage (liver cirrhosis), formation of scar tissue in the liver (liver fibrosis), fatty degeneration of the liver [all uncommon], inflammation of the liver (acute hepatitis) [rare] and liver failure [very rare]
- **allergy symptoms such as skin rash including red itchy skin, swelling of the hands, feet, ankles, face, lips, mouth or throat (which may cause difficulty in swallowing or breathing) and feeling you are going to faint;** these may be signs of severe allergic reactions or an anaphylactic shock [rare]
- **symptoms of kidney damage such as swelling of the hands, ankles or feet or changes in frequency of urination or decrease (oliguria) or absence of urine (anuria);** these may be signs of kidney failure [rare]
- **symptoms of infections, e.g. fever, chills, achiness, sore throat;** methotrexate can make you more susceptible to infections. Severe infections like a certain type of pneumonia (*Pneumocystis carinii pneumonia*) or blood poisoning (sepsis) may occur [rare]
- **symptoms such as weakness of one side of the body (stroke) or pain, swelling, redness and unusual warmth in one of your legs (deep vein thrombosis); This may happen when a dislodged blood clot causes a blockage of a blood vessel** (thromboembolic event) [rare]
- **fever and serious deterioration of your general condition, or sudden fever accompanied by a sore throat or mouth, or urinary problems;** methotrexate can cause a sharp fall in certain white blood cells (agranulocytosis) and severe bone marrow suppression [very rare]
- **unexpected bleeding, e.g. bleeding gums, blood in the urine, vomiting blood or bruising**, these can be signs of a severely reduced number of blood platelets caused by severe courses of bone marrow depression [very rare]
- **symptoms such as severe headache often in combination with fever, neck stiffness, feeling sick, vomiting, disorientation and sensitivity to light** may indicate an inflammation of the membranes of the brain (acute aseptic meningitis) [very rare]
- certain brain disorders (encephalopathy/ leukoencephalopathy) have been reported in cancer patients receiving methotrexate. Such side effects cannot be excluded when methotrexate therapy is used to treat other diseases. Signs of this kind of brain disorders may be **altered mental state, movement disorders (ataxia), visual disturbances or disturbances of memory [not known]**
- **severe skin rash or blistering of the skin (this can also affect your mouth, eyes and genitals);** these may be signs of conditions called Stevens Johnson syndrome or burned skin syndrome (toxic epidermal necrolysis/Lyell's syndrome) [very rare]

In the following, please find the other side effects that may occur:
Very common: may affect more than 1 in 10 people
- Inflammation of the mouth lining, indigestion, feeling sick, loss of appetite, abdominal pain.
- Abnormal liver function test (ASAT, ALAT, bilirubin, alkaline phosphatase).

Common: may affect up to 1 in 10 people
- Mouth ulcers, diarrhoea
- Rash, reddening of the skin, itching
- Headache, tiredness, drowsiness
- Reduced blood cell formation with decrease in white and/or red blood cells and/or platelets.

Uncommon: may affect up to 1 in 100 people
- Throat inflammation.
- Inflammation of the bowels, vomiting, inflammation of pancreas, black or tarry stools, gastrointestinal ulcers and bleeding.
- Increased sensitivity to light, loss of hair, increased number of rheumatic nodules, skin ulcer, shingles, inflammation of blood vessels, herpes-like skin rash, hives.
- Onset of diabetes mellitus.
- Dizziness, confusion, depression.
- Decrease in serum albumin.
- Decrease in the number of all blood cells and platelets.
- Inflammation and ulcer of the urinary bladder or vagina, reduced kidney function, disturbed urination.
- Joint pain, muscle pain, reduction of bone mass.

Rare: may affect up to 1 in 1,000 people
- Inflammation of gum tissue.
- Increased skin pigmentation, acne, blue spots on the skin due to vessel bleeding (ecchymosis, petechiae), allergic inflammation of blood vessels.
- Decreased number of anti-bodies in the blood.
- Infection (incl. reactivation of inactive chronic infection), red eyes (conjunctivitis).
- Mood swings (mood alterations).
- Visual disturbances.
- Inflammation of the sac around the heart, accumulation of fluid in the sac around the heart, obstruction of cardiac filling due to fluid in the sac around the heart.
- Low blood pressure.
- Formation of scar tissue in the lung (pulmonary fibrosis), shortness of breath and bronchial asthma, accumulation of fluid in the sac around the lung.
- Stress fracture.
- Electrolyte disturbances.
- Fever, wound-healing impairment.

Very rare: may affect up to 1 in 10,000 people
- Acute toxic dilatation of the gut (toxic megacolon).
- Increased pigmentation of the nails, inflammation of the cuticles (acute paronychia), deep infection of hair follicles (furunculosis), visible enlargement of small blood vessels.
- Pain, loss of strength or sensation of numbness or tingling in arms and legs, changes in taste (metallic taste), convulsions, paralysis, meningism.
- Impaired vision, non-inflammatory eye disorder (retinopathy).
- Loss of sexual drive, impotence, male breast enlargement, defective sperm formation (oligospermia), menstrual disorder, vaginal discharge.
- Enlargement of lymphatic nodes (lymphoma).
- Lymphoproliferative disorders (excessive growth of white blood cells).

Not known: frequency cannot be estimated from the available data
- Increased number of certain white blood cells.
- Nosebleed.
- Proteins in urine.
- Feeling of weakness.
- Bone damage in the jaw (secondary to excessive growth of white blood cells).
- Tissue destruction at injection site

Subcutaneous application of methotrexate is locally well tolerated. Only mild local skin reactions (such as burning sensations, erythema, swelling, discolouration, severe itching, pain) were observed, decreasing during therapy.

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 Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Metoject PEN
Keep out of the sight and reach of children.
Do not store above 25 °C.
Keep the pre-filled pen in the outer carton in order to protect from light.
Do not use after the expiry date stated on the packaging. The expiry date refers to the last day of that month.

Medicines should not be disposed via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. The measures will help to protect the environment.

If your pre-filled pen shows any signs of deterioration, consult your doctor or pharmacist who will tell you what to do.

6. Contents of the pack and other information
What Metoject PEN contains
- The active substance is methotrexate.

1 pre-filled pen with 0.15 ml solution contains 7.5 mg methotrexate.
1 pre-filled pen with 0.2 ml solution contains 10 mg methotrexate.
1 pre-filled pen with 0.25 ml solution contains 12.5 mg methotrexate.
1 pre-filled pen with 0.3 ml solution contains 15 mg methotrexate.

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

What Metoject PEN looks like and contents of the pack
Pre-filled pen containing a clear, yellow-brown solution in pre-filled colourless glass syringe with a plunger stopper of rubber and embedded injection needle. The syringe is externally equipped with the device for self-administration.

Metoject PEN is available in pack of 1 pre-filled pen.
Alcohol pads included in the package.

Manufacturer and product licence holder
Manufactured by medac Gesellschaft für klinische Spezialpräparate mbH, Theaterstr. 6, 22880 Wedel, Germany.
Procured from the EU by product licence holder Star Pharmaceuticals Ltd, 5 Sandridge Close, Harrow, Middlesex HA1 1XD. Repackaged by Servipharm Ltd.

POM

Metoject® PEN 7.5 mg solution for injection in pre-filled pen
PL 20636/2643
Metoject® PEN 10 mg solution for injection in pre-filled pen
PL 20636/2644
Metoject® PEN 12.5 mg solution for injection in pre-filled pen
PL 20636/2645
Metoject® PEN 15 mg solution for injection in pre-filled pen
PL 20636/2646

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Is this leaflet hard to see or read?
Call 020 8423 2111 to obtain the leaflet in a format suitable for you.

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2643, 2644,2645, 2646
08.10.20[11]

Metex® PEN 7.5 mg solution for injection in pre-filled pen
Metex® PEN 10 mg solution for injection in pre-filled pen
Metex® PEN 12.5 mg solution for injection in pre-filled pen
Metex® PEN 15 mg solution for injection in pre-filled pen

(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.

Your medicine is available using the above name but will be referred to as Metex PEN throughout this leaflet. Metex PEN is also available in other strengths than those listed above.

What is in this leaflet

1. What Metex PEN is and what it is used for
2. What you need to know before you use Metex PEN
3. How to use Metex PEN
4. Possible side effects
5. How to store Metex PEN
6. Contents of the pack and other information

1. What Metex PEN is and what it is used for

Metex PEN is indicated for the treatment of
- active rheumatoid arthritis in adult patients.
- polyarthritic forms of severe, active juvenile idiopathic arthritis, when the response to nonsteroidal anti-inflammatory drugs (NSAIDs) has been inadequate.
- moderate to severe psoriasis in adult patients, and severe psoriatic arthritis in adults.
- mild to moderate Crohn's disease in adult patients when adequate treatment with other medicines is not possible.

Rheumatoid arthritis (RA) is a chronic collagen disease, characterised by inflammation of the synovial membranes (joint membranes). These membranes produce a fluid which acts as a lubricant for many joints. The inflammation causes thickening of the membrane and swelling of the joint.

Juvenile arthritis concerns children and adolescents less than 16 years. Polyarthritic forms are indicated if 5 or more joints are affected within the first 6 months of the disease.

Psoriasis is a common chronic skin disease, characterised by red patches covered by thick, dry, silvery, adherent scales.

Psoriatic arthritis is a kind of arthritis with psoriatic lesions of the skin and nails, especially at the joints of fingers and toes.

Metex PEN modifies and slows down the progression of the disease.

Crohn's disease is a type of inflammatory bowel disease that may affect any part of the gastrointestinal tract causing symptoms such as abdominal pain, diarrhoea, vomiting or weight loss.

2. What you need to know before you use Metex PEN

Do not use Metex PEN:
- if you are allergic to methotrexate or any of the other ingredients of this medicine (listed in section 6).
- if you suffer from liver or severe kidney diseases or blood diseases.
- if you regularly drink large amounts of alcohol.
- if you suffer from a severe infection, such as tuberculosis, HIV or other immunodeficiency syndromes.
- if you suffer from mouth ulcers, stomach ulcer or intestinal ulcer.
- if you are pregnant or breast-feeding (see section "Pregnancy, breast-feeding and fertility").
- if you receive vaccinations with live vaccines at the same time.

Warnings and precautions

Talk to your doctor or pharmacist before taking Metex PEN if:
- you are elderly or if you feel generally unwell and weak.
- you have problems with the way your liver works.
- you suffer from dehydration (water loss).

Special precautionary measures for treatment with Metex PEN

Methotrexate temporarily affects sperm and egg production, which is reversible in most cases. Methotrexate can cause miscarriage and severe birth defects. You must avoid becoming pregnant when using methotrexate and for at least six months after treatment has stopped.
See also section "Pregnancy, breast-feeding and fertility".

Recommended follow-up examinations and safety measures

Even when Metex PEN is administered in low doses, severe side effects can occur. In order to detect them in time, check-ups and laboratory tests have to be carried out by your doctor.

Before therapy

Before starting the treatment, blood samples will be taken in order to check that you have enough blood cells, tests to check your liver function, serum albumin (a protein in the blood) and kidney function. Your doctor will also check if you suffer from tuberculosis (infectious disease in combination with little nodules in the affected tissue) and a chest X-ray will be taken.

During therapy

You will have the following tests at least once a month during the first six months and at least every three months thereafter:
- Examination of the mouth and throat for changes of the mucosa.
- Blood tests.
- Check of liver function.
- Check of kidney function.
- Check of respiratory system and if necessary lung function test.

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.

Methotrexate may affect your immune system and vaccination results. It may also affect the result of immunological tests. Inactive, chronic infections (such as herpes zoster [shingles], tuberculosis, hepatitis B or C) may flare up. **During therapy with Metex PEN you must not be vaccinated with live vaccines.**

Radiation-induced dermatitis and sun-burn can reappear under methotrexate therapy (recall-reaction). Psoriatic lesions can exacerbate during UV-irradiation and simultaneous administration of methotrexate.
Enlarged lymph nodes (lymphoma) may occur and if this is the case, therapy must be stopped.

Diarrhoea can be a possible side effect of Metex PEN 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.

Other medicines and Metex PEN

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Please note that this also applies to medicines that you will take **in the future.**

The effect of the treatment may be affected if Metex PEN is administered at the same time as certain other medicines:
- **Antibiotics** such as: tetracyclines, chloramphenicol, non-absorbable broad-spectrum antibiotics, penicillines, glycopeptides, sulphonamides, ciprofloxacin and cefalotin (medicines to prevent/fight certain infections).
- **Non-steroidal anti-inflammatory** drugs or **salicylates** (medicines against pain and/or inflammation such as acetylsalicylic acid, diclofenac and ibuprofen or pyrazole).
- **Probenecid** (medicine against gout).
- Weak organic acids like loop **diuretics** ("water tablets").
- Medicines, which may have adverse effects on the **bone marrow,** such as trimethoprim-sulphamethoxazole (an antibiotic) and pyrimethamine.
- Other **medicines used to treat rheumatoid arthritis** such as leflunomide, sulphasalazine and azathioprine.
- Mercaptopurine (a **cytostatic** medicine).
- Retinoids (medicine against **psoriasis** and other dermatological diseases).
- Theophylline (medicine against **bronchial asthma** and other lung diseases).
- Some medicines against **stomach trouble** such as omeprazole and pantoprazole.
- Hypoglycaemics (medicines that are used to **lower the blood sugar**).

Vitamins containing **folic acid** may impair the effect of your treatment and should only be taken when advised by your doctor.

Vaccination with live vaccine must be avoided.

Metex PEN with food, drink and alcohol

Alcohol as well as large amounts of coffee, caffeine-containing soft drinks and black tea should be avoided during treatment with Metex PEN.

Pregnancy, breast-feeding and fertility

Pregnancy

Do not use Metex PEN during pregnancy or if you are trying to become pregnant. 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. Therefore, it is very important that methotrexate is not given to pregnant patients or patients planning to become pregnant. In women of child-bearing age, any possibility of pregnancy must be excluded with appropriate measures, e.g. pregnancy test before starting treatment.
You must avoid becoming pregnant whilst taking methotrexate and for at least 6 months after treatment is stopped by using reliable contraception throughout this time (see also section "Warnings and precautions").
If you do become pregnant during treatment or suspect you might be pregnant, speak to your doctor as soon as possible. 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.

Breast-feeding

Stop breast-feeding prior to and during treatment with Metex PEN.

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. Methotrexate may be genotoxic. This means that the medicine may cause genetic mutation. Methotrexate can affect sperm production with the potential to cause birth defects. Therefore, you should avoid fathering a child or to donate semen whilst taking methotrexate and for at least 6 months after treatment is stopped.

Driving and using machines

Treatment with Metex PEN may cause adverse reactions affecting the central nervous system, such as tiredness and dizziness. Thus the ability to drive a vehicle and/or to operate machines may, in certain cases, be compromised. If you feel tired or drowsy do not drive or use machines.

Metex PEN contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per dose; that is to say essentially "sodium-free".

3. How to use Metex PEN

Important warning about the dose of Metex PEN (methotrexate):
Use Metex PEN **only once a week** for the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, psoriasis and psoriatic arthritis, and Crohn's disease. Using too much of Metex PEN (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.

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

Your doctor decides on the dose, which is adjusted individually to you. Usually it takes 4 – 8 weeks before there is any effect of the treatment.

Metex PEN is administered subcutaneously (under the skin) by or under the supervision of a physician or healthcare staff as an injection **once a week only.** Together with your doctor you decide on a suitable weekday each week on which you receive your injection.

Use in children and adolescents

The doctor decides on the appropriate dose in children and adolescents with polyarthritic forms of juvenile idiopathic arthritis.
Metex PEN is not recommended in children less than 3 years of age due to insufficient experience in this age group.

Instructions for use

Recommendations
- Carefully read the instructions below before starting your injection.
- Always use the injection technique advised by your doctor, pharmacist or nurse.

Additional information

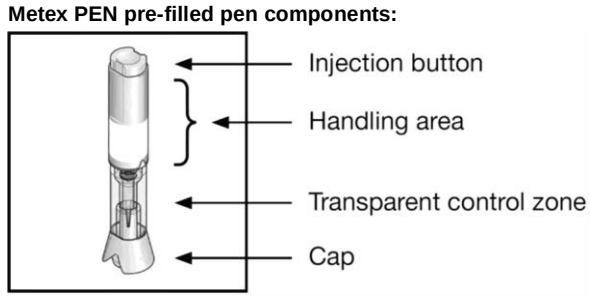
The manner of handling and throwing away of the medicine and pre-filled pen must be in accordance with local requirements. Pregnant healthcare personnel should not handle and/or administer Metex PEN.

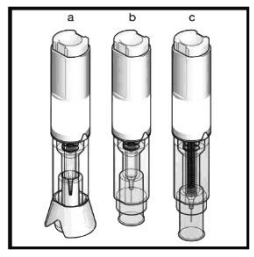
Methotrexate should not come into contact with the surface of the skin or mucosa. In the event of contamination, the affected area must be rinsed immediately with plenty of water.

What you need in order to administer your injection using the Metex PEN pre-filled pen

You need:
- 1 Metex PEN pre-filled pen
- 1 alcohol pad

Metex PEN pre-filled pen components:



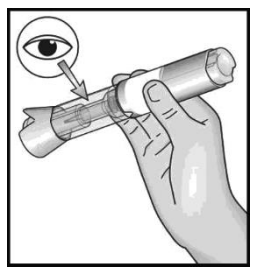


a) With cap before injection

b) After cap removal before injection

c) After injection

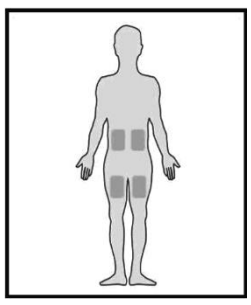
What you need to do before administering your injection:
1. Wash your hands very carefully.
2. Remove the system from its packaging.
3. Check the Metex PEN pre-filled pen before using it:



If the Metex PEN pre-filled pen appears to be damaged **do not use** it. Use another one and contact your doctor, pharmacist or nurse.
In case a small air bubble is visible through the transparent control zone, this will not affect your dose nor will it harm you.
If you are not able to see or to check the system correctly prior to injection, ask someone around you for assistance.

4. Set the Metex PEN pre-filled pen on a clean flat surface (such as a table).

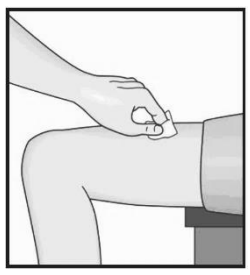
Where you should administer the injection



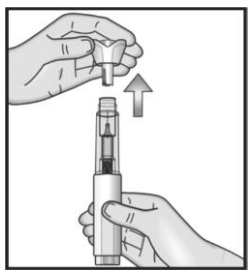
The most appropriate zones for your injection are:
- upper thighs,
- abdomen except around the navel.

- If someone around you administers the injection for you, the person may also use the top of the zone at the back of the arm, just below the shoulder.
- Change the injection area with each injection. This will minimise any reactions at the injection site.
- Never inject into areas where the skin is tender, bruised, red or hard or where you have scars or stretch marks. If you have psoriasis, you should not try to inject directly into any raised, thick, red or scaly skin patches or lesions.

How to prepare the injection



5. Clean your skin in the chosen injection zone using the enclosed alcohol pad.

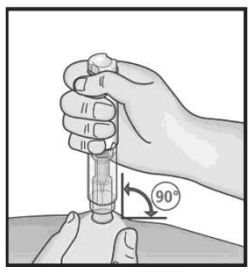


- Do not remove the cap before you are ready to administer the injection.

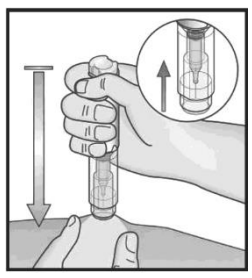
6. Hold the pen with one hand in the handling area with the cap pointing upwards. Use your other hand to gently pull the cap straight off (do not bend or twist the cap). The cap has a small needle shield that should come off with the cap automatically. If the needle shield does not come off, use another pen and contact your doctor, pharmacist or nurse.

- If you are unable to remove the cap, ask someone around you for assistance.

Note: Once you have removed the cap, perform your injection without delay.

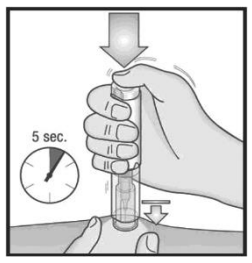


7. With your free hand, build a skin fold by gently squeezing the area of the cleaned skin at the injection site.
- The fold must be held pinched until the Metex PEN pre-filled pen is removed from the skin after the injection.



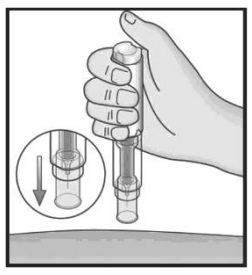
8. Position the uncapped transparent end of Metex PEN pre-filled pen perpendicular to the fold of skin.
9. **Without pressing the button**, push the Metex PEN pre-filled pen firmly onto your skin in order to unlock the button.
- If you are unable to push the Metex PEN pre-filled pen to the stop-point, ask someone around you for assistance.

How to administer the injection:



10. While holding the Metex PEN pre-filled pen firmly against the skin, **now press the button** with your thumb.
11. You will hear a click which indicates the start of the injection. Keep holding the pen against the raised skin until all of the medicine is injected. This can take up to **5 seconds.**

Note:
Do not remove the Metex PEN pre-filled pen from the skin before the end of the injection to avoid incomplete injection.
If the injection is not triggered, release the button, make sure that the Metex PEN pre-filled pen is pressed firmly against the skin and push hard on the button.
If you have troubles with your hearing, count 5 seconds from the moment you have pressed the button and then lift the Metex PEN pre-filled pen from the injection site.



12. Remove the Metex PEN pre-filled pen from the injection site, perpendicular to the skin (pull up).
13. The protective shield automatically moves into place over the needle. The protective shield is then locked and the needle is protected.
14. In case of a slight bleeding use a plaster.

Before throwing away the Metex PEN pre-filled pen, check visually that there is no liquid left in the pen, at the bottom of the **transparent control zone.** If there is liquid left in the pen, not all of the medicine has been injected correctly and you should consult your doctor.

Note
To avoid any injury, **never insert your fingers in the opening of the protective tube** covering the needle. **Do not destroy the pen**.

Whom should you contact in case of need
- For any problem or question, contact your doctor, pharmacist or nurse.

If you or someone around you is injured by the needle, consult your doctor immediately and throw away the Metex PEN pre-filled pen.

Method and duration of administration
Metex PEN is injected **once weekly!**
The duration of the treatment is determined by the treating physician.
Treatment of rheumatoid arthritis, juvenile idiopathic arthritis, psoriasis vulgaris, psoriatic arthritis and Crohn's disease with Metex PEN is a long-term treatment.

At the start of your therapy, Metex PEN will be injected by medical staff. However, your doctor may decide that you are able to learn how to inject Metex PEN under the skin yourself. You will then receive appropriate training. **Under no circumstances should you try to inject Metex PEN yourself before you have received such training.**

You can also find guidance on how to use Metex PEN in the section "Instructions for use" at the end of this leaflet.
Please note that all of the contents have to be used.

The manner of handling and throwing away of the medicine and pre-filled pen must be in accordance with local requirements. Pregnant healthcare personnel should not handle and/or administer Metex PEN.

Methotrexate should not come into contact with the surface of the skin or mucosa. In the event of contamination, the affected area must be rinsed immediately with plenty of water.

If you use more Metex PEN than you should
If you use more Metex PEN than you should, talk to your doctor immediately.

If you forget to use Metex PEN
Do not take a double dose to make up for a forgotten dose.

If you stop using Metex PEN
If you stop using Metex PEN, talk to your doctor immediately.

If you have the impression that the effect of Metex PEN is too strong or too weak, talk to your doctor or pharmacist.

4. Possible side effects
Like all medicines, this medicine can cause side effects, although not everybody gets them.
The frequency as well as the degree of severity of the side effects depends on the dosage level and the frequency of administration. As severe side effects may occur even at low dosage, it is important that you are monitored regularly by your doctor. Your doctor will do **tests to check for abnormalities** developing in the blood (such as low white blood cells, low platelets, lymphoma) and changes in the kidneys and the liver.

Tell your doctor immediately if you experience any of the following symptoms, as these may indicate a serious, potentially life-threatening side effect, which require urgent specific treatment:
- **persistent dry, non-productive cough, shortness of breath and fever;** these may be signs of an inflammation of the lungs [common]
- **spitting or coughing blood;** these might be signs of bleeding from the lungs [not known]
- **symptoms of liver damage such as yellowing of the skin and whites of the eyes;** methotrexate can cause chronic liver damage (liver cirrhosis), formation of scar tissue in the liver (liver fibrosis), fatty degeneration of the liver [all uncommon], inflammation of the liver (acute hepatitis) [rare] and liver failure [very rare]
- **allergy symptoms such as skin rash including red itchy skin, swelling of the hands, feet, ankles, face, lips, mouth or throat (which may cause difficulty in swallowing or breathing) and feeling you are going to faint;** these may be signs of severe allergic reactions or an anaphylactic shock [rare]
- **symptoms of kidney damage such as swelling of the hands, ankles or feet or changes in frequency of urination or decrease (oliguria) or absence of urine (anuria);** these may be signs of kidney failure [rare]
- **symptoms of infections, e.g. fever, chills, achiness, sore throat;** methotrexate can make you more susceptible to infections. Severe infections like a certain type of pneumonia (*Pneumocystis carinii pneumonia*) or blood poisoning (sepsis) may occur [rare]
- **symptoms such as weakness of one side of the body (stroke) or pain, swelling, redness and unusual warmth in one of your legs (deep vein thrombosis); This may happen when a dislodged blood clot causes a blockage of a blood vessel** (thromboembolic event) [rare]
- **fever and serious deterioration of your general condition, or sudden fever accompanied by a sore throat or mouth, or urinary problems;** methotrexate can cause a sharp fall in certain white blood cells (agranulocytosis) and severe bone marrow suppression [very rare]
- **unexpected bleeding, e.g. bleeding gums, blood in the urine, vomiting blood or bruising**, these can be signs of a severely reduced number of blood platelets caused by severe courses of bone marrow depression [very rare]
- **symptoms such as severe headache often in combination with fever, neck stiffness, feeling sick, vomiting, disorientation and sensitivity to light** may indicate an inflammation of the membranes of the brain (acute aseptic meningitis) [very rare]
- certain brain disorders (encephalopathy/ leukoencephalopathy) have been reported in cancer patients receiving methotrexate. Such side effects cannot be excluded when methotrexate therapy is used to treat other diseases. Signs of this kind of brain disorders may be **altered mental state, movement disorders (ataxia), visual disturbances or disturbances of memory [not known]**
- **severe skin rash or blistering of the skin (this can also affect your mouth, eyes and genitals);** these may be signs of conditions called Stevens Johnson syndrome or burned skin syndrome (toxic epidermal necrolysis/Lyell's syndrome) [very rare]

In the following, please find the other side effects that may occur:
Very common: may affect more than 1 in 10 people
- Inflammation of the mouth lining, indigestion, feeling sick, loss of appetite, abdominal pain.
- Abnormal liver function test (ASAT, ALAT, bilirubin, alkaline phosphatase).

Common: may affect up to 1 in 10 people
- Mouth ulcers, diarrhoea
- Rash, reddening of the skin, itching
- Headache, tiredness, drowsiness
- Reduced blood cell formation with decrease in white and/or red blood cells and/or platelets.

Uncommon: may affect up to 1 in 100 people
- Throat inflammation.
- Inflammation of the bowels, vomiting, inflammation of pancreas, black or tarry stools, gastrointestinal ulcers and bleeding.
- Increased sensitivity to light, loss of hair, increased number of rheumatic nodules, skin ulcer, shingles, inflammation of blood vessels, herpes-like skin rash, hives.
- Onset of diabetes mellitus.
- Dizziness, confusion, depression.
- Decrease in serum albumin.
- Decrease in the number of all blood cells and platelets.
- Inflammation and ulcer of the urinary bladder or vagina, reduced kidney function, disturbed urination.
- Joint pain, muscle pain, reduction of bone mass.

Rare: may affect up to 1 in 1,000 people
- Inflammation of gum tissue.
- Increased skin pigmentation, acne, blue spots on the skin due to vessel bleeding (ecchymosis, petechiae), allergic inflammation of blood vessels.
- Decreased number of anti-bodies in the blood.
- Infection (incl. reactivation of inactive chronic infection), red eyes (conjunctivitis).
- Mood swings (mood alterations).
- Visual disturbances.
- Inflammation of the sac around the heart, accumulation of fluid in the sac around the heart, obstruction of cardiac filling due to fluid in the sac around the heart.
- Low blood pressure.
- Formation of scar tissue in the lung (pulmonary fibrosis), shortness of breath and bronchial asthma, accumulation of fluid in the sac around the lung.
- Stress fracture.
- Electrolyte disturbances.
- Fever, wound-healing impairment.

Very rare: may affect up to 1 in 10,000 people
- Acute toxic dilatation of the gut (toxic megacolon).
- Increased pigmentation of the nails, inflammation of the cuticles (acute paronychia), deep infection of hair follicles (furunculosis), visible enlargement of small blood vessels.
- Pain, loss of strength or sensation of numbness or tingling in arms and legs, changes in taste (metallic taste), convulsions, paralysis, meningism.
- Impaired vision, non-inflammatory eye disorder (retinopathy).
- Loss of sexual drive, impotence, male breast enlargement, defective sperm formation (oligospermia), menstrual disorder, vaginal discharge.
- Enlargement of lymphatic nodes (lymphoma).
- Lymphoproliferative disorders (excessive growth of white blood cells).

Not known: frequency cannot be estimated from the available data
- Increased number of certain white blood cells.
- Nosebleed.
- Proteins in urine.
- Feeling of weakness.
- Bone damage in the jaw (secondary to excessive growth of white blood cells).
- Tissue destruction at injection site

Subcutaneous application of methotrexate is locally well tolerated. Only mild local skin reactions (such as burning sensations, erythema, swelling, discolouration, severe itching, pain) were observed, decreasing during therapy.

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 Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Metex PEN
Keep out of the sight and reach of children.
Do not store above 25 °C.
Keep the pre-filled pen in the outer carton in order to protect from light.
Do not use after the expiry date stated on the packaging. The expiry date refers to the last day of that month.

Medicines should not be disposed via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. The measures will help to protect the environment.

If your pre-filled pen shows any signs of deterioration, consult your doctor or pharmacist who will tell you what to do.

6. Contents of the pack and other information
What Metex PEN contains
- The active substance is methotrexate.

1 pre-filled pen with 0.15 ml solution contains 7.5 mg methotrexate.
1 pre-filled pen with 0.2 ml solution contains 10 mg methotrexate.
1 pre-filled pen with 0.25 ml solution contains 12.5 mg methotrexate.
1 pre-filled pen with 0.3 ml solution contains 15 mg methotrexate.

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

What Metex PEN looks like and contents of the pack
Pre-filled pen containing a clear, yellow-brown solution in pre-filled colourless glass syringe with a plunger stopper of rubber and embedded injection needle. The syringe is externally equipped with the device for self-administration.

Metex PEN is available in pack of 1 pre-filled pen.
Alcohol pads included in the package.

Manufacturer and product licence holder
Manufactured by medac Gesellschaft für klinische Spezialpräparate mbH, Theaterstr. 6, 22880 Wedel, Germany.
Procured from the EU by product licence holder Star Pharmaceuticals Ltd, 5 Sandridge Close, Harrow, Middlesex HA1 1XD. Repackaged by Servipharm Ltd.

POM

Metex® PEN 7.5 mg solution for injection in pre-filled pen
PL 20636/2643
Metex® PEN 10 mg solution for injection in pre-filled pen
PL 20636/2644
Metex® PEN 12.5 mg solution for injection in pre-filled pen
PL 20636/2645
Metex® PEN 15 mg solution for injection in pre-filled pen
PL 20636/2646

Leaflet issue and revision date (Ref): 08.10.20[11]

Blind or partially sighted?
Is this leaflet hard to see or read?
Call 020 8423 2111 to obtain the leaflet in a format suitable for you.

PATIENT INFORMATION LEAFLET

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08.10.20[11]

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Methotrexate 15 mg solution for injection in pre-filled pen

(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.

Your medicine is available using the above name but will be referred to as Methotrexate PEN throughout this leaflet. Methotrexate PEN is also available in other strengths than those listed above.

What is in this leaflet

1. What Methotrexate PEN is and what it is used for
2. What you need to know before you use Methotrexate PEN
3. How to use Methotrexate PEN
4. Possible side effects
5. How to store Methotrexate PEN
6. Contents of the pack and other information

1. What Methotrexate PEN is and what it is used for

Methotrexate PEN is indicated for the treatment of
- active rheumatoid arthritis in adult patients.
- polyarthritic forms of severe, active juvenile idiopathic arthritis, when the response to nonsteroidal anti-inflammatory drugs (NSAIDs) has been inadequate.
- moderate to severe psoriasis in adult patients, and severe psoriatic arthritis in adults.
- mild to moderate Crohn's disease in adult patients when adequate treatment with other medicines is not possible.

Rheumatoid arthritis (RA) is a chronic collagen disease, characterised by inflammation of the synovial membranes (joint membranes). These membranes produce a fluid which acts as a lubricant for many joints. The inflammation causes thickening of the membrane and swelling of the joint.

Juvenile arthritis concerns children and adolescents less than 16 years. Polyarthritic forms are indicated if 5 or more joints are affected within the first 6 months of the disease.

Psoriasis is a common chronic skin disease, characterised by red patches covered by thick, dry, silvery, adherent scales.

Psoriatic arthritis is a kind of arthritis with psoriatic lesions of the skin and nails, especially at the joints of fingers and toes.

Methotrexate PEN modifies and slows down the progression of the disease.

Crohn's disease is a type of inflammatory bowel disease that may affect any part of the gastrointestinal tract causing symptoms such as abdominal pain, diarrhoea, vomiting or weight loss.

2. What you need to know before you use Methotrexate PEN

Do not use Methotrexate PEN:
- if you are allergic to methotrexate or any of the other ingredients of this medicine (listed in section 6).
- if you suffer from liver or severe kidney diseases or blood diseases.
- if you regularly drink large amounts of alcohol.
- if you suffer from a severe infection, such as tuberculosis, HIV or other immunodeficiency syndromes.
- if you suffer from mouth ulcers, stomach ulcer or intestinal ulcer.
- if you are pregnant or breast-feeding (see section "Pregnancy, breast-feeding and fertility").
- if you receive vaccinations with live vaccines at the same time.

Warnings and precautions

Talk to your doctor or pharmacist before taking Methotrexate PEN if:
- you are elderly or if you feel generally unwell and weak.
- you have problems with the way your liver works.
- you suffer from dehydration (water loss).

Special precautionary measures for treatment with Methotrexate PEN

Methotrexate temporarily affects sperm and egg production, which is reversible in most cases. Methotrexate can cause miscarriage and severe birth defects. You must avoid becoming pregnant when using methotrexate and for at least six months after treatment has stopped.
See also section "Pregnancy, breast-feeding and fertility".

Recommended follow-up examinations and safety measures

Even when Methotrexate PEN is administered in low doses, severe side effects can occur. In order to detect them in time, check-ups and laboratory tests have to be carried out by your doctor.

Before therapy

Before starting the treatment, blood samples will be taken in order to check that you have enough blood cells, tests to check your liver function, serum albumin (a protein in the blood) and kidney function. Your doctor will also check if you suffer from tuberculosis (infectious disease in combination with little nodules in the affected tissue) and a chest X-ray will be taken.

During therapy

You will have the following tests at least once a month during the first six months and at least every three months thereafter:
- Examination of the mouth and throat for changes of the mucosa.
- Blood tests.
- Check of liver function.
- Check of kidney function.
- Check of respiratory system and if necessary lung function test.

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.

Methotrexate may affect your immune system and vaccination results. It may also affect the result of immunological tests. Inactive, chronic infections (such as herpes zoster [shingles], tuberculosis, hepatitis B or C) may flare up. **During therapy with Methotrexate PEN you must not be vaccinated with live vaccines.**

Radiation-induced dermatitis and sun-burn can reappear under methotrexate therapy (recall-reaction). Psoriatic lesions can exacerbate during UV-irradiation and simultaneous administration of methotrexate.
Enlarged lymph nodes (lymphoma) may occur and if this is the case, therapy must be stopped.

Diarrhoea can be a possible side effect of Methotrexate PEN 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.

Other medicines and Methotrexate PEN

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Please note that this also applies to medicines that you will take **in the future.**

The effect of the treatment may be affected if Methotrexate PEN is administered at the same time as certain other medicines:
- **Antibiotics** such as: tetracyclines, chloramphenicol, non-absorbable broad-spectrum antibiotics, penicillines, glycopeptides, sulphonamides, ciprofloxacin and cefalotin (medicines to prevent/fight certain infections).
- **Non-steroidal anti-inflammatory** drugs or **salicylates** (medicines against pain and/or inflammation such as acetylsalicylic acid, diclofenac and ibuprofen or pyrazole).
- **Probenecid** (medicine against gout).
- Weak organic acids like loop **diuretics** ("water tablets").
- Medicines, which may have adverse effects on the **bone marrow,** such as trimethoprim-sulphamethoxazole (an antibiotic) and pyrimethamine.
- Other **medicines used to treat rheumatoid arthritis** such as leflunomide, sulphasalazine and azathioprine.
- Mercaptopurine (a **cytostatic** medicine).
- Retinoids (medicine against **psoriasis** and other dermatological diseases).
- Theophylline (medicine against **bronchial asthma** and other lung diseases).
- Some medicines against **stomach trouble** such as omeprazole and pantoprazole.
- Hypoglycaemics (medicines that are used to **lower the blood sugar**).

Vitamins containing **folic acid** may impair the effect of your treatment and should only be taken when advised by your doctor.

Vaccination with live vaccine must be avoided.

Methotrexate PEN with food, drink and alcohol

Alcohol as well as large amounts of coffee, caffeine-containing soft drinks and black tea should be avoided during treatment with Methotrexate PEN.

Pregnancy, breast-feeding and fertility

Pregnancy

Do not use Methotrexate PEN during pregnancy or if you are trying to become pregnant. 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. Therefore, it is very important that methotrexate is not given to pregnant patients or patients planning to become pregnant. In women of child-bearing age, any possibility of pregnancy must be excluded with appropriate measures, e.g. pregnancy test before starting treatment.
You must avoid becoming pregnant whilst taking methotrexate and for at least 6 months after treatment is stopped by using reliable contraception throughout this time (see also section "Warnings and precautions").
If you do become pregnant during treatment or suspect you might be pregnant, speak to your doctor as soon as possible. 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.

Breast-feeding

Stop breast-feeding prior to and during treatment with Methotrexate PEN.

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. Methotrexate may be genotoxic. This means that the medicine may cause genetic mutation. Methotrexate can affect sperm production with the potential to cause birth defects. Therefore, you should avoid fathering a child or to donate semen whilst taking methotrexate and for at least 6 months after treatment is stopped.

Driving and using machines

Treatment with Methotrexate PEN may cause adverse reactions affecting the central nervous system, such as tiredness and dizziness. Thus the ability to drive a vehicle and/or to operate machines may, in certain cases, be compromised. If you feel tired or drowsy do not drive or use machines.

Methotrexate PEN contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per dose; that is to say essentially "sodium-free".

3. How to use Methotrexate PEN

Important warning about the dose of Methotrexate PEN (methotrexate):
Use Methotrexate PEN **only once a week** for the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, psoriasis and psoriatic arthritis, and Crohn's disease. Using too much of Methotrexate PEN (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.

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

Your doctor decides on the dose, which is adjusted individually to you. Usually it takes 4 – 8 weeks before there is any effect of the treatment.

Methotrexate PEN is administered subcutaneously (under the skin) by or under the supervision of a physician or healthcare staff as an injection **once a week only.** Together with your doctor you decide on a suitable weekday each week on which you receive your injection.

Use in children and adolescents

The doctor decides on the appropriate dose in children and adolescents with polyarthritic forms of juvenile idiopathic arthritis.
Methotrexate PEN is not recommended in children less than 3 years of age due to insufficient experience in this age group.

Instructions for use

Recommendations
- Carefully read the instructions below before starting your injection.
- Always use the injection technique advised by your doctor, pharmacist or nurse.

Additional information

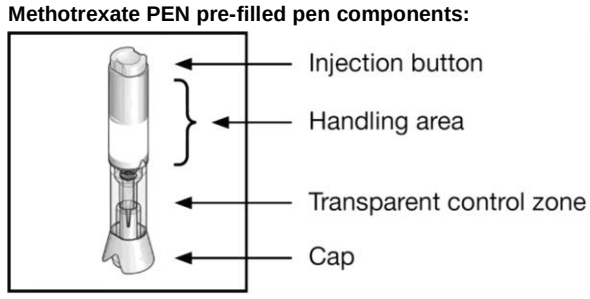
The manner of handling and throwing away of the medicine and pre-filled pen must be in accordance with local requirements. Pregnant healthcare personnel should not handle and/or administer Methotrexate PEN.

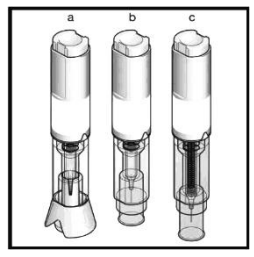
Methotrexate should not come into contact with the surface of the skin or mucosa. In the event of contamination, the affected area must be rinsed immediately with plenty of water.

What you need in order to administer your injection using the Methotrexate PEN pre-filled pen

You need:
- 1 Methotrexate PEN pre-filled pen
- 1 alcohol pad

Methotrexate PEN pre-filled pen components:



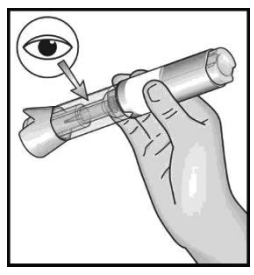


a) With cap before injection

b) After cap removal before injection

c) After injection

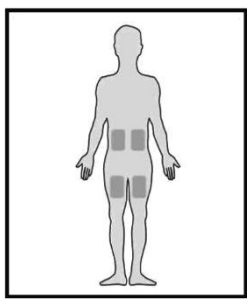
What you need to do before administering your injection:
1. Wash your hands very carefully.
2. Remove the system from its packaging.
3. Check the Methotrexate PEN pre-filled pen before using it:



If the Methotrexate PEN pre-filled pen appears to be damaged **do not use** it. Use another one and contact your doctor, pharmacist or nurse.
In case a small air bubble is visible through the transparent control zone, this will not affect your dose nor will it harm you.
If you are not able to see or to check the system correctly prior to injection, ask someone around you for assistance.

4. Set the Methotrexate PEN pre-filled pen on a clean flat surface (such as a table).

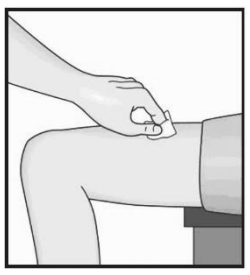
Where you should administer the injection



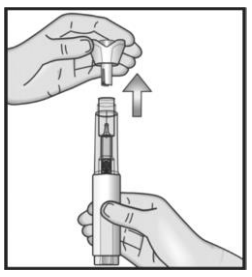
The most appropriate zones for your injection are:
- upper thighs,
- abdomen except around the navel.

- If someone around you administers the injection for you, the person may also use the top of the zone at the back of the arm, just below the shoulder.
- Change the injection area with each injection. This will minimise any reactions at the injection site.
- Never inject into areas where the skin is tender, bruised, red or hard or where you have scars or stretch marks. If you have psoriasis, you should not try to inject directly into any raised, thick, red or scaly skin patches or lesions.

How to prepare the injection



5. Clean your skin in the chosen injection zone using the enclosed alcohol pad.

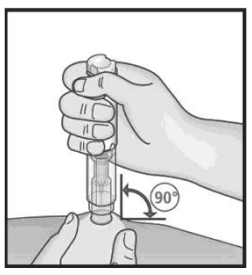


- Do not remove the cap before you are ready to administer the injection.

6. Hold the pen with one hand in the handling area with the cap pointing upwards. Use your other hand to gently pull the cap straight off (do not bend or twist the cap). The cap has a small needle shield that should come off with the cap automatically. If the needle shield does not come off, use another pen and contact your doctor, pharmacist or nurse.

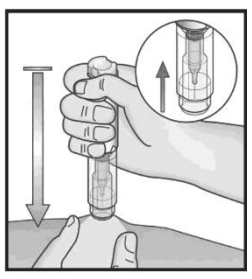
- If you are unable to remove the cap, ask someone around you for assistance.

Note: Once you have removed the cap, perform your injection without delay.



7. With your free hand, build a skin fold by gently squeezing the area of the cleaned skin at the injection site.

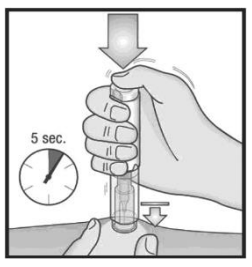
- The fold must be held pinched until the Methotrexate PEN pre-filled pen is removed from the skin after the injection.



8. Position the uncapped transparent end of Methotrexate PEN pre-filled pen perpendicular to the fold of skin.
9. **Without pressing the button**, push the Methotrexate PEN pre-filled pen firmly onto your skin in order to unlock the button.

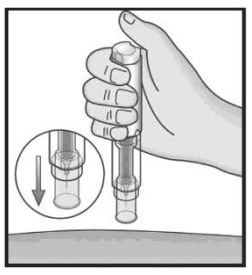
- If you are unable to push the Methotrexate PEN pre-filled pen to the stop-point, ask someone around you for assistance.

How to administer the injection:



10. While holding the Methotrexate PEN pre-filled pen firmly against the skin, **now press the button** with your thumb.
11. You will hear a click which indicates the start of the injection. Keep holding the pen against the raised skin until all of the medicine is injected. This can take up to **5 seconds.**

Note:
Do not remove the Methotrexate PEN pre-filled pen from the skin before the end of the injection to avoid incomplete injection.
If the injection is not triggered, release the button, make sure that the Methotrexate PEN pre-filled pen is pressed firmly against the skin and push hard on the button.
If you have troubles with your hearing, count 5 seconds from the moment you have pressed the button and then lift the Methotrexate PEN pre-filled pen from the injection site.



12. Remove the Methotrexate PEN pre-filled pen from the injection site, perpendicular to the skin (pull up).
13. The protective shield automatically moves into place over the needle. The protective shield is then locked and the needle is protected.
14. In case of a slight bleeding use a plaster.

Before throwing away the Methotrexate PEN pre-filled pen, check visually that there is no liquid left in the pen, at the bottom of the **transparent control zone.** If there is liquid left in the pen, not all of the medicine has been injected correctly and you should consult your doctor.

Note
To avoid any injury, **never insert your fingers in the opening of the protective tube** covering the needle. **Do not destroy the pen**.

Whom should you contact in case of need
- For any problem or question, contact your doctor, pharmacist or nurse.

If you or someone around you is injured by the needle, consult your doctor immediately and throw away the Methotrexate PEN pre-filled pen.

Method and duration of administration
Methotrexate PEN is injected **once weekly!**
The duration of the treatment is determined by the treating physician.
Treatment of rheumatoid arthritis, juvenile idiopathic arthritis, psoriasis vulgaris, psoriatic arthritis and Crohn's disease with Methotrexate PEN is a long-term treatment.

At the start of your therapy, Methotrexate PEN will be injected by medical staff. However, your doctor may decide that you are able to learn how to inject Methotrexate PEN under the skin yourself. You will then receive appropriate training.
Under no circumstances should you try to inject Methotrexate PEN yourself before you have received such training.

You can also find guidance on how to use Methotrexate PEN in the section "Instructions for use" at the end of this leaflet.
Please note that all of the contents have to be used.

The manner of handling and throwing away of the medicine and pre-filled pen must be in accordance with local requirements. Pregnant healthcare personnel should not handle and/or administer Methotrexate PEN.

Methotrexate should not come into contact with the surface of the skin or mucosa. In the event of contamination, the affected area must be rinsed immediately with plenty of water.

If you use more Methotrexate PEN than you should
If you use more Methotrexate PEN than you should, talk to your doctor immediately.

If you forget to use Methotrexate PEN
Do not take a double dose to make up for a forgotten dose.

If you stop using Methotrexate PEN
If you stop using Methotrexate PEN, talk to your doctor immediately.

If you have the impression that the effect of Methotrexate PEN is too strong or too weak, talk to your doctor or pharmacist.

4. Possible side effects
Like all medicines, this medicine can cause side effects, although not everybody gets them.
The frequency as well as the degree of severity of the side effects depends on the dosage level and the frequency of administration. As severe side effects may occur even at low dosage, it is important that you are monitored regularly by your doctor. Your doctor will do **tests to check for abnormalities** developing in the blood (such as low white blood cells, low platelets, lymphoma) and changes in the kidneys and the liver.

Tell your doctor immediately if you experience any of the following symptoms, as these may indicate a serious, potentially life-threatening side effect, which require urgent specific treatment:
- **persistent dry, non-productive cough, shortness of breath and fever;** these may be signs of an inflammation of the lungs [common]
- **spitting or coughing blood;** these might be signs of bleeding from the lungs [not known]
- **symptoms of liver damage such as yellowing of the skin and whites of the eyes;** methotrexate can cause chronic liver damage (liver cirrhosis), formation of scar tissue in the liver (liver fibrosis), fatty degeneration of the liver [all uncommon], inflammation of the liver (acute hepatitis) [rare] and liver failure [very rare]
- **allergy symptoms such as skin rash including red itchy skin, swelling of the hands, feet, ankles, face, lips, mouth or throat (which may cause difficulty in swallowing or breathing) and feeling you are going to faint;** these may be signs of severe allergic reactions or an anaphylactic shock [rare]
- **symptoms of kidney damage such as swelling of the hands, ankles or feet or changes in frequency of urination or decrease (oliguria) or absence of urine (anuria);** these may be signs of kidney failure [rare]
- **symptoms of infections, e.g. fever, chills, achiness, sore throat;** methotrexate can make you more susceptible to infections. Severe infections like a certain type of pneumonia (*Pneumocystis carinii pneumonia*) or blood poisoning (sepsis) may occur [rare]
- **symptoms such as weakness of one side of the body (stroke) or pain, swelling, redness and unusual warmth in one of your legs (deep vein thrombosis); This may happen when a dislodged blood clot causes a blockage of a blood vessel** (thromboembolic event) [rare]
- **fever and serious deterioration of your general condition, or sudden fever accompanied by a sore throat or mouth, or urinary problems;** methotrexate can cause a sharp fall in certain white blood cells (agranulocytosis) and severe bone marrow suppression [very rare]
- **unexpected bleeding, e.g. bleeding gums, blood in the urine, vomiting blood or bruising**, these can be signs of a severely reduced number of blood platelets caused by severe courses of bone marrow depression [very rare]
- **symptoms such as severe headache often in combination with fever, neck stiffness, feeling sick, vomiting, disorientation and sensitivity to light** may indicate an inflammation of the membranes of the brain (acute aseptic meningitis) [very rare]
- certain brain disorders (encephalopathy/ leukoencephalopathy) have been reported in cancer patients receiving methotrexate. Such side effects cannot be excluded when methotrexate therapy is used to treat other diseases. Signs of this kind of brain disorders may be **altered mental state, movement disorders (ataxia), visual disturbances or disturbances of memory [not known]**
- **severe skin rash or blistering of the skin (this can also affect your mouth, eyes and genitals);** these may be signs of conditions called Stevens Johnson syndrome or burned skin syndrome (toxic epidermal necrolysis/Lyell's syndrome) [very rare]

In the following, please find the other side effects that may occur:
Very common: may affect more than 1 in 10 people
- Inflammation of the mouth lining, indigestion, feeling sick, loss of appetite, abdominal pain.
- Abnormal liver function test (ASAT, ALAT, bilirubin, alkaline phosphatase).

Common: may affect up to 1 in 10 people
- Mouth ulcers, diarrhoea
- Rash, reddening of the skin, itching
- Headache, tiredness, drowsiness
- Reduced blood cell formation with decrease in white and/or red blood cells and/or platelets.

Uncommon: may affect up to 1 in 100 people
- Throat inflammation.
- Inflammation of the bowels, vomiting, inflammation of pancreas, black or tarry stools, gastrointestinal ulcers and bleeding.
- Increased sensitivity to light, loss of hair, increased number of rheumatic nodules, skin ulcer, shingles, inflammation of blood vessels, herpes-like skin rash, hives.
- Onset of diabetes mellitus.
- Dizziness, confusion, depression.
- Decrease in serum albumin.
- Decrease in the number of all blood cells and platelets.
- Inflammation and ulcer of the urinary bladder or vagina, reduced kidney function, disturbed urination.
- Joint pain, muscle pain, reduction of bone mass.

Rare: may affect up to 1 in 1,000 people
- Inflammation of gum tissue.
- Increased skin pigmentation, acne, blue spots on the skin due to vessel bleeding (ecchymosis, petechiae), allergic inflammation of blood vessels.
- Decreased number of anti-bodies in the blood.
- Infection (incl. reactivation of inactive chronic infection), red eyes (conjunctivitis).
- Mood swings (mood alterations).
- Visual disturbances.
- Inflammation of the sac around the heart, accumulation of fluid in the sac around the heart, obstruction of cardiac filling due to fluid in the sac around the heart.
- Low blood pressure.
- Formation of scar tissue in the lung (pulmonary fibrosis), shortness of breath and bronchial asthma, accumulation of fluid in the sac around the lung.
- Stress fracture.
- Electrolyte disturbances.
- Fever, wound-healing impairment.

Very rare: may affect up to 1 in 10,000 people
- Acute toxic dilatation of the gut (toxic megacolon).
- Increased pigmentation of the nails, inflammation of the cuticles (acute paronychia), deep infection of hair follicles (furunculosis), visible enlargement of small blood vessels.
- Pain, loss of strength or sensation of numbness or tingling in arms and legs, changes in taste (metallic taste), convulsions, paralysis, meningism.
- Impaired vision, non-inflammatory eye disorder (retinopathy).
- Loss of sexual drive, impotence, male breast enlargement, defective sperm formation (oligospermia), menstrual disorder, vaginal discharge.
- Enlargement of lymphatic nodes (lymphoma).
- Lymphoproliferative disorders (excessive growth of white blood cells).

Not known: frequency cannot be estimated from the available data
- Increased number of certain white blood cells.
- Nosebleed.
- Proteins in urine.
- Feeling of weakness.
- Bone damage in the jaw (secondary to excessive growth of white blood cells).
- Tissue destruction at injection site

Subcutaneous application of methotrexate is locally well tolerated. Only mild local skin reactions (such as burning sensations, erythema, swelling, discolouration, severe itching, pain) were observed, decreasing during therapy.

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 Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Methotrexate PEN
Keep out of the sight and reach of children.
Do not store above 25 °C.
Keep the pre-filled pen in the outer carton in order to protect from light.
Do not use after the expiry date stated on the packaging. The expiry date refers to the last day of that month.

Medicines should not be disposed via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. The measures will help to protect the environment.

If your pre-filled pen shows any signs of deterioration, consult your doctor or pharmacist who will tell you what to do.

6. Contents of the pack and other information
What Methotrexate PEN contains
- The active substance is methotrexate.

1 pre-filled pen with 0.15 ml solution contains 7.5 mg methotrexate.
1 pre-filled pen with 0.2 ml solution contains 10 mg methotrexate.
1 pre-filled pen with 0.25 ml solution contains 12.5 mg methotrexate.
1 pre-filled pen with 0.3 ml solution contains 15 mg methotrexate.

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

What Methotrexate PEN looks like and contents of the pack
Pre-filled pen containing a clear, yellow-brown solution in pre-filled colourless glass syringe with a plunger stopper of rubber and embedded injection needle. The syringe is externally equipped with the device for self-administration.

Methotrexate PEN is available in pack of 1 pre-filled pen.
Alcohol pads included in the package.

Manufacturer and product licence holder
Manufactured by medac Gesellschaft für klinische Spezialpräparate mbH, Theaterstr. 6, 22880 Wedel, Germany.
Procured from the EU by product licence holder Star Pharmaceuticals Ltd, 5 Sandridge Close, Harrow, Middlesex HA1 1XD. Repackaged by Servipharm Ltd.

POM

Methotrexate 7.5 mg solution for injection in pre-filled pen
PL 20636/2643
Methotrexate 10 mg solution for injection in pre-filled pen
PL 20636/2644
Methotrexate 12.5 mg solution for injection in pre-filled pen
PL 20636/2645
Methotrexate 15 mg solution for injection in pre-filled pen
PL 20636/2646

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Call 020 8423 2111 to obtain the leaflet in a format suitable for you.