PACKAGE LEAFLET: INFORMATION FOR THE USER

Methofill 50mg/ml solution for injection in pre-filled syringe
methotrexate

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Methofill is and what it is used for

Methofill contains methotrexate as active substance

Methotrexate is a substance with following properties:
- it interferes with the growth of certain cells in the body that reproduce quickly
- it reduces the activity of the immune system (the body's own defence mechanism)
- it has anti-inflammatory effects

Methofill 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,
- severe recalcitrant disabling psoriasis, which is not adequately responsive to other forms of therapy such as phototherapy, PUVA, and retinoids, and severe psoriatic arthritis in adult patients.
- 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.

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

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

Methofill 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 Methofill

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

Warnings and precautions
Talk to your doctor or pharmacist or nurse before taking Methofill 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).

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.

Special precautionary measures for treatment with Methofill
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 Methofill 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 alterations of the mucosa
- Blood tests
- Check of liver function

- Check of kidney function
- Check of respiratory system and if necessary lung function test

Methotrexate may affect your immune system and vaccination results. It may also affect the result of immunological tests. Inactive, chronic infections (e.g. herpes zoster [shingles], tuberculosis, hepatitis B or C) may flare up. During therapy with Methofill 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 therapy must then be stopped.

Diarrhoea can be a toxic effect of Methofill and requires an interruption of therapy. If you suffer from diarrhoea please speak to your doctor.

Encephalopathy (a brain disorder)/leukoencephalopathy (a special disorder of the white brain substance) have been reported in cancer patients receiving methotrexate therapy and cannot be excluded for methotrexate therapy in other disease.

Other medicines and Methofill
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

The effect of the treatment may be affected if Methofill is administered at the same time as certain other drugs:

- Medicines harming the liver or the blood count, e.g. leflunomide
- Antibiotics (medicines to prevent/fight certain infections) such as: tetracyclines, chloramphenicol, and non-absorbable broad-spectrum antibiotics, penicillines, glycopeptides, sulphonamides (sulphur containing medicines that prevent/fight certain infections), ciprofloxacin and cefalotin
- Non-steroidal anti-inflammatory drugs or salicylates (medicines against pain and/or inflammation)
- Probenecid (medicine against gout)
- Weak organic acids like loop diuretics (“water tablets”) or some medicines used for treatment of pain and inflammatory diseases (e.g. acetylsalicylic acid, diclofenac and ibuprofen) and pyrazole (e.g. metamizol for treating pain)
- Medicinal products, which may have adverse effects on the bone marrow, e.g. trimethoprim-sulphamethoxazole (an antibiotic) and pyrimethamine
- Sulphasalazine (antirheumatic medicine)
- Azathioprine (an immunosuppressive agent sometimes used in severe forms of rheumatoid arthritis)
- Mercaptopurine (a cytostatic agent)
- Retinoids (medicine against psoriasis and other dermatological diseases)
- Theophylline (medicine against bronchial asthma and other lung diseases)
- Proton-pump inhibitors (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.

Methofill 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 Methofill.

Pregnancy, breast-feeding and fertility

Pregnancy

Do not use Methofill 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. a 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.

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.

Breast-feeding has to be stopped prior to and during treatment with Methofill.

Driving and using machines

Treatment with Methofill may cause adverse reactions affecting the central nervous system, e.g. 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 you should not drive or use machines.

Methofill contains sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially "sodium-free".

3. How to use Methofill

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

Methofill 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.

Important warning about the dose of Methofill (methotrexate):

Use Methofill **only once a week** for the treatment of Rheumatoid arthritis, Juvenile arthritis, Psoriatic arthritis, Psoriasis, Crohn's disease. Using too much of Methofill (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.

Use in children and adolescents
The doctor decides on the appropriate dose in children and adolescents with polyarthritic forms of juvenile idiopathic arthritis.

Methofill is not recommended in children less than 3 years of age due to insufficient experience in this age group.

Method and duration of administration
Methofill 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 Methofill is a long-term treatment.

At the start of your treatment, Methofill may be injected by medical staff. However, your doctor may decide that you can learn how to inject Methofill yourself. You will receive appropriate training for you to do this. Under no circumstances should you attempt to inject yourself, unless you have been trained to do so.
Please refer to the instructions for use at the end of the leaflet.

Please note that all of the contents have to be used.

The manner of handling and disposal must be consistent with that of other cytostatic preparations in accordance with local requirements. Pregnant health care personnel should not handle and/or administer Methofill .

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

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

If you stop using Methofill
If you stop using Methofill , talk to your doctor immediately.

If you have the impression that the effect of Methofill is too strong or too weak, you should 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 - may affect up to 1 in 10 people]
- **spitting or coughing blood**
- **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 - may affect up to 1 in 100 people], inflammation of the liver (acute hepatitis) [rare - may affect up to 1 in 1,000 people] and liver failure [very rare - may affect up to 1 in 10,000 people]
- **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 - may affect up to 1 in 1,000 people]
- **symptoms of kidney damage such as swelling of the hands, ankles or feet or changes in frequency of urination (oliguria) or decrease or absence of urine (anuria);** these may be signs of kidney failure [rare - may affect up to 1 in 1,000 people]
- **symptoms of infections, e.g. fever, chills, achiness, sore throat;** methotrexate can make you more susceptible to infections. Rarely [may affect up to 1 in 1,000 people] severe infections like a certain type of pneumonia (*Pneumocystis carinii pneumonia*) or blood poisoning (sepsis) may occur
- **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 - may affect up to 1 in 1,000 people]
- **fever and serious deterioration of your general condition, or sudden fever accompanied by a sore throat or mouth, or urinary problems**; methotrexate can very rarely [may affect up to 1 in 10,000 people] cause a sharp fall in certain white blood cells (agranulocytosis) and severe bone marrow suppression
- **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 - may affect up to 1 in 10,000 people]
- **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 - may affect up to 1 in 10,000 people]
- 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-frequency cannot be estimated from the available data]
- **severe skin rash or blistering of the skin (this can also affect your mouth, eyes and genitals)**; these may be signs of the very rare [may affect up to 1 in 10,000 people] conditions called

Stevens Johnson syndrome or burned skin syndrome (toxic epidermal necrolysis/Lyell's syndrome)

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 (pulmonaryfibrosis, 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 / having less sensitivity to stimulation than normal, 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.
- Bleeding from the lungs
- Bone damage in the jaw (secondary to excessive growth of white blood cells)
- Tissue destruction at injection site
- Redness and shedding of skin
- Swelling

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 Methofill

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

Store below 30 °C.
Keep the pre-filled syringes in the outer carton in order to protect from light.

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

Do not use Methofill if you notice sign of colour change or contain visible particles.

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

6. Contents of the pack and other information

What Methofill contains

- The active substance is methotrexate. 1 ml of solution contains methotrexate disodium corresponding to 50 mg methotrexate.

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

What Methofill looks like and contents of the pack

Methofill pre-filled syringes contain a clear, yellow to brown solution. Pre-filled syringes prefixed with needle safety guard. Package containing pre-filled syringe (s), with or without blister and alcohol swab. The blister packs are for individual syringes with prefixed needle safety guard.

The following pack sizes are available:

- For 0.15 mL, 0.20 mL, 0.30 mL and 0.40 mL: packs containing 1, 2, 4, 5, 6, 8, 10, 12 and 24 prefilled syringe(s) with fixed needle covered with rigid needle shield. Further pre-filled syringes prefixed with needle safety guard.

- For 0.25 mL, 0.35 mL, 0.45 mL, 0.55 mL and 0.60 mL: packs containing 1, 4, 5, 6, 8 and 12 prefilled syringe(s) with fixed needle covered with rigid needle shield. Further pre-filled syringes prefixed with needle safety guard.

- For 0.50 mL: packs containing 1, 2, 4, 5, 6, 8, 10 and 12 prefilled syringe(s) with fixed needle covered with rigid needle shield. Further pre-filled syringes prefixed with needle safety guard.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

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

Manufacturer:
Accord Healthcare Limited,
Sage House, 319 Pinner Road,
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United Kingdom

Wessling Hungary Kft.,
Anonymus u. 6., Budapest, 1045, Hungary

Accord Healthcare Polska Sp.z o.o.,
ul. Lutomierska 50,95-200 Pabianice, Poland

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

Country	**Proposed Name**
Sweden	Injexate 50 mg/mL injektionsvätska, lösning i förfylld spruta
Austria	Injexate 50 mg/mL Injektionslösung in einer Fertigspritze
Belgium	Methofill 50 mg/ml oplossing voor injectie in een voorgevulde spuit

Bulgaria	Injexate 50 mg/mL solution for injection in pre-filled syringe
Cyprus	Injexate 50 mg/mL ενέσιμο διάλυμα σε προγεμισμένη σύριγγα
Czech Republic	INJEXATE 50 MG/ML injekční roztok v předplněné injekční stříkačce
Denmark	Injexate
Germany	Methofill 50 mg/ml Injektionslösung in einer Fertigspritze
Finland	Injexate 50 mg/mL injektioneste, liuos esitäytetyssä ruiskussa
France	INJEXATE 50 mg/mL, Soluzione iniettabile in siringa preriempita
Hungary	METHOFILL 50 mg/ml oldatos injekció előretöltött fecskendőben
Ireland	Methofill 50 mg/mL solution for injection in pre-filled syringe
Italy	Metother
Lithuanian	Metother 50 mg/mL injekcinis tirpalas užpildytame švirkšte
The Netherlands	Injexate 7.5 mg = 0.15 ml/10 mg = 0.20 ml/ 12.5 mg = 0.25 ml/15 mg = 0.30 ml/17.5 mg = 0.35 ml/20 mg = 0.40 ml/22.5 mg = 0.45 ml/25 mg = 0.50 ml/27.5 mg = 0.55 ml/30 mg = 0.60 ml oplossing voor injectie in voorgevulde spuit
Norway	Methofill
Poland	Methofill
Slovak Republic	Injexate 50 mg/ml injekčný roztok naplnený v injekčnej striekačke
United Kingdom	Methofill 7.5 mg/10 mg/12.5 mg/15 mg/17.5 mg/20 mg/22.5 mg/25 mg/27.5 mg/30 mg solution for injection in pre-filled syringe

This leaflet was last revised in 12/2020

Instructions for use

Carefully read the instructions below before starting your injection, and always use the injection technique advised by your doctor, pharmacist or nurse.

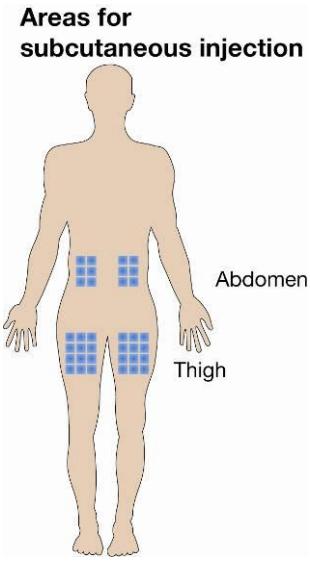
For any problem or question, contact your doctor, pharmacist or nurse.

Preparation
Select a clean, well-lit and flat working surface.
Collect necessary items before you begin:

- 1 Methofill pre-filled syringe with needle safety guard

Wash your hands carefully. Before use, check the Methofill syringe for visual defects (or cracks).

Injection site



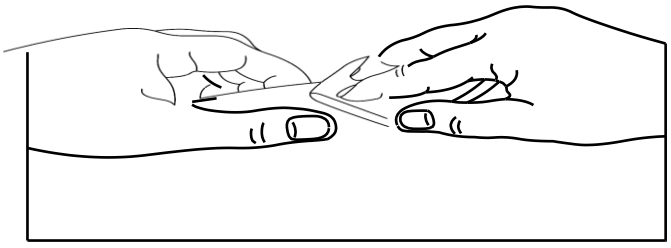
The best sites for injection are:
- upper thighs,
- abdomen except around the navel.

- If someone is helping you with the injection, he/she may also give the injection into the back of your arms, just below the shoulder.
- Change the injection site with each injection. This may reduce the risk of developing irritations at the injection site.
- Never inject into skin that is tender, bruised, red, hard, scarred or where you have stretch marks. If you have psoriasis, you should try not to inject directly into any raised, thick, red or scaly skin patches or lesions

Injecting the solution

1. Unpack the methotrexate pre-filled syringe with prefixed needle safety guard and read the package leaflet carefully. Remove the pre-filled syringe with prefixed needle safety guard from the packaging at room temperature.

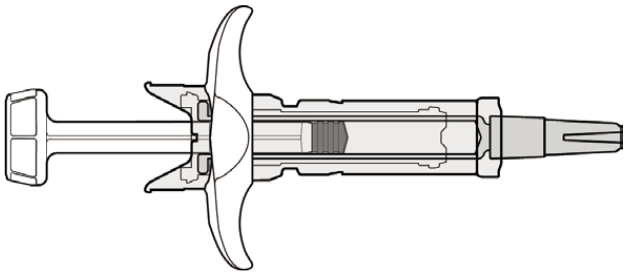
2. Disinfection



Choose an injection site and disinfect it with a alcohol swab. Allow at least 60 seconds for the disinfectant to dry.

3. Ensure the system is intact/ not damaged

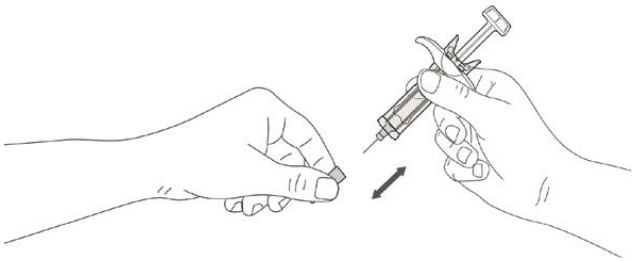
Do not use the product:
- If you see any damage (syringe or needle safety guard breakage) or lose components;



- If the needle safety guard is on safety position before use as shown on picture 7 because this indicate system already operated.

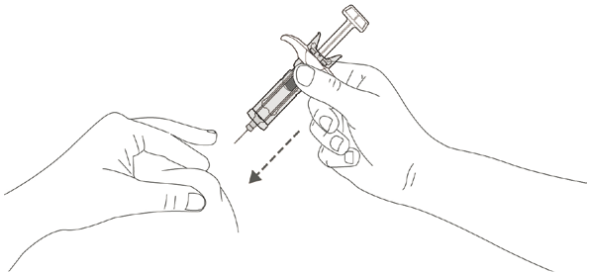
In general the product should not be used if it does not conform to the figure on the left side.
If so discard the product in a biohazard (sharps) container

4. Remove the protective cap



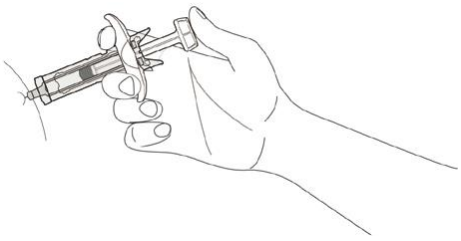
- Hold the body of the needle safety guard in one hand with the needle end pointing away from you and without touching the plunge rod;
- Pull the needle cap straight off with your other hand;
- After removal, throw away the needles cap in a biohazard (sharps) container.

5. Insert the Needle



- Lightly pinch the skin at the injection site with one hand;
- With the other hand insert the needle into the injection site without touching the plunger rod head (with 90 degree angle).

6. Injection



- Place the thumb on the plunger rod head;
- Depress the plunger rod and **push firmly** at the end of the injection to ensure that syringe emptying is completed. Hold the skin securely until the injection is completed.

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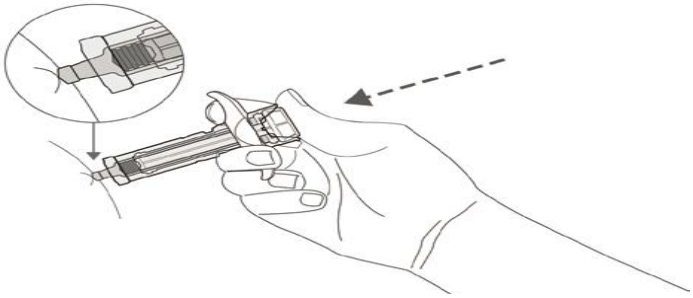
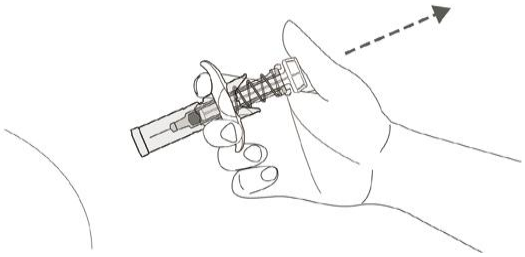
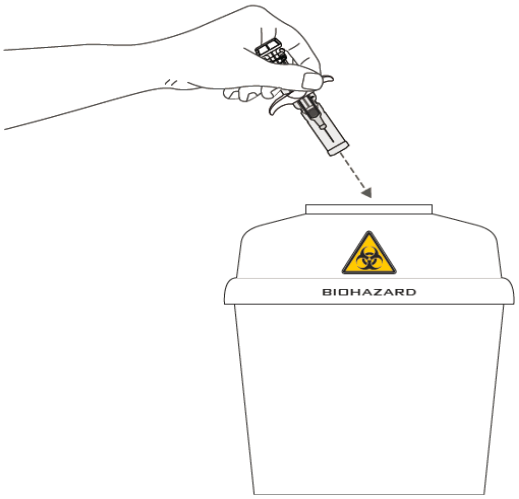


7. Needle stick protection



The safety system will activate once the plunger rod is fully depressed:
- Keep the syringe still and slowly lift your thumb off of the plunger rod head;
- The plunger rod will move up with your thumb and the spring retracts the needle from the site, into the Needle safety guard.

8. Discard the Needle safety guard



Once the syringe has been used, immediately discard the needle safety guard into biohazard (sharp) containers. **Do not throw away the used needle safety guard syringe in a household trash.**

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 or someone around you is injured by the needle, consult your doctor immediately and do not use this pre-filled syringe.

Disposal and other handling
The manner of handling and throwing away of the medicine and pre-filled syringe must be in consistent with that of other cytostatic preparations in accordance with local requirements. Pregnant healthcare personnel should not handle and/or administer Methofill.