PATIENT PACKAGE INSERT IN ACCORDANCE WITH
THE PHARMACISTS' REGULATIONS (PREPARATIONS) – 1986

The medicine is dispensed with a doctor's prescription only.

Enbrel® 25 mg solution for injection

Enbrel® 50 mg solution for injection

Ready-to-use solution for subcutaneous injection

Composition:

Active ingredient and its quantity:

Enbrel® 25 mg solution for injection: etanercept 25 mg/0.5 ml

Enbrel® 50 mg solution for injection: etanercept 50 mg/ml

Inactive ingredients and allergens – see section 2 under "Important information about some of this medicine's ingredients" and section 6 "Further Information".

Read this leaflet carefully in its entirety before using the medicine. This leaflet contains concise information about the medicine. If you have further questions, contact the doctor or the pharmacist.

This medicine has been prescribed for the treatment of your ailment. Do not pass it on to others. It may harm them even if it seems to you that their ailment is similar.

In addition to the leaflet, Enbrel® 25 mg solution for injection and Enbrel® 50 mg solution for injection also have a patient safety information card. This card contains important safety information that you need to know and follow before you start treatment and during treatment with Enbrel® 25 mg solution for injection and Enbrel® 50 mg solution for injection. Review the patient safety information card and patient information leaflet before you start using this medicine. Keep the card for additional review, if required.

1. WHAT IS THE MEDICINE INTENDED FOR?

Enbrel® is intended for the treatment of adults for the following indications:

- Active **rheumatoid arthritis** in adults for whom treatment with disease modifying anti-rheumatic drugs (DMARDS), including methotrexate, has been inadequate; Enbrel® can be used in combination with methotrexate in patients who do not respond adequately to treatment with methotrexate alone.
- Active and progressive **psoriatic arthritis** in adults for whom treatment with disease modifying anti-rheumatic drugs (DMARDS) has been inadequate.
- **Axial spondyloarthritis:**
  - Active and severe **non radiographic axial spondyloarthritis** in adults who do not respond adequately to treatment with non-steroidal anti-inflammatory drugs.
  - Severe and active **ankylosing spondylitis** in adults who do not respond adequately to other standard treatment.
- Moderate or severe **plaque psoriasis** in adults who are candidates for systemic therapy or phototherapy.

Enbrel® is intended for the treatment of children and adolescents for the following indications:

- **Juvenile idiopathic arthritis:**
  - Polyarthritis [rheumatoid factor positive or negative] and extended oligoarthritis in children and adolescents from the age of 2 years who have had an inadequate response to treatment with methotrexate or cannot receive methotrexate.
  - Psoriatic arthritis in children and adolescents from the age of 12 years who have had an inadequate response to treatment with methotrexate or cannot receive methotrexate.
  - Enthesitis related arthritis in children and adolescents from the age of 12 years who had an inadequate response to treatment or cannot receive any other standard treatment.
- Severe chronic **pediatric plaque psoriasis** in children and adolescents from the age of 6 years who had an inadequate response to or cannot receive systemic therapy or phototherapy

Therapeutic group: TNF antagonist and selective immunosuppressant

2. BEFORE USING THE MEDICINE

Do not use the medicine if:

- You/the child are sensitive (allergic) to the active ingredient etanercept or to any of the other ingredients contained in the medicine.

  If you/the child experience an allergic reaction such as chest tightness, wheezing, dizziness or rash, do not continue injecting Enbrel®, and contact the doctor immediately.
- You/the child have or are at risk of developing a serious blood infection called sepsis.
- You/the child have an infection of any kind.

Special warnings regarding use of the medicine:

- **Women of childbearing age: use contraception during the course of treatment with Enbrel® and during three weeks following completion of treatment with Enbrel®. See additional information in the "Pregnancy and breastfeeding" section.**
- **Contact the doctor immediately if** you/the child experience an allergic reaction such as chest tightness, wheezing, dizziness or rash. In such a case, do not continue injecting Enbrel®.
- **Tell the doctor if** you/the child develop a new infection, or are due to undergo surgery during the course of treatment with Enbrel®. The doctor may want to monitor you/the child during the treatment with Enbrel®.
- **Tell the doctor if** you/the child have a history of recurrent infections, or if you/the child suffer from diabetes or another condition that may increase the risk of infection.

- **Contact the doctor immediately if** you/the child recently traveled abroad and you/the child develop symptoms of an infection such as fever, chills or cough. The doctor may decide to continue monitoring infections after completion of treatment with Enbrel®.
- **Before commencing treatment with Enbrel®**, the doctor will check for symptoms and signs of tuberculosis, since cases of tuberculosis have been reported in patients treated with Enbrel®. The evaluation for tuberculosis may include review of the medical history, a chest X-ray and a Mantoux test.
  Tell the doctor if you/the child are suffering or have suffered from tuberculosis or if you or the child were in contact with someone who has or had tuberculosis.
  Contact the doctor immediately if symptoms of tuberculosis (such as persistent cough, weight loss, tiredness and moderate fever), or symptoms of any other infection occur during or after completion of treatment with Enbrel®.
- **Contact the doctor immediately if** symptoms such as persistent fever, sore throat, tendency to subcutaneous hematomas, bleeding or pallor occur. These symptoms may indicate life-threatening blood disorders requiring discontinuation of treatment with Enbrel®.
- **Tell the doctor if** you/the child have hepatitis B or if you/the child had hepatitis B in the past.
  Before commencing treatment with Enbrel®, the doctor will check for the presence of viral hepatitis B.

  Treatment with Enbrel® may result in recurrence of the disease in patients previously infected with the hepatitis B virus. In case of disease recurrence, stop the treatment with Enbrel®.
- **Tell the doctor if** you/the child suffer from viral hepatitis C. The doctor may monitor the treatment with Enbrel® in case the infection worsens.
- **Tell the doctor if** you/the child suffer from multiple sclerosis, inflammation of the optic nerve or inflammation of the spinal cord, so it could be determined whether treatment with Enbrel® is appropriate for you.
- **Tell the doctor if** you/the child have a history of congestive heart failure, as caution must be exercised in such case.
- **Tell the doctor if** you/the child were exposed to chickenpox during the course of treatment with Enbrel®. The doctor will determine if there is a need for prophylactic treatment.
- **Before commencing treatment with Enbrel®, tell the doctor if** the user or the person injecting the medicine has a known hypersensitivity (allergy) to latex, since the needle cap of the syringe is made of latex (dry natural rubber).
- **Tell the doctor if** you/the child have a history of alcohol addiction. Do not use Enbrel® to treat alcoholic hepatitis.
- **Tell the doctor if** you/the child suffer from Wegener's granulomatosis, an inflammation of the blood vessels, since Enbrel® is not recommended for treatment of this rare disease.
- **Tell the doctor if** you/the child suffer from diabetes and/or are taking medicines to treat diabetes. The doctor will consider whether there is a need to adjust the dosages of medicines for diabetes during the course of treatment with Enbrel®.

- **Before commencing treatment with Enbrel®, tell the doctor if** you/the child have cancer (e.g., lymphoma) or if you/the child have a history of cancer. Enbrel® may increase the risk of developing cancer.
  Patients suffering from severe rheumatoid arthritis for a long period may be at increased risk of developing lymphoma.

  Children and adults treated with Enbrel® may have an increased risk of developing lymphoma or any another cancer.

  Several children and adolescents who were treated with Enbrel® or with any other medicine that works in a way similar to Enbrel® developed cancer, including unusual cancer types, which sometimes resulted in death.

  There have been some case reports in which patients receiving Enbrel® developed different types of skin cancer. Therefore, you should be closely monitored by the attending doctor and have periodic skin tests performed. **Contact the doctor immediately** if you notice any changes in your/the child's skin.

Children and adolescents:

- It is recommended that children be vaccinated before commencing treatment with Enbrel®. **Tell the doctor if** you/the child are due to receive a vaccine. Do not give certain vaccines (such as an oral polio vaccine) during the course of treatment with Enbrel®.

Drug interactions

If you/the child are taking, or have recently taken, other medicines, including non-prescription medicines and nutritional supplements, tell the doctor or the pharmacist. Especially if you/the child are taking:

- **Sulfasalazine** intended for the treatment of inflammatory bowel diseases and rheumatoid arthritis.
- **Abatacept** intended for the treatment of rheumatoid arthritis.
- **Anakinra** intended for the treatment of rheumatoid arthritis.

Do not use preparations containing the active ingredients **anakinra or abatacept** during the course of treatment with Enbrel®.

Use of the medicine, food and beverage

Enbrel® can be used regardless of food and beverages.

Pregnancy and breastfeeding

Enbrel® should be used during pregnancy only if clearly needed. Women of childbearing age should use contraception during the course of treatment with Enbrel® and for three weeks after completing the treatment.

You should consult your doctor if you are pregnant, think you may be pregnant, or are planning to get pregnant.

If Enbrel® was used during pregnancy, the baby may be at a higher risk of infection. In addition, one study found more birth defects when the mother had received

Enbrel® during pregnancy, compared with mothers who had not received Enbrel® or similar medicines (TNF antagonists), but there was no report of a particular kind of birth defect.

Another study found no increased risk of birth defects when the mother had received Enbrel® during pregnancy. Your doctor will help you decide whether the benefits of treatment outweigh the potential risk to your baby.

Before vaccinating the baby, it is important to inform the doctor and the medical staff treating the baby that Enbrel® was used during pregnancy (further information is provided in the "Special warnings regarding use of the medicine – children and adolescents" section).

Do not breastfeed during the treatment with Enbrel®, since Enbrel® passes into breast milk.

Driving and using machines

Enbrel® is not expected to affect the ability to drive or use machines.

Important information about some of this medicine's ingredients

Enbrel® contains sodium.
This medicine contains less than 1 millimole sodium (23 mg) per each dosage unit, that is to say, essentially sodium free.

3. HOW SHOULD YOU USE THE MEDICINE?

Enbrel® is administered as a subcutaneous injection. Do not swallow.

Always use the preparation according to the doctor's instructions. Check with the doctor or pharmacist if you are uncertain regarding the dosage and treatment regimen of the preparation.

The dosage and treatment regimen will be determined by the doctor only.

The doctor will determine the duration of treatment and if further treatment is needed, in accordance with the response.

If no improvement is seen after 12 weeks of treatment with Enbrel®, the doctor may decide to stop the treatment.

Do not exceed the recommended dose.

Manner of use:

Detailed instructions for preparing and injecting – see section **"Instructions for preparing and injecting". It is recommended to keep a follow up diary to remember on which day(s) of the week you should inject Enbrel®.**

If a higher dosage was accidentally injected, contact a doctor immediately. If a child has accidentally swallowed the medicine, immediately contact a doctor or proceed to a hospital emergency room and bring the medicine package with you.

If you forget to inject the Enbrel® dose at the scheduled time, inject a dose as soon as you remember (if the next scheduled dose is supposed to be given on the

next day, skip the missed dose). Then continue to inject the medicine on the usual days. If you did not remember to inject the dose until the day on which the next dose is supposed to be given, do not inject a double dose to compensate for the missing dose.

Persist with the treatment as recommended by the doctor.

If you stop using the medicine, the symptoms of the disease may return. Consult the doctor or pharmacist regarding treatment discontinuation.

Do not take medicines in the dark! Check the label and the dose <u>each time</u> you take a medicine. Wear glasses if you need them.

If you have further questions regarding use of the medicine, consult the doctor or pharmacist.

4. SIDE EFFECTS

As with any medicine, use of Enbrel® may cause side effects in some users. Do not be alarmed when reading the list of side effects. You/the child may not suffer from any of them.

Stop using the medicine and immediately contact the doctor or seek medical assistance if you/the child experience any of the following symptoms of **severe allergy:**

- Difficulty swallowing or breathing.
- Swelling of the face, neck, hands or feet.
- Nervousness or anxiety, rapid heartbeats, sudden redness of the skin and/or sensation of warmth.
- Severe rash, severe itch or severe hives (urticaria): an effect characterized by red or pale, raised and itchy skin lesions.

Contact the doctor <u>immediately</u> if you/the child experience any of the following severe symptoms indicating rare side effects which may sometimes be fatal:

- Signs of **serious infections**, such as high fever that can be accompanied by cough, shortness of breath, chills, weakness, or a hot, red, tender, painful area on the skin or joints.
- Signs of **blood disorders**, such as bleeding, tendency to subcutaneous hematomas or pallor.
- Signs of **nerve disorders**, such as numbness or sensation of paresthesia, changes in vision, eye pain, or onset of weakness in an arm or leg.
- Signs of **heart failure or heart failure worsening**, such as fatigue or shortness of breath during activity, swelling in the ankles, a feeling of fullness in the neck or abdomen, night-time shortness of breath or cough, bluish color of the nails or the lips.
- Signs of **cancer**: Cancer can affect any part of the body including the skin and blood, and possible signs will depend on the type and location of the cancer. These signs may include weight loss, fever, swelling (with or without pain), persistent cough, presence of lumps or growths on the skin.

- Signs of **autoimmune reactions** (where antibodies may harm normal tissues in the body) such as pain, stinging, weakness, abnormal breathing, abnormal thinking, abnormal sensation, or abnormal vision.
- Signs of **lupus or lupus-like syndrome**, such as weight changes, persistent rash, fever, joint or muscle pain, or fatigue.
- Signs of **inflammation of the blood vessels**, such as pain, fever, redness or warmth of the skin, or itching.

Additional side effects

Very common side effects (may occur in more than 1 in 10 people):

- Infections (including cold, sinusitis, bronchitis, urinary tract infections, skin infections)
- Injection site reactions (including bleeding, subcutaneous hematomas, redness, itching, pain or swelling). These effects are usually common at the beginning of treatment, and their frequency usually declines after about one month. Some patients have developed a reaction at the injection site after injecting at a site recently used for injection.
- Headache.

Common side effects (may occur in up to 1 in 10 people):

- Allergic reactions
- Fever
- Rash
- Itching
- Antibodies directed against normal tissues.

Uncommon side effects (may occur in up to 1 in 100 people):

- Serious infections (including pneumonia, infections in deep skin tissues, joint infections, blood infection, and infections at various areas)
- Worsening of congestive heart failure
- Low red blood cell count
- Low white blood cell count
- Low neutrophil (a type of white blood cell) count
- Low blood platelet count
- Skin cancer - other than melanoma
- Localized swelling of the skin (angioedema)
- Hives (urticaria), an effect characterized by elevated red or pale, and itchy skin lesions
- Eye inflammation
- New onset or worsening of psoriasis
- Inflammation of the blood vessels affecting multiple organs
- Elevated liver function blood tests (in patients also receiving methotrexate treatment, the frequency of elevated liver function blood tests is common)
- Abdominal cramps and pain, diarrhea, weight loss or blood in stool (signs indicating bowel problems).

Rare side effects (may occur in up to 1 in 1,000 people):

- Serious allergic reactions (including severe localized swelling of the skin and wheezing)
- Lymphoma (a type of blood cancer)
- Leukemia (a cancer affecting the blood and bone marrow)
- Melanoma (a type of skin cancer)
- Combined low platelet, white blood cell and red blood cell count
- Nervous system disorders (accompanied by severe muscle weakness and symptoms and signs similar to those of multiple sclerosis or of inflammation of the optic nerve or spinal cord)
- Tuberculosis
- Onset of congestive heart failure
- Seizures
- Lupus or lupus-like syndrome (symptoms such as persistent rash, fever, joint pain and tiredness)
- Skin rash, which may lead to severe blistering and peeling of the skin
- Lichenoid reaction (itchy reddish-purple rash and/or white-gray threadlike lines on mucous membranes)
- Inflammation of the liver caused by the body's own immune system (autoimmune hepatitis; in patients also receiving methotrexate treatment, the side effect is uncommon)
- Immune system disorders that may affect the lungs, skin and lymph nodes (sarcoidosis)
- Inflammation or scarring of the lungs (in patients also receiving methotrexate treatment, the side effect of inflammation or scarring of the lungs is uncommon).

Very rare side effects (may occur in up to 1 in 10,000 people):

- Failure of the bone marrow to produce essential blood cells.

Side effects of unknown frequency:

- Merkel cell carcinoma, a type of skin cancer
- Kaposi's sarcoma (a rare cancer related to infection with human herpesvirus 8. Kaposi's sarcoma most commonly appears as purple lesions on the skin)
- Increased activity of white blood cells associated with inflammation (macrophage activation syndrome)
- Recurrence of hepatitis B
- Worsening of a condition called dermatomyositis (muscle inflammation and weakness accompanied by skin rash).

Additional side effects in children and adolescents

Side effects and their frequencies observed in children and adolescents are similar to those described above.

If a side effect has appeared, if one of the side effects gets worse, or when you suffer from a side effect that has not been mentioned in the leaflet, you should consult the doctor.

Side effects can be reported to the Ministry of Health by clicking on the link "Report Side Effects of Drug Treatment" found on the Ministry of Health homepage (www.health.gov.il) that directs you to the online form for reporting side effects, or by entering the link: https://sideeffects.health.gov.il

5. HOW SHOULD THE MEDICINE BE STORED?

- **Avoid poisoning!** This medicine and any other medicine must be kept in a closed place out of the reach and sight of children and/or infants in order to avoid poisoning. Do not induce vomiting unless explicitly instructed to do so by the doctor.
- Do not use the medicine after the expiry date (exp. date) that appears on the carton package and the syringe. The expiry date refers to the last day of that month.
- **Storage conditions:** Store refrigerated 2°C-8°C (this temperature range is predominant in most household refrigerators). **Do not freeze.** Store in the original package to protect from light. Wait 15-30 minutes to allow the solution to reach room temperature after taking the syringe out from the refrigerator. It is recommended to use immediately afterwards. Do not heat the medicine!
- The preparation can be stored outside of the refrigerator, at a temperature up to a maximum of 25°C for a single period of up to 4 weeks (no later than the expiry date). Do not refrigerate again after this period. If the preparation was not used within 4 weeks of taking it out of the refrigerator, discard it and do not use it.
  It is advisable to write down the date on which you started storing the preparation outside of the refrigerator, and the date after which you should no longer use the preparation (no later than 4 weeks from the date you took it out of the refrigerator).
- Check the solution before use. The solution should be clear or slightly opalescent, colorless to slightly yellowish or light brown and may contain small white or almost transparent particles of protein. Do not use the solution if its color differs from that described above, if the solution is cloudy, or if it contains particles other than those described above. If you are not sure regarding the appearance of the solution, consult with the pharmacist.

6. FURTHER INFORMATION

- **In addition to the active ingredient, the medicine also contains:**
  Sucrose, sodium chloride, L-Arginine hydrochloride, sodium phosphate monobasic dihydrate, sodium phosphate dibasic dihydrate, water for injections.
- **What does the medicine look like and what is the content of the package**
  - **Enbrel® 25 mg solution for injection:**
    Each syringe contains 0.5 ml clear and colorless to slightly yellowish or light brown solution. Each package contains a tray with 4 syringes and 4 alcohol swabs.

- **Enbrel® 50 mg solution for injection:**

  Each syringe contains 1 ml clear and colorless to slightly yellowish or light brown solution. Each package contains a tray with 4 syringes and 4 alcohol swabs.

- **License holder's name and address:**
  Pfizer Pharmaceuticals Israel Ltd., 9 Shenkar St., Herzliya Pituach 46725.

- Registration number of the medicine in the National Drug Registry of the Ministry of Health:
  Enbrel® 25 mg solution for injection: 142-52-31949
  Enbrel® 50 mg solution for injection: 142-53-31950

Instructions for preparing and injecting
Injecting Enbrel® solution for injection
using a pre-filled syringe

These instructions are divided into the following subsections:
Step 1: Preparing for an injection
Step 2: Choosing an injection area
Step 3: Injecting the Enbrel® solution – ready-to-use solution for injection
Step 4: Disposing of the equipment

Introduction

The instructions below explain how to prepare and inject Enbrel® ready-to-use solution for injection.
Please read the instructions carefully, and follow them by the order they appear.
Your doctor or nurse will instruct you regarding the self-injection technique or how to inject to your child.
Do not attempt to inject the medicine until you are sure that you understand how to prepare and inject the dose.
Do not mix Enbrel® solution with other medicines.

Step 1: Preparing for injection

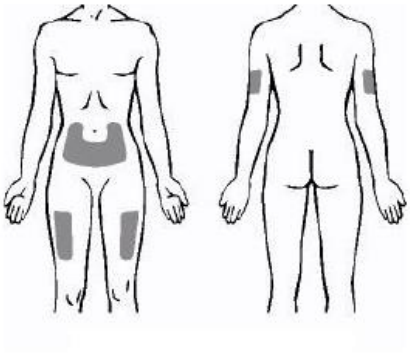
1. Select a flat, clean and well-lit working surface.
2. Take the package containing the syringes out of the refrigerator and place it on the flat working surface. Pull the paper cover from one of the top corners of the tray and remove one syringe and one alcohol swab and place them on the working surface. Do not shake the syringe containing the solution (hereinafter "the syringe"). Fold the paper cover back over the syringes and place the package containing the remaining syringes back into the refrigerator.
   See section 5 "How should the medicine be stored?" regarding the method of storage of Enbrel® ready-to-use solution for injection. If you have any questions about the storage of the medicine, contact your doctor, nurse, or pharmacist for further instructions.
3. **Wait for 15 to 30 minutes to allow the solution in the syringe to reach room temperature. Do not remove** the needle cover while waiting.
   Waiting until the solution reaches room temperature will make the injection more comfortable for you.
   Do not warm Enbrel® ready-to-use solution for injection in any other way (for example, in a microwave or in hot water).
4. Gather the additional supplies required for injection.
   The additional items are an alcohol swab and a cotton ball or gauze.
5. Wash your hands with soap and warm water.
6. Before use, inspect the solution. It should be clear or slightly opalescent, colorless to slightly yellowish or light brown, and may contain small white or almost transparent particles of protein.
   Do not use the solution if its color differs from that described above, if it is cloudy, or if it contains particles other than those described above. If you are not sure regarding the appearance of the solution, consult the pharmacist.

Step 2: Choosing an injection area

1. The three recommended injection areas for Enbrel® ready-to-use solution for injection are: (a) the front of the middle thighs; (b) the abdomen, except for the 5

cm area right around the navel; (c) the outer area of the upper arms (see Diagram 1).
If you are self-injecting Enbrel® ready-to-use solution for injection, you should not choose the outer area of the upper arms as an injection site.

Diagram 1

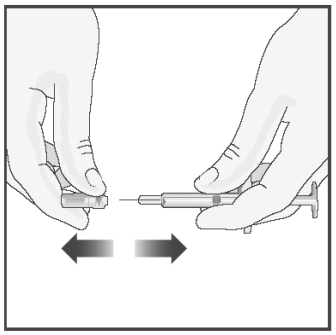


2. A different injection area should be used for each new dose. Make sure that the dose is injected at least 3 cm away from the previous injection site.
   Do not inject into a site where the skin is tender, bruised, red or hard. Avoid injecting the dose into sites with scars or stretch marks (keeping notes of the previous injection sites may be helpful).
3. If you or your child have psoriasis, do not try to inject directly into an affected area, such as raised, thick, red, or cracked skin (psoriasis skin lesions).

Step 3: Injecting the Enbrel® solution – ready-to-use solution for injection

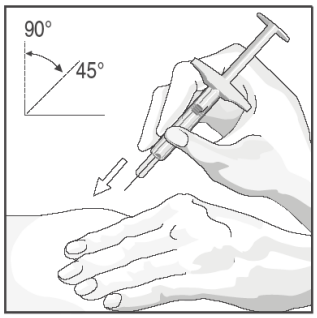
1. Wipe the injection area with the alcohol swab by circular motion. **Do not touch** this area after disinfection and before the injection.
2. Pick up the syringe from the flat working surface. Remove the needle cover by pulling it firmly straight off the needle (see Diagram 2).
   Be careful not to bend or twist the cover during removal to avoid damage to the needle.
   After removing the needle cover, there may be a drop of liquid at the end of the needle; this is normal. Do not touch the needle or allow it to touch any surface. Do not touch the plunger of the syringe. Doing so may cause the liquid to leak out.

Diagram 2



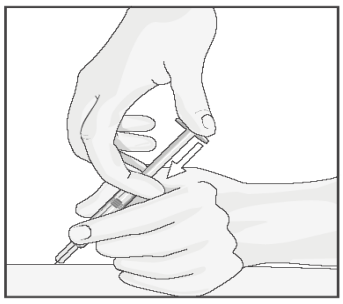
3. When the clean injection area has dried, pinch and hold it with one hand. With the other hand, hold the syringe like a pencil.
4. With a quick, short motion, push the needle into the skin at an angle between 45° and 90° (see Diagram 3).
   With experience, you will find the angle that is most comfortable for you or your child.
   Be careful not to push the needle into the skin too slowly, or with great force.

Diagram 3



5. When the needle is completely inserted into the skin, release the skin that you are holding. With your free hand, hold the syringe near its base to stabilize it. Then push the plunger to inject all of the solution at a **slow**, steady rate (see Diagram 4).

Diagram 4



6. When the syringe is empty, pull the needle out of the skin, being careful to keep it at the same angle as inserted.
   There may be mild bleeding at the injection area. You can press a cotton ball or gauze over the injection area for 10 seconds. Do not rub the injection site. If needed, you may use an adhesive bandage.

Step 4: Disposing of the equipment

The syringe is intended for single use.
Do not re-use the syringe and the needle.
Do not cover the needle following injection.
Dispose of the needle and syringe as instructed by your doctor, nurse or pharmacist.

If you have any questions, please contact a doctor, nurse or pharmacist who are well familiar with Enbrel® ready-to-use solution for injection.

Revised in 07/2021 according to MOH guidelines.