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

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

Enbrel®

Powder and solvent for solution for subcutaneous injection

Composition:
Each vial with powder contains:
Etanercept 25 mg.
Inactive ingredients and allergens - see "Further Information" section in the leaflet.

Read this leaflet carefully in its entirety before using the medicine. This leaflet contains concise information about the medicine. If you have further questions, refer to the doctor or pharmacist. This medicine has been prescribed to treat you, do not pass it on to others. It may harm them even if it seems to you that their medical condition is similar.

1. WHAT IS THIS MEDICINE INTENDED FOR?

Enbrel® is intended to treat rheumatoid arthritis in adults, polyarticular juvenile idiopathic arthritis in children and adolescents from two years of age, psoriatic arthritis in adults, severe ankylosing spondylitis in aduts and to treat moderate to severe plaque psoriasis in adults and severe plaque psoriasis in children and adolescents from the age of six.

Therapeutic group: immunosuppressant.

2. BEFORE USING THE MEDICINE

☒ Do not use the medicine if:

- You/the child are sensitive (allergic) to the active ingredient etanercept or any of the other ingredients contained in the medicine.
- You/the child experience an allergic reaction such as chest tightness, wheezing, dizziness or rash; do not continue injecting Enbrel®, and refer to the doctor immediately.
- You/the child have or are at risk of a serious blood infection called sepsis.
- You/the child have an infection of any kind.

Special warnings regarding use of the medicine:

- **Women of child-bearing age: use contraception during the course of treatment with Enbrel® and during the three weeks following completion of treatment with Enbrel®. See additional information in the "Pregnancy and breastfeeding" subsection.**
- **Refer to 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 inject more 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 course of 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 increases the risk of infection.
- **Refer to 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 to monitor the infection 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 taking Enbrel®. The evaluation for tuberculosis may include a detailed 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.
- **Refer to the doctor immediately if** you develop symptoms of tuberculosis (such as persistent cough, weight loss, listlessness, mild fever), or symptoms of any other infection during or after completion of treatment with Enbrel®.
- **Refer to the doctor immediately if** symptoms such as persistent fever, sore throat, tendency to bruise under the skin, bleeding or paleness occur. These symptoms may indicate a life-threatening blood disturbance that requires termination 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 hepatitis B infection.
  Treatment with Enbrel® may result in reactivation of the disease in patients previously infected with the hepatitis B virus. If the disease recurs, stop treatment with Enbrel®.
- **Tell the doctor if** you/the child suffer from hepatitis C. The doctor may monitor the treatment with Enbrel® if 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 he will be able to determine if 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 a case.
- **Tell your doctor if** you/the child are exposed to chickenpox during the course of treatment with Enbrel®. The doctor will determine if there is a need for prophylactic treatment.
- **Tell the doctor if** you/the child have a history of alcohol addiction. Do not use Enbrel® to treat hepatic alcoholism.
- **Tell the doctor if** you/the child are suffering from Wegner 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 decide whether there is a need to adjust the dosages of the 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 have a history of cancer. Enbrel® may increase the risk of developing cancer.
  Patients suffering from severe rheumatoid arthritis, who have had the disease for a long time, may be at increased risk of developing lymphoma.
  Children and adolescents treated with Enbrel® may have an increased risk of developing lymphoma or another cancer.
  Some children and adolescents who were treated with Enbrel® or any other medicine that works in a similar way as Enbrel® developed cancer, including unusual types, which sometimes resulted in death.
  There have been some 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. **Refer to 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 any vaccines . Do not give certain vaccines (such as oral polio vaccine) during the course of treatment with Enbrel®.
- **Tell the doctor if** the child suffers from abdominal cramps and pain, diarrhea, weight loss or blood in the stools. Cases of inflammatory bowel disorder have been reported among children with idiopathic arthritis under treatment with Enbrel®.

❗ If you/the child are taking, or have recently taken, other medicines, including non-prescription medicines and nutritional supplements, tell the doctor or pharmacist. It is particularly important to inform the doctor or pharmacist if you/or 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 **anakinra or abatacept** during the course of treatment with Enbrel®.

❗ Use of the medicine and food and beverage
Enbrel® can be used without regard to food or beverages.

❗ Pregnancy and breastfeeding
It is recommended not to become pregnant during the course of treatment with Enbrel®, as there is no information regarding the effects of Enbrel® during pregnancy.
Therefore, women of child-bearing age must use contraception during the course of treatment with Enbrel® and for three weeks after completing the treatment.
Consult a doctor if you become pregnant.
If Enbrel® was used during pregnancy, the baby may be at increased risk of infection.
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 relating to use of this medicine – children and adolescents" subsection).
Do not breastfeed during the course of treatment with Enbrel®, since Enbrel® passes into breast milk.

❗ Driving and use of machinery
Enbrel® is not expected to affect your ability to drive or operate machinery.

3. HOW SHOULD YOU USE THE MEDICINE?

Enbrel® is administered subcutaneously after being prepared. Do not swallow.
Always use according to the doctor's instructions. Check with the doctor or pharmacist if you are uncertain.
The dosage and treatment regimen will be determined by the doctor only. The usual dosage is generally:

For adults above the age of 18:
Rheumatoid arthritis, psoriatic arthritis in adults or ankylosing spondylitis:
A subcutaneous injection of 25 mg twice a week or 50 mg once a week. Nonetheless, the doctor may decide on a different frequency.

Plaque psoriasis:
A subcutaneous injection of 25 mg twice a week or 50 mg once a week.
Alternatively, a subcutaneous injection of 50 mg twice a week for up to 12 weeks and afterwards, if necessary, 25 mg twice a week or 50 mg once a week.

Children and adolescents:
The dose and the frequency of dosing in children and adolescents depends on their body weight and type of disease.
Polyarticular juvenile idiopathic arthritis in children and adolescents above two years of age:
0.4 mg/kg bodyweight (up to a maximum of 25 mg) twice a week.

Plaque psoriasis in children and adolescents from age 6:
0.8 mg/kg bodyweight (up to a maximum of 50 mg), once a week.
The doctor will determine the duration of treatment and if there is a need for further treatment, 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.
The doctor will show you how to prepare and measure the correct dose.
Do not exceed the recommended dose.

Directions for use:
Detailed instructions on how to prepare and inject - see subsection **"Instructions for preparing and injecting".**
It is recommended to keep a diary to remember which day(s) of the week you should inject Enbrel®.

If a higher dosage was accidentally injected, refer to a doctor immediately. If a child accidentally swallowed the medicine, immediately refer to a doctor or proceed to a hospital emergency room and bring the package of the medicine 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 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 that the next injection is due, do not inject a double dose to make up for a missing dose.

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

Do not take medicines in the dark! Check the label and the dose each time you take 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 treatment and immediately refer to the doctor or to medical assistance if you/the child experience any of the following **severe allergic** symptoms:

- Difficulty swallowing or breathing.
- Swelling of the face, neck, hands or feet.
- Nervousness or anxiety, rapid heart rate, sudden redness of the skin and/or warm sensation.
- Severe rash, severe itch or severe urticaria: an effect characterized by red, raised and itchy patches on the skin.

Refer to the doctor immediately if you/the child experience any of the following severe symptoms which indicate rare side effects that can sometimes be fatal:

- Signs of **serious infections**, such as high fever that may be accompanied by cough, shortness of breath, chills, weakness, or a hot, red, tender, sore area on the skin or joints.
- Signs of **blood disorders**, such as bleeding, tendency for subcutaneous hematomas or paleness.
- Signs of **nerve disorders**, such as numbness or tingling sensation, changes in vision, eye pain, or onset of weakness in an arm or leg.
- Signs of **worsening heart failure**, such as fatigue or shortness of breath with activity, swelling in the ankles, a feeling of fullness in the neck or abdomen, night-time shortness of breath or coughing, 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, itching, weakness, and abnormal breathing, unusual thinking, sensation, or 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:

- Infections (including cold, sinusitis, bronchitis, urinary tract infections and skin infections)
- Injection site reactions (including bleeding, 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 developed an allergy at an injection site that was used before

Occurring frequently

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

Occurring infrequently

- Serious infections (including pneumonia, deep-skin infections, joint infections, blood infection, and infections at various sites)
- Low blood platelet count
- Skin cancer - other than melanoma
- Localized swelling of the skin (angioedema)
- Hives (urticaria) an effect characterized by elevated red and itchy skin patches
- Eye inflammation
- New or worsening psoriasis
- Rash
- Inflammation or scarring of the lungs
- Inflammation of the blood vessels affecting multiple organs

Occurring rarely

- Serious allergic reactions (including severe localized swelling of the skin and wheezing)
- Lymphoma (a type of blood cancer)
- Melanoma (a type of skin cancer)
- Low platelet, white, and red blood cell count
- Nervous system disorders (with severe muscle weakness and symptoms and signs similar to those of multiple sclerosis or of inflammation of the optic nerve or of inflammation of the spinal cord)
- Tuberculosis
- Worsening congestive heart failure
- Seizures
- Lupus or lupus-like syndrome (symptoms such as persistent rash, fever, joint pain, and tiredness)
- Decrease in red blood cell count
- Decrease in white blood cell count
- Low neutrophil (a type of white blood cell) count
- Elevated liver functions
- Skin rash, which may lead to severe blistering and peeling of the skin
- Inflammation of the liver caused by the body's own immune system (autoimmune hepatitis)
- Immune system disorders that can affect the lungs, skin and lymph nodes (sarcoidosis)

Occurring very rarely

- Failure of the bone marrow to produce essential blood cells

Occurring at an unknown frequency

- Leukemia (cancer affecting the blood system and bone marrow)
- Merkel cell carcinoma
- Excessive 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)

If one of the side effects worsens, or if you are suffering from a side effect not mentioned in the leaflet, consult the doctor.

5. HOW SHOULD THE MEDICINE BE STORED?

- **Avoid poisoning!** This medicine and any other medicine must be kept in a safe place out of the reach of children and/or infants 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. 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.
  It is recommended to use immediately after preparing. The solution can be used within 6 hours, if stored below 25°C. Carefully dispose of any Enbrel® solution that was not injected within 6 hours. Do not heat the medicine!
  The preparation can be stored outside of the refrigerator, at a temperature of 25°C±2°C for up to one month (no later than the expiry date). Do not refrigerate again after this time. If the preparation was not used within one month 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 to store the preparation outside of the refrigerator, and the date after which you should no longer use the preparation (no later than one month from the date you took it out of the refrigerator).
- Check the solution before use. The solution should be clear, colorless to slightly yellowish without particles or crystals. Do not use a cloudy solution or a solution that contains particles.

6. FURTHER INFORMATION

In addition to the active ingredient, the medicine also contains:
Mannitol (E421), Sucrose, Trometamol.
The syringe contains:
1 ml sterile water for injection

- **What the medicine looks like and the contents of the package**
  The package contains 4 trays.
  Each tray contains:
  1 vial with white powder that contains the active ingredient, etanercept 25 mg
  1 pre-filled solvent syringe that contains sterile water for injection
  1 needle
  1 vial adapter
  2 alcohol swabs
- **License holder and address:** Pfizer Pharmaceuticals Israel Ltd., 9 Shenkar St., Herzliya Pituach 46725.
- **Manufacturer and address:** Wyeth Pharmaceuticals Ltd., UK.

This leaflet was checked and approved by the Ministry of Health in March 2014.

Registration number of the medicine in the National Drug Registry of the Ministry of Health: 11912 30000 06

INSTRUCTIONS FOR PREPARING AND INJECTING – ENBREL® POWDER AND SOLVENT FOR PREPARING A SOLUTION FOR SUBCUTANEOUS INJECTION

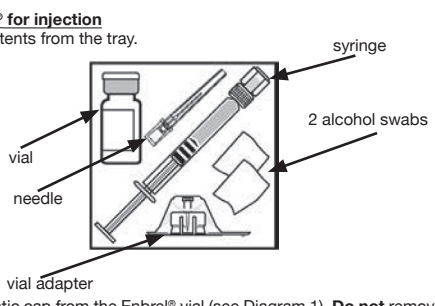
Introduction:
The instructions below explain how to prepare and inject Enbrel®.
Please read the instructions carefully and perform the steps in the order in which they are presented.
Your doctor or nurse will teach you the self-injection technique or how to inject your child.
Do not try to prepare or inject Enbrel® to yourself or your child before you are sure you understood how to mix and inject the dose.
Do not mix this injection in the same syringe or the same vial with other medicines.

Setting up for the injection

- Wash your hands thoroughly.
- Select a clean, well-lit, flat working surface.
- The tray should contain all the items listed below (if not, do not use this tray and consult your pharmacist). Only use these items, **do not use a different syringe**.
  1 vial containing Enbrel®
  1 syringe containing the solvent (water for injection)
  1 needle
  1 vial adapter
  2 alcohol swabs
- Check the expiry dates on both the label of the vial and the syringe. Do not use them after the expiry date, indicated as a month and year.

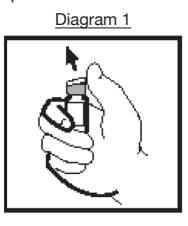
Preparing Enbrel® for injection

- Remove the contents from the tray.



- Remove the plastic cap from the Enbrel® vial (see Diagram 1). **Do not** remove the gray stopper or the aluminum ring around the top of the vial.

Diagram 1



- Use a new alcohol swab to clean the gray stopper on the vial. After cleaning, do not touch the stopper with your hands.
- Place the Enbrel® vial upright on a clean, flat surface, such as a table.
- Remove the paper that covers the vial adapter.
- While the adapter is still in its plastic wrapping, place the vial adapter on the tip of the vial (see Diagram 2).
- Hold the vial with one hand on the flat surface. Using the other hand, **press down firmly** on the package of the vial adapter, until **you feel that the pin of the vial adapter has penetrated the cap of the vial** (see Diagram 3). **Do not** press down at an angle (see Diagram 4). It is very important that the pin of the vial adapter will fully cover the cap of the vial.

Diagram 2

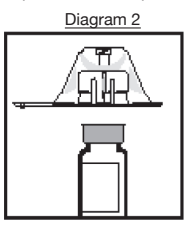
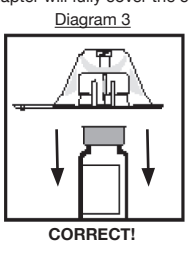
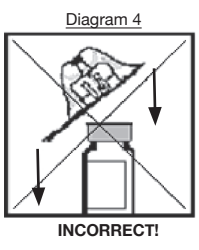


Diagram 3



CORRECT!

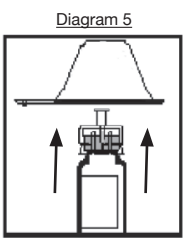
Diagram 4



INCORRECT!

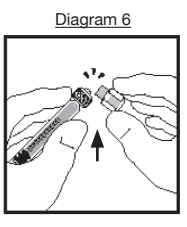
- While still holding the vial with one hand, remove the plastic cover from the vial adapter (see Diagram 5).

Diagram 5



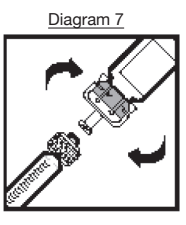
- Remove the white protective cover from the tip of the syringe. To remove the white cover from the tip of the syringe, "break" the perforated region of the cover and take if off the syringe by bending it up and down until it breaks off (see Diagram 6). **Do not remove the white "ring" that remains on the syringe.**

Diagram 6



- Do not use the syringe if the cover was broken to begin with. Start over with a new tray.
- While holding the glass container of the syringe (and not the white ring) with one hand and the vial adapter (not the vial) with the other hand, attach the syringe to the vial adapter on the vial, by inserting the tip of the syringe to the opening and by turning clockwise until completely secured (see Diagram 7).

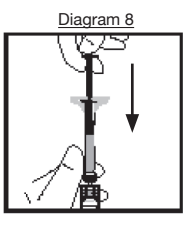
Diagram 7



Adding the solvent

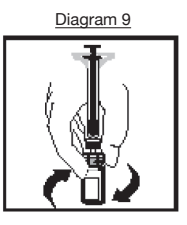
- While holding the vial upright on a flat surface, press the plunger **very slowly** into the syringe until all of the solvent in the syringe is in the vial. In this manner, you will prevent formation of foam (many bubbles) (see Diagram 8).
- When all of the solvent is transferred from the syringe to the Enbrel® vial, the plunger may go back up on its own, due to air pressure. This should not be of concern.

Diagram 8



- Leave the syringe in its place. Gently move the vial a few times in circular motions, until the powder dissolves (see Diagram 9). **Do not shake** the vial. Wait until all the powder dissolves (usually less than 10 minutes). The solution should be clear and colorless, with no lumps, flakes, or particles. Some foam may remain in the vial – this is normal.
- **Do not use** Enbrel® if all the powder in the vial is not dissolved within 10 minutes. Start again with another dose tray.

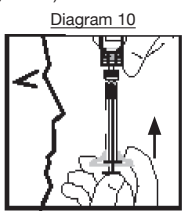
Diagram 9



Withdrawing the Enbrel® solution from the vial

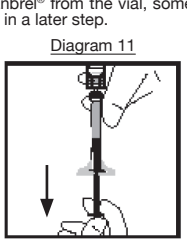
- With the needle still inserted in the vial, hold the vial upside down at eye level. Fully push the plunger into the syringe (see Diagram 10).

Diagram 10



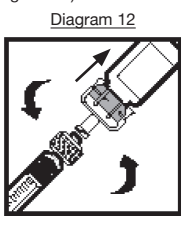
- Then, slowly pull back the plunger to draw the liquid into the syringe (see Diagram 11). For adult patients, draw up the entire volume of liquid. For children, only draw up the volume the doctor has prescribed. After removing Enbrel® from the vial, some air may remain in the syringe. Do not worry; you will remove the air in a later step.

Diagram 11



- With the vial still upside down, release the syringe from the vial adapter that is on the vial, by turning counter-clockwise (see Diagram 12).

Diagram 12

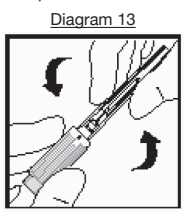


- Place the filled syringe on a clean and flat surface. Be careful not to push the plunger of the syringe downward.
  (note: after completing these steps, a small amount of liquid may remain in the vial. This is normal).

Attaching the needle to the syringe

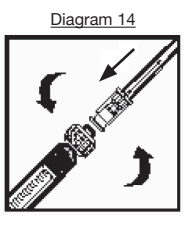
- The needle is provided in a plastic package that keeps it sterile.
- To open the plastic container, hold the short and wide end in one hand and with the other hand, hold the long part of the plastic container.
- To break the seal, bend the long end up and down until is snaps off (see Diagram 13).

Diagram 13



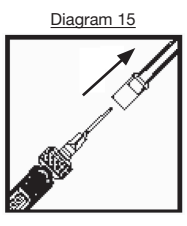
- When the seal has been broken off, remove the short, wide end of the plastic container.
- The needle remains in the long part of the package.
- While holding the container and the needle in one hand, pick up the syringe and insert the tip of the syringe into the opening of the needle.
- Attach the syringe to the needle by turning clockwise, until it is completely closed (see Diagram 14).

Diagram 14



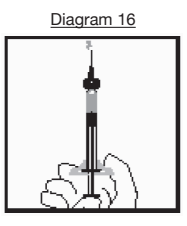
- Carefully remove the needle cover by steadily pulling it straight off of the syringe. Take care not to touch the needle and not to allow the needle to touch any other surface (see Diagram 15). **Take care not to bend or distort the cover while removing it to prevent damaging the needle.**

Diagram 15



- Hold the syringe upright and expel the air bubbles by slowly pushing the plunger until all air is expelled (see Diagram 16).

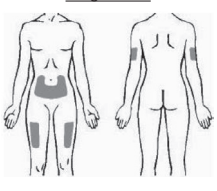
Diagram 16



Choosing an injection site

- The three recommended injection sites for Enbrel® 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 17). If you are injecting Enbrel® to yourself, do not choose the outer area of the upper arms as an injection site.

Diagram 17

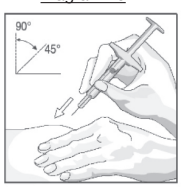


- A different site should be used for each new dose. Make sure that the dose is injectd at least 3 cm from the previous injection site. **Do not** inject into areas where the skin is tender, bruised, red, or hard. Avoid injecting the dose into areas with scars or stretch marks (Keep notes on the location of the previous injections).
- 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).

Preparing the injection site and injecting Enbrel®

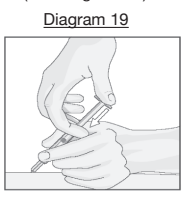
- Wipe the injection site with an alcohol swab, using a circular motion. **Do not** touch this area after the disinfection and before giving the injection.
- When the injection site has dried, pinch and hold it with one hand. With the other hand, hold the syringe like a pencil.
- With a quick and short motion, push the needle into the skin at an angle between 45° and 90° (see Diagram 18). 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 too forcefully.

Diagram 18



- 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. Now, push the plunger to inject all of the solution at a **slow**, steady rate (see Diagram 19).

Diagram 19



- When the syringe is empty, remove the needle from the skin, being careful to keep it at the same angle it was when it was inserted. There may be slight bleeding at the injection site. You can press a cotton ball or a gauze over the injection site for 10 seconds. Do not rub the injection site. A bandage can be used, if necessary.

Disposing the equipment

- Do not reuse a syringe and needle.
  Dispose of the needle and syringe in accordance with the instructions given by the doctor, nurse or pharmacist.

All questions will be addressed by a doctor, nurse or pharmacist familiar with the medicine.