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

This medicine is dispensed with a doctor's prescription only

Enbrel® 50 mg solution for injection

Ready-to-use solution for subcutaneous injection

Active ingredient and its quantity:

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 the entire leaflet carefully before using this medicine. This leaflet contains concise information about this medicine. If you have any further questions, contact your doctor or pharmacist.

This medicine has been prescribed for you/your child. Do not pass it on to others. It may harm them, even if it seems to you that their medical condition is similar to yours.

In addition to the leaflet, the preparation Enbrel 50 mg solution for injection also has a patient safety information card. This card contains important safety information that you need to know and that you should follow before you start treatment and during treatment with Enbrel 50 mg solution for injection. Carefully read the patient safety information card and patient leaflet before you start using this medicine. Keep the card in case you need to read it again.

1. WHAT IS THIS 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 THIS MEDICINE

Do not use this medicine if:

- You/the child are sensitive (allergic) to the active ingredient etanercept or to any of the other ingredients contained in the medicine (listed in section 6).

  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 pen 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 other 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 nonprescription medicines and dietary supplements, tell your doctor or pharmacist. Particularly 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 only be used during pregnancy 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.

Talk to your doctor if you want to breastfeed while on Enbrel treatment. Before vaccinating the baby, it is important to inform the doctor and the medical staff treating the baby that Enbrel was used during pregnancy and breastfeeding.

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 TO USE THIS MEDICINE?

Enbrel is administered as a subcutaneous injection. Do not swallow.
Always use this preparation according to your doctor's instructions. Check with the doctor or pharmacist if you are uncertain about the dosage and treatment regimen of the preparation.

The dosage and treatment regimen will be determined by your 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 injecting – see section **"Instructions for use". 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.

Adhere to 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 dose <u>each time</u> you take medicine. Wear glasses if you need them.

If you have any further questions about using this medicine, consult your doctor or pharmacist.

4. SIDE EFFECTS

As with any medicine, use of Enbrel, may cause side effects in some users. Do not be alarmed by this list of side effects; You/the child may not experience 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)
- Damage to the tiny filters inside your kidneys leading to poor kidney function (glomerulonephritis).

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 you experience any side effect, if any side effect gets worse, or if you experience a side effect not mentioned in this leaflet, consult your doctor.

You can report side effects to the Ministry of Health by following the link "Report Side Effects of Drug Treatment" on the Ministry of Health home page (www.health.gov.il) which links to an online form for reporting side effects or by using the link: https://sideeffects.health.gov.il

5. HOW TO STORE THE MEDICINE?

- **Prevent poisoning!** This and any other medicine should be kept in a closed place, out of the reach and sight of children and/or infants to avoid poisoning. Do not induce vomiting unless explicitly instructed to do so by a doctor.
- Do not use the medicine after the expiry date (exp. date) which is stated on the carton package and the pen. 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 outer package to protect from light. Wait 15-30 minutes to allow the solution to reach room temperature after taking the pen 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, this medicine also contains:**
  Sucrose, sodium chloride, L-Arginine hydrochloride, sodium dihydrogen phosphate dihydrate, disodium phosphate dihydrate, water for injections.

- **What the medicine looks like and contents of the pack**
  Enbrel 50 mg solution for injection in a pre-filled pen (MYCLIC):
  Each pen contains 1 ml clear and colorless to slightly yellowish or light brown solution. Each package contains a tray with 4 pens and 4 alcohol swabs.

- **Registration holder and address:** Pfizer Pharmaceuticals Israel Ltd., 9 Shenkar St., Herzliya Pituach 46725.

- **Registration number of the medicine in the Ministry of Health's National Drug Registry:**
  Enbrel 50 mg solution for injection: 142-53-31950

Instructions for use
Injecting Enbrel solution for injection
using a pre-filled pen (MYCLIC)

Introduction

- The instructions below explain how to use the MYCLIC pen to inject Enbrel.
- Please read the instructions carefully, and follow them step by step.
- Your doctor will tell you how to inject Enbrel. Do not attempt to inject the medicine until you are sure that you understand how to use the MYCLIC pen properly.
- If you have questions about how to inject, please ask your doctor for help.

The MYCLIC pre-filled pen

Before injection

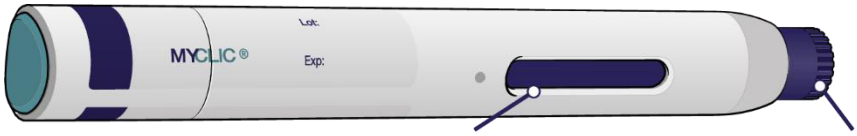
White needle cap

Green activation button

Expiry date

Clear inspection window

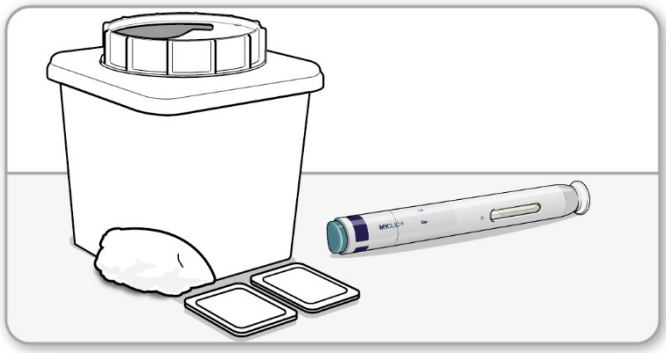
After injection



Filled inspection window

Open end – safety shield

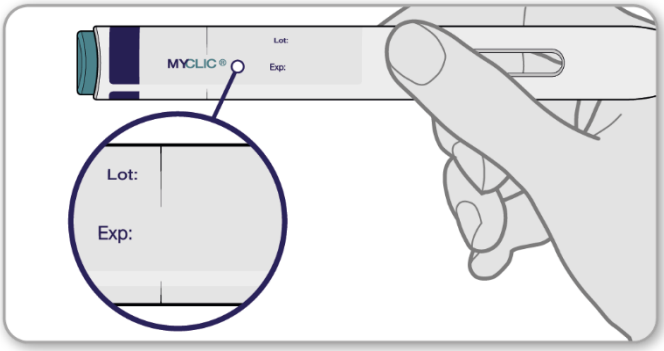
Step 1: Preparing for an Enbrel injection



- **Gather** the following items for each injection on a flat, clean, well-lit surface:
  - One MYCLIC pre-filled pen.
  - One alcohol swab.
  - A suitable sharps container (not included).

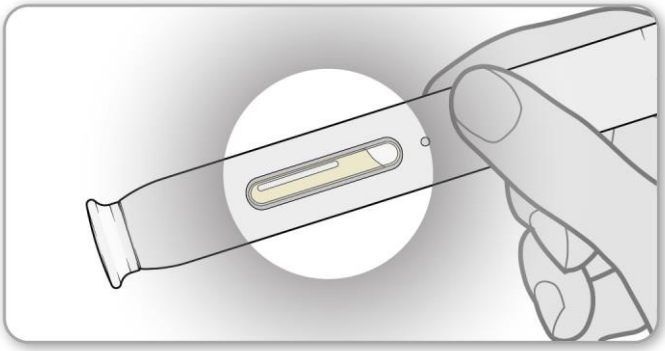
  - Clean cotton balls or gauze pads (not included).
- **Do not** shake the pen.
- **Do not** remove the white cap until instructed to do so.
- For a more comfortable injection, leave your pen at room temperature for 15 to 30 minutes with the white cap in place.
- **Do not** warm the pen in any other way.

Step 2: Checking the label for expiry date and dose



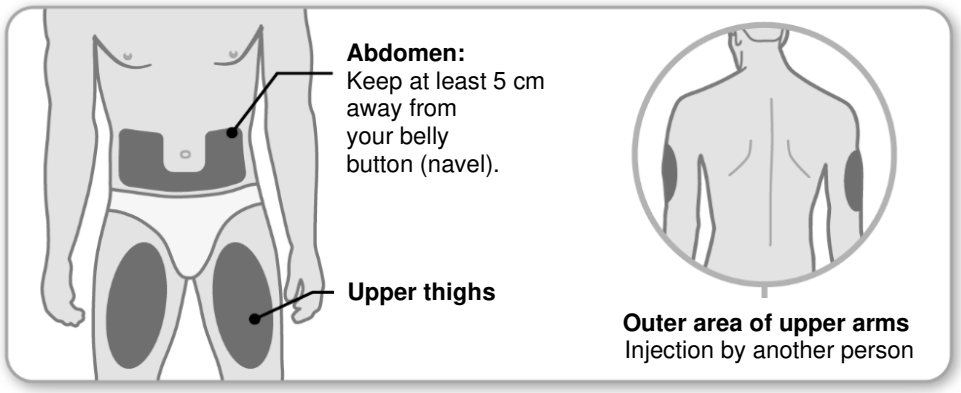
- **Check** the expiry date (month/year) stated on the pen label.
- **Make sure** the correct dose strength is shown on the pen label.
- If the expiry date has passed or it is not your prescribed dose, **do not** use the pen and contact your doctor for assistance.

Step 3: Inspecting the medicine



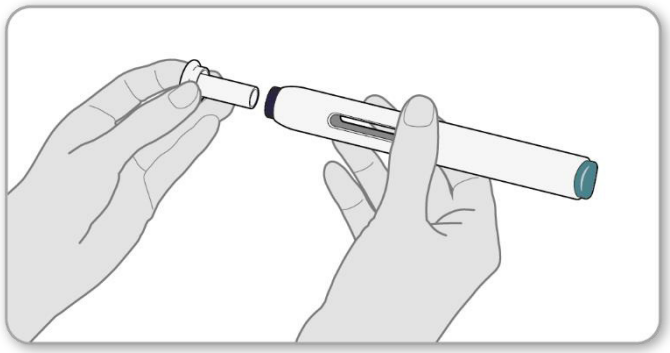
- **Inspect** the medicine in the pen by looking through the clear inspection window. The solution should be clear or slightly opalescent, colourless to pale yellow or pale brown, and may contain small white or almost transparent particles of protein. This appearance is normal for Enbrel.
- **Do not** use the medicine if it is discoloured, cloudy, or if particles other than those described above are present. If you are concerned regarding the appearance of the medicine, contact your doctor for assistance.
- **Note:** You may see an air bubble in the window. This is normal.

Step 4: Choosing and disinfecting the injection site



- **Choose** an injection site in the middle part of the front of the upper thighs or abdominal area 5 cm away from the belly button (navel). The outer area of the back of the upper arms may also be used only if another person is injecting the medicine.
- **Each** injection should be given at least 3 cm from the area where you have recently injected. **Do not** inject into tender, bruised or hard skin. Avoid scars or stretch marks. If you have psoriasis, **do not** inject directly into any raised, thick, red or scaly skin.
- **Clean** the injection site with soap and water, or an alcohol swab if convenient.
- **Allow** the site to dry. **Do not** touch, fan or blow on the cleaned injection site.

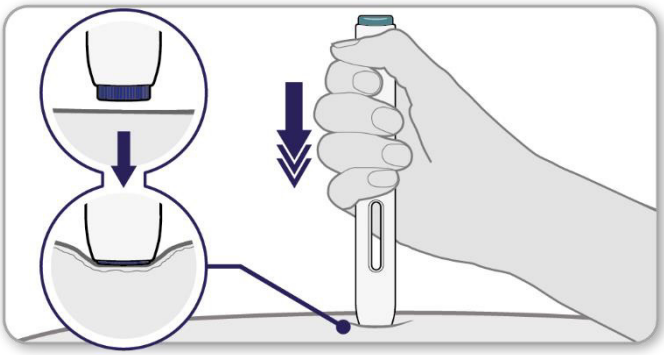
Step 5: Removing the needle cap



- **Remove** the white needle cap by pulling it straight off. **Do not** bend the cap while removing it.
- **Do not** re-attach the cap once it has been removed.
- After removal of the cap, you will see a purple needle safety shield extending slightly from the end of the pen. **Do not** push on the end of the safety shield with the fingers or thumbs.
- **Do not** use the pen if it is dropped with the needle cap off.

Note: You may notice a drop of liquid at the needle tip. This is normal.

Step 6: Pushing the pen firmly against the skin

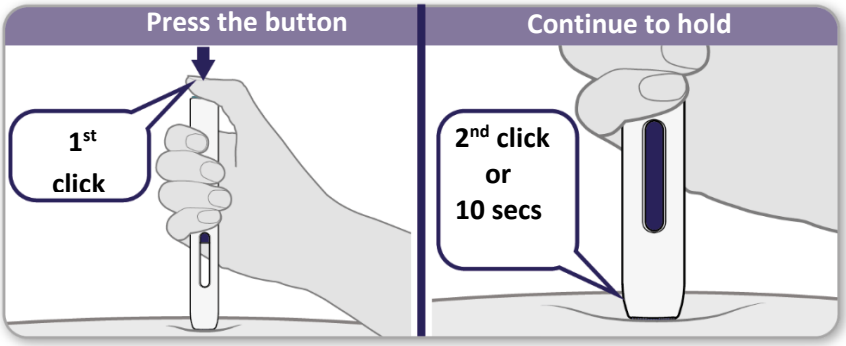


- **Push** the open end of the pen firmly against the skin at 90 degrees so the purple needle safety shield is pushed completely inside the pen.

Note: You will only be able to press the green button when the needle shield is completely pushed inside the pen.

Pinching or stretching the skin before injection may make the injection site firmer, making it easier to press the injection button.

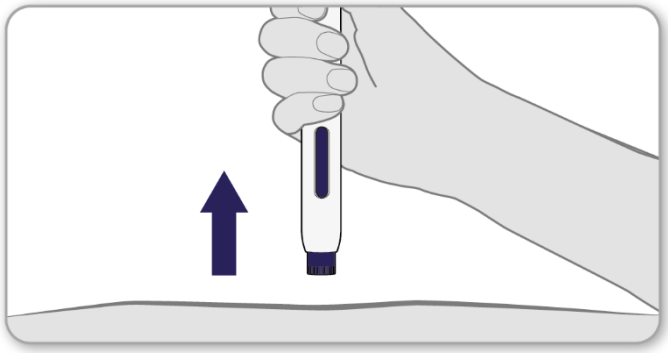
Step 7: Starting the injection



- **Press** the green button all the way down until you hear a **"click".** The click means the start of the injection.
- **Continue to hold** your pen firmly against the skin until you hear a **2nd "click"**, or until 10 seconds after the first click (whichever happens first).

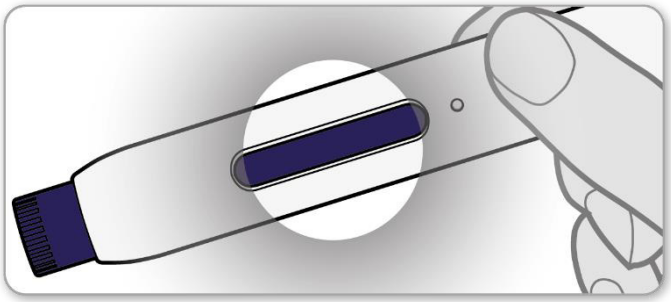
Note: If you are unable to start the injection as described, press the pen more firmly against the skin, then press the green button again.

Step 8: Lifting off the skin



- **Remove** the pen from the skin by lifting it straight off the injection site.
- The purple needle safety shield will automatically extend to cover the needle.

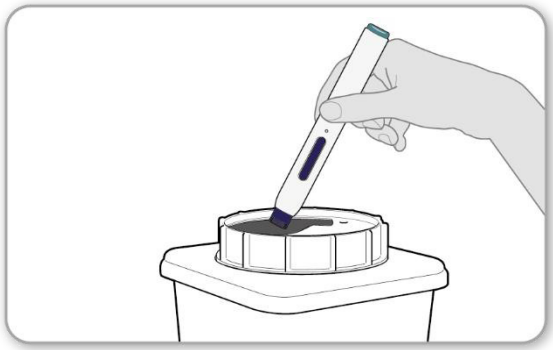
Step 9: Checking the inspection window



- **Check** the pen's inspection window. It should be completely purple.
- If the window is not purple, you may not have received the full dose. Contact your doctor for assistance. **Do not** try to use the pen again. **Do not** try to use another pen.
- If you notice a spot of blood at the injection site, you should press a cotton ball or gauze over the injection site for 10 seconds. **Do not** rub the injection site.

Note: The injection button may stay pressed in. This is normal.

Step 10: Disposing of the equipment



- **Dispose** of the used pen as instructed by your doctor. **Do not** attempt to recap the pen.
- **Do not** press on the end of the needle safety shield. If you have any questions, talk to your doctor.

-End of Instructions for Use-

Revised in 06/2024.