

ANNEX III
PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Enbrel 25 mg powder and solvent for solution for injection Etanercept

Read all (both sides) of this leaflet carefully before you start using this medicine.

- Keep this leaflet. You may need to read it again.
- Your doctor will also give you a Patient Alert Card, which contains important safety information that you need to be aware of before and during treatment with Enbrel.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you or a child in your care. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours or those of the child you are caring for.
- If you are concerned about any side effect, or if you notice any side effects that are not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

Information in this leaflet is organised under the following 7 sections:

1. **What Enbrel is and what it is used for**
2. **Before you use Enbrel**
3. **How to use Enbrel**
4. **Possible side effects**
5. **How to store Enbrel**
6. **Further information**
7. **Instructions for preparing and giving an injection of Enbrel (See overleaf)**

1. WHAT ENBREL IS AND WHAT IT IS USED FOR

Etanercept, the active ingredient in Enbrel, is made from two human proteins. It blocks the activity of another protein in the body that causes inflammation. Etanercept works by reducing the inflammation associated with certain diseases.

In adults (aged 18 and over), Enbrel can be used for moderate or severe **rheumatoid arthritis**, **psoriatic arthritis**, severe **ankylosing spondylitis** and moderate or severe **psoriasis** – in each case usually when other widely used treatments have not worked well enough or are not suitable for you.

For rheumatoid arthritis, Enbrel is usually used in combination with methotrexate, although it may also be used alone if treatment with methotrexate is unsuitable for you. Whether used alone or in combination with methotrexate, Enbrel can slow down the damage to your joints caused by the rheumatoid arthritis, and improve your ability to do normal daily activities.

For psoriatic arthritis patients with multiple joint involvement, Enbrel can improve your ability to do normal daily activities. For patients with multiple symmetrical painful or swollen joints (e.g. hands, wrists and feet), Enbrel can slow down the structural damage to those joints caused by the disease.

In children and adolescents (aged 4-17 years), Enbrel can be used for **juvenile idiopathic arthritis** affecting many joints, when a medicine called methotrexate has not worked well enough or is not suitable for the child.

Enbrel is not effective in the treatment of Wegener's granulomatosis, a rare inflammatory disease. If you or the child in your care have Wegener's granulomatosis talk to your doctor.

2. BEFORE YOU USE ENBREL

Do not use Enbrel

- **Allergy:** If you, or the child you are caring for, are allergic to etanercept or any of the other ingredients of Enbrel. If you or the child experience allergic reactions such as chest tightness, wheezing, dizziness or rash, do not inject more Enbrel, and contact your doctor immediately.
- **Serious blood infection:** If you or the child have, or are at risk of developing a serious blood infection called sepsis. If you are not sure, please contact your doctor.
- **Infections:** If you or the child have an infection of any kind. If you are unsure, please talk to your doctor.

Take special care with Enbrel

- **Infections/surgery:** If you or the child develop a new infection, or are about to have any major surgery, your doctor may wish to monitor the treatment with Enbrel.
- **Infections/diabetes:** Tell your doctor if you or the child have a history of recurrent infections, or suffer from diabetes or other conditions that increase the risk of infection.
- **Infections/monitoring:** Your doctor may decide to continue to monitor you or the child for the presence of infections after you or the child stop using Enbrel.
- **Tuberculosis:** As cases of tuberculosis have been reported in patients treated with Enbrel, your doctor will check for signs and symptoms of tuberculosis before starting Enbrel. This may include a thorough medical history, a chest X-ray and a tuberculin test. The conduct of these tests should be recorded on the Patient Alert Card. It is very important that you tell your doctor if you or the child have ever had tuberculosis, or have been in close contact with someone who has had tuberculosis. If symptoms of tuberculosis (such as persistent cough, weight loss, listlessness, mild fever), or any other infection appear during or after therapy, tell your doctor immediately.
- **Hepatitis B:** Your doctor may decide to test for the presence of hepatitis B infection before you or the child begin treatment with Enbrel.
- **Hepatitis C:** Tell your doctor if you or the child have hepatitis C. Your doctor may wish to monitor the treatment with Enbrel in case the infection worsens.
- **Blood disorders:** Seek medical advice immediately if you or the child have any signs or symptoms such as persistent fever, sore throat, bruising, bleeding or paleness. Such symptoms may point to the existence of potentially life-threatening blood disorders, which may require discontinuation of Enbrel.
- **Nervous system and eye disorders:** Tell your doctor if you or the child have multiple sclerosis, optic neuritis (inflammation of the nerves of the eyes) or transverse myelitis (inflammation of the spinal cord). Your doctor will determine if Enbrel is an appropriate treatment.
- **Congestive heart failure:** Tell your doctor if you or the child have a history of congestive heart failure, because Enbrel needs to be used with caution under these circumstances.
- **Vaccinations:** If possible, children should be up to date with all vaccinations before using Enbrel. Some vaccines, such as oral polio vaccine, should not be given while using Enbrel. Please consult your doctor before you or the child receive any vaccines.
- **Chickenpox:** Tell your doctor if you or the child are exposed to chickenpox when using Enbrel. Your doctor will determine if preventive treatment for chickenpox is appropriate.

Using other medicines

Tell the doctor or pharmacist if you or the child are taking or have recently taken any other medicines, even those not prescribed by the doctor. You or the child should not use Enbrel with medicines that contain the active ingredients anakinra or abatacept.

Taking Enbrel with food and drink

Enbrel can be taken with or without food or drink.

Pregnancy and breast-feeding

The effects of Enbrel in pregnant women are not known, and so the use of Enbrel during pregnancy is not recommended. People using Enbrel should not become pregnant. If the patient becomes pregnant, you should consult the patient's doctor.

People using Enbrel should not breast-feed, since it is not known if Enbrel passes into human breast milk.

Driving and using machines

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

3. HOW TO USE ENBREL

Always use Enbrel exactly as the doctor has told you. You should check with the doctor or pharmacist if you are not sure.

If you feel that the effect of Enbrel is too strong or too weak, talk to your doctor or doctor or pharmacist.

Dosing for adult patients (aged 18 years or over)

Rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis

The usual dose is 25 mg given twice a week or 50 mg once a week as an injection under the skin. However, your doctor may determine an alternative frequency at which to inject Enbrel.

Plaque psoriasis

The usual dose is 25 mg twice a week or 50 mg once a week.

Alternatively, 50 mg may be given twice a week for up to 12 weeks, followed by 25 mg twice a week or 50 mg once a week.

Your doctor will decide how long you should take Enbrel and whether retreatment is needed based on your response. If Enbrel has no effect on your condition after 12 weeks, your doctor may tell you to stop taking this medicine.

Dosing for children and adolescents (aged 4 to 17 years)

The appropriate dose for the child will vary depending on body weight. The doctor will provide detailed directions for preparing and measuring the appropriate dose for the child.

Method and route of administration

Enbrel is administered by an injection under the skin (by subcutaneous injection).

The powder must be dissolved before use. **Detailed instructions on how to prepare and inject Enbrel are provided in section 7, “INSTRUCTIONS FOR PREPARING AND GIVING AN INJECTION OF ENBREL”.** Do not mix the Enbrel solution with any other medicine.

To help you remember, it may be helpful to write in a diary which day(s) of the week Enbrel should be used.

If you use more Enbrel than you should

If you have used more Enbrel than you should (either by injecting too much on a single occasion, or by using it too frequently), talk to a doctor or pharmacist immediately. Always have the outer carton of the medicine with you, even if it is empty.

If you forget to inject Enbrel

If you forget a dose, you should inject it as soon as you remember, unless the next scheduled dose is the next day, in which case you should skip the missed dose. Then continue to inject the medicine on the usual day(s). If you do not remember until the day that the next injection is due, do not take a double dose (two doses on the same day) to make up for a forgotten dose.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Enbrel can cause side effects, although not everybody gets them.

Other side effects that are not listed in this leaflet may occur. If you are concerned about any side effect, or if you notice any side effects that are not listed in this leaflet, please tell your doctor or pharmacist.

Allergic reactions

If any of the following happen, do not inject more Enbrel. Tell your doctor immediately, or go to the casualty department at your nearest hospital.

- Trouble swallowing or breathing.
- Swelling of the face, throat, hands, or feet.
- Feeling nervous or anxious, throbbing sensations, sudden reddening of the skin and/or a warm feeling.
- Severe rash, itching, or hives (elevated patches of red or pale skin that often itch).

Serious allergic reactions are uncommon. However, any of the above symptoms may indicate an allergic reaction to Enbrel, so you should seek immediate medical attention.

Serious side effects

If you notice any of the following, you or the child may need urgent medical attention.

- 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, bruising, or paleness.
- Signs of **nerve disorders**, such as numbness or tingling, 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 colour of the nails or the lips.

These are rare or uncommon side effects, but are serious conditions (some of which may rarely be fatal). If these signs occur, tell your doctor immediately, or visit the casualty department at your nearest hospital.

Other side effects

The side effects and frequencies (likelihood of occurring) listed below are those that have been seen in adult patients. The side effects seen in children and adolescents are similar to those seen in adults.

- **Very common** (may occur in more than 1 in 10 patients): Infections (including colds, sinusitis, bronchitis, urinary tract infections and skin infections); injection site reactions (including bleeding, bruising, redness, itching, pain, and swelling). Reactions at the injection site are very common, but do not occur as often after the first month of treatment. Some patients have developed a reaction at an injection site that was used before.
- **Common** (may occur in less than 1 in 10, but more than 1 in 100 patients): allergic reactions; fever; itching; antibodies directed against normal tissue (autoantibody formation).
- **Uncommon** (may occur in less than 1 in 100, but more than 1 in 1,000 patients): serious infections (including pneumonia, deep skin infections, joint infections, blood infection, and infections at various sites); localized swelling of the skin (angioedema); low blood platelet count; hives (elevated patches of red or pale skin that often itch); psoriasis; rash; inflammation or scarring of the lungs.
- **Rare** (may occur in less than 1 in 1,000 patients): serious allergic reactions (including severe localized swelling of the skin and wheezing); combined low platelet, red, and white blood cell count; nervous system disorders (with signs and symptoms similar to those of multiple sclerosis or inflammation of the nerves of the eyes or spinal cord); tuberculosis; worsening congestive heart failure; seizures; lupus or lupus-like syndrome (symptoms may include persistent rash, fever, joint pain, and tiredness); inflammation of the blood vessels; low red blood cell count, low white blood cell count, low neutrophil (a type of white blood cell) count; elevated liver blood tests; skin rash which may lead to severe blistering and peeling of the skin..
- **Very rare** (may occur in less than 1 in 10,000 patients): failure of the bone marrow to produce crucial blood cells.
- **Not known:** excessive activation of white blood cells associated with inflammation (macrophage activation syndrome).

5. HOW TO STORE ENBREL

Keep out of the reach and sight of children.

Do not use Enbrel after the expiry date (EXP), which is stated on the carton.

Store in a refrigerator (2° – 8°C). Do not freeze.

After preparing the Enbrel solution, immediate use is recommended. However, the solution may be used for up to 6 hours if stored in the refrigerator (2°C – 8°C).

Do not use if you notice the solution is not clear or contains particles. The solution should be clear, colourless or pale yellow, with no lumps or flakes or particles.

Carefully dispose of any Enbrel solution that has not been injected within 6 hours.

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

6. FURTHER INFORMATION

What Enbrel contains

The active substance in Enbrel is etanercept. Each vial of Enbrel 25 mg contains 25 mg of etanercept.

The other ingredients are:

Powder: Mannitol, sucrose and trometamol.

Solvent: Water for injections.

What Enbrel looks like and contents of the pack

Enbrel 25 mg is supplied as a white powder and solvent for solution for injection. Each pack contains 4, 8 or 24 single dose vials, 4, 8 or 24 pre-filled syringes of water for injections, 4, 8 or 24 needles, 4, 8 or 24 vial adaptors and 8, 16 or 48 alcohol swabs. Not all pack sizes may be marketed.

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This leaflet was last approved on {date}

Detailed information on this product is available on the website of the European Medicines Agency (EMA) <http://www.emea.europa.eu>

7. INSTRUCTIONS FOR PREPARING AND GIVING AN INJECTION OF ENBREL

This section is divided into the following sub-sections:

- a. **Introduction**
- b. **Setting up for an injection**
- c. **Preparing the Enbrel dose for injection**
- d. **Adding solvent**
- e. **Withdrawing the Enbrel solution from the vial**
- f. **Placing the needle on the syringe**
- g. **Choosing an injection site**
- h. **Preparing the injection site and injecting the Enbrel solution**
- i. **Disposing of supplies**

a. **Introduction**

The following instructions explain how to prepare and inject Enbrel. Please read the instructions carefully and follow them step by step. You will be instructed by your doctor or his/her assistant on the techniques of self-injection or on giving an injection to a child. Do not attempt to administer an injection until you are sure that you understand how to prepare and give the injection.

This injection should not be mixed with any other medicine.

b. **Setting up for an injection**

- Wash your hands thoroughly.
- Select a clean well-lit, flat working surface.
- The dose tray should contain the items listed below. (If not, don't use the dose tray and consult your pharmacist). Use only the items listed. **DO NOT** use any other syringe.

1 Enbrel vial

1 Pre-filled syringe containing clear, colourless solvent (water for injections)

1 Needle

1 Vial adaptor

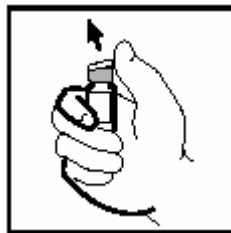
2 Alcohol swabs

- Inspect the expiry dates on both the vial label and the syringe label. They should not be used after the month and year shown.

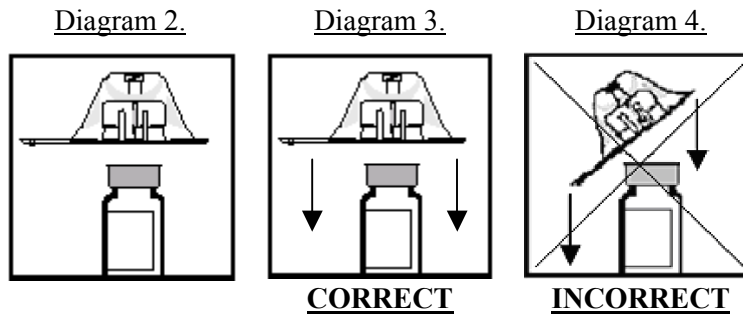
c. **Preparing the Enbrel dose for injection**

- Remove the contents of the tray
- Remove the plastic cap from the Enbrel vial (see Diagram 1). **Do NOT** remove the grey stopper or aluminium ring around the top of the vial.

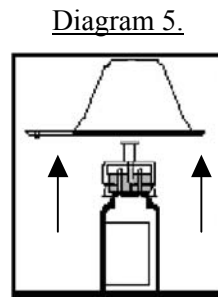
Diagram 1.



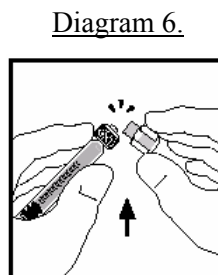
- Use a new alcohol swab to clean the grey stopper on the Enbrel vial. After cleaning, do not touch the stopper with your hands or allow it to touch any surface.
- Place the vial upright on a clean, flat surface.
- Remove the paper backing from the vial adaptor package.
- While still in the plastic package, place the vial adaptor on top of the Enbrel vial so that the vial adaptor spike is centered within the raised circle on top of the vial stopper (see Diagram 2).
- Hold the vial firmly on the flat surface with one hand. With the other hand, push **STRAIGHT DOWN FIRMLY** on the adaptor package until you feel the adaptor spike penetrate the vial stopper and **FEEL AND HEAR THE ADAPTOR RIM LOCK INTO PLACE** (see Diagram 3). **DO NOT** push down the adaptor at an angle (see Diagram 4). It is important that the vial adaptor spike completely penetrates the vial stopper.



- While holding the vial in one hand, remove the plastic packaging from the vial adaptor (see Diagram 5).



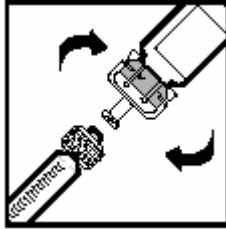
- Remove the protective cover from the syringe tip by breaking the white cap along the perforation. This is done by holding the collar of the white cap while grasping the end of the white cap with the other hand and bending it down and then up until it is broken (see Diagram 6). **DO NOT remove the white collar that remains on the syringe.**



- Do not use the syringe if this perforation is already broken. Start again with another dose tray.

- Holding the glass barrel of the syringe (not the white collar) in one hand, and the vial adaptor (not the vial) in the other, connect the syringe to the vial adaptor by inserting the tip into the opening and turn clockwise until completely secured (see Diagram 7).

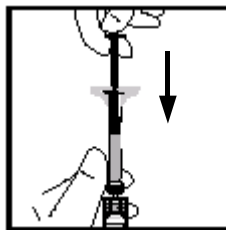
Diagram 7.



d. Adding solvent

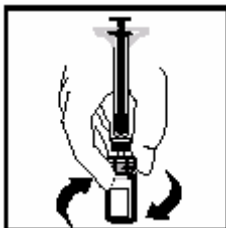
- While holding the vial upright on the flat surface, push the plunger VERY SLOWLY until all the solvent is in the vial. This will help to reduce foaming (lots of bubbles) (see Diagram 8).
- Once the solvent is added to the Enbrel, the plunger may move up by itself. This is due to air pressure and should not be of concern.

Diagram 8.



- With the syringe still attached, gently move the vial in circles a few times, to dissolve the powder (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 colourless, with no lumps, flakes, or particles. Some white 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.

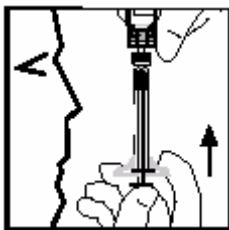
Diagram 9.



e. Withdrawing the Enbrel solution from the vial

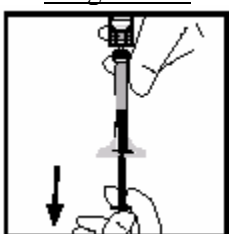
- With the syringe still attached to the vial and vial adaptor, hold the vial upside down at eye level. Push the plunger all the way into the syringe (see Diagram 10).

Diagram 10.



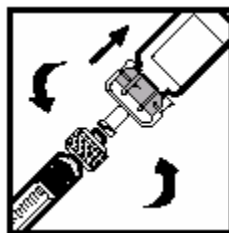
- Then, slowly pull the plunger back to draw the liquid into the syringe (see Diagram 11). For adult patients, withdraw the entire volume. For children, remove only the portion of liquid as directed by your child's doctor. After you have withdrawn the Enbrel from the vial, you may have some air in the syringe. Do not be concerned, as you will remove the air in a later step.

Diagram 11.



- With the vial held upside down, unscrew the syringe from the vial adaptor by turning it anti-clockwise (see Diagram 12).

Diagram 12.



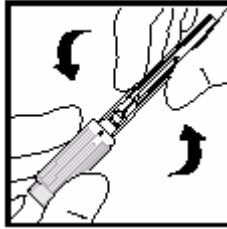
- Place the filled syringe on the clean, flat surface. Make sure that the tip does not touch anything. Be careful not to push down on the plunger.

(Note: After you have completed these steps, a small amount of liquid may remain in the vial. This is normal.)

f. Placing the needle on the syringe

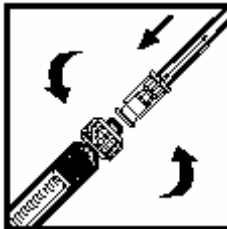
- The needle has been placed in a plastic container to keep it sterile.
- To open the plastic container, hold the short, wide end in one hand. Place your other hand on the longer portion of the container.
- To break the seal, bend the larger end down and then up until broken (see Diagram 13).

Diagram 13.



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

Diagram 14.



- Remove the needle cover by firmly pulling it straight off the syringe taking care not to touch the needle or allow the needle to touch any surfaces (see Diagram 15). Be careful not to bend or twist the cover during removal to avoid damage to the needle.

Diagram 15.



- While holding the syringe upright, remove any air bubbles by slowly pushing on the plunger until the air is removed (see Diagram 16).

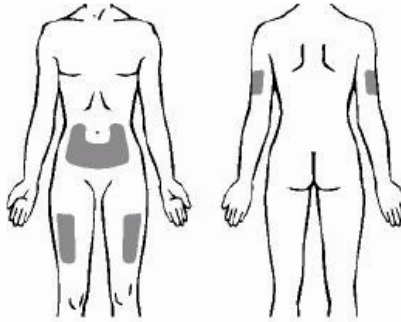
Diagram 16.



g. Choosing an injection site

- The three recommended injection sites for Enbrel include: (1) the front of the middle thighs; (2) the abdomen, except for the 5 cm area right around the navel; and (3) the outer area of the upper arms (see Diagram 17). If you are self injecting, you should not use the outer area of the upper arms.

Diagram 17.

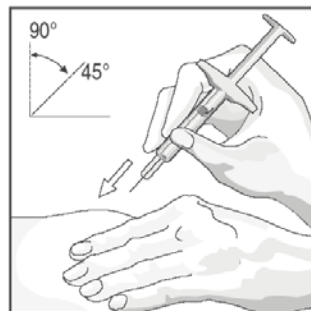


- A different site should be used for each new injection. Each new injection should be given at least 3 cm from an old site. **DO NOT** inject into areas where the skin is tender, bruised, red, or hard. Avoid areas with scars or stretch marks. (It may be helpful to keep notes on the location of the previous injections.)
- If you or the child have psoriasis, you should try not to inject directly into any raised, thick, red, or scaly skin patches (“psoriasis skin lesions”).

h. Preparing the injection site and injecting the Enbrel solution

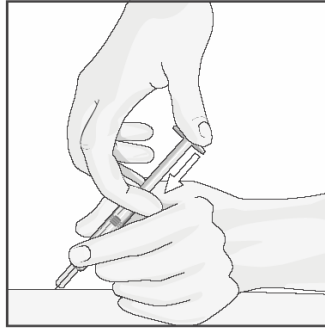
- Wipe the site where Enbrel is to be injected with an alcohol swab, using a circular motion. **DO NOT** touch this area again before giving the injection.
- When the cleaned area of skin has dried, pinch and hold it firmly with one hand. With the other hand, hold the syringe like a pencil.
- With a quick, short motion, push the needle all the way 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 the child. Be careful not to push the needle into the skin too slowly, or with great force.

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 stabilise it. Then 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.
 - Press a cotton ball over the injection site for 10 seconds. Slight bleeding may occur. **Do NOT** rub the injection site. A bandage is optional.
- i. Disposing of supplies**
- The syringe and needles should **NEVER** be re-used. Dispose of the needles and syringe as instructed by your doctor, nurse or pharmacist.

If you have any questions, please talk to a doctor, nurse or pharmacist who is familiar with Enbrel.