

**ANNEX III**  
**PACKAGE LEAFLET**

## PACKAGE LEAFLET: INFORMATION FOR THE USER

### Enbrel 25 mg solution for injection in pre-filled syringe 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.

### **Important information about latex**

Before using Enbrel, contact your doctor if it will be handled by, or given to, someone with an allergy to latex, since the needle cover in the Enbrel pack is made from latex.

## **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 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. This is a single-use syringe for patients weighing 62.5 kg or more. 25 mg vials are available for paediatric use from which doses less than 25 mg can be administered. 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).

**Detailed instructions on how to 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 your 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 taking a syringe from the refrigerator, **the Enbrel solution should be allowed to reach room temperature (15-30 minutes)**. Immediate use is then recommended.

Make sure the solution in the pre-filled syringe is clear, colourless or pale yellow, and practically free from visible particles. Otherwise, do not inject the solution. Use a different Enbrel pre-filled syringe, then contact your pharmacist for assistance.

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 pre-filled syringe contains 0.5 ml of solution, providing 25 mg of etanercept.

The other ingredients are sucrose, sodium chloride, L-arginine hydrochloride, sodium phosphate monobasic dihydrate and sodium phosphate dibasic dihydrate, and water for injections.

### What Enbrel looks like and contents of the pack

Enbrel is supplied as a pre-filled syringe containing a clear, colourless or pale yellow solution for injection. Each pack contains 4, 8 or 24 pre-filled syringes and 8, 16 or 48 alcohol swabs. Not all pack sizes may be marketed.

### Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:

Wyeth Europa Ltd.  
Huntercombe Lane South  
Taplow, Maidenhead  
Berkshire, SL6 0PH  
United Kingdom

Manufacturer:

Wyeth Pharmaceuticals  
New Lane  
Havant  
Hampshire, PO9 2NG  
United Kingdom

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

**België/Belgique/Belgien  
Luxembourg/Luxemburg**

Wyeth Pharmaceuticals S.A./N.V.  
Tél/Tel: +32 10 49 47 11  
Fax: +32 10 49 48 70

**Ireland**

Wyeth Pharmaceuticals  
Tel: + 353 1 449 3500  
Fax: + 353 1 449 3522

**Polska**

Wyeth Sp. z o.o  
Tel: +48 22 457 1000  
Fax: + 48 22 457 1001

**Česká Republika**

Wyeth Whitehall Czech s.r.o.  
Tel: +420 2 67 294 111  
Fax: +420 2 67 294 199

**Ísland**

Icepharma hf.  
Tel:+354 540 8000  
Fax:+354 540 8001

**Portugal**

Wyeth Lederle Portugal (Farma)  
Lda.  
Tel: + 351 21 412 82 00  
Fax: +351 21 412 01 11

**Danmark**

Wyeth Danmark  
Tlf: + 45 44 88 88 05  
Fax: +45 44 88 88 06

**Italia**

Wyeth Lederle S.p.A.  
Tel: + 39 06 927151  
Fax: + 39 06 23325555

**Slovenská Republika**

Wyeth Whitehall Export GmbH  
organizačná zložka  
Tel: 42-1-2-654-128-16  
Fax: 42-1-2-654-128-17

**Deutschland**

Wyeth Pharma GmbH  
Tel: +49 180 2 29 93 84 Fax: +49  
251 204 1128

**Κύπρος**

Wyeth Hellas (Cyprus Branch)  
AEBE  
Τηλ: +357 22 817690  
Φαξ: + 357 22 751855

**Suomi/Finland**

Wyeth  
Puh/Tel: + 358 20 7414 870  
Fax: + 358 20 7414 879

**България/Eesti/Latvija/Lietuva/  
Österreich/România/Slovenija**

Wyeth-Lederle Pharma GmbH  
Tel/Tälr:+43 1 89 1140  
Факс/Faks/Fakss/Faksas/Fax:+43  
1 89 114600

**Magyarország**

Wyeth Kft  
Tel: +36 1 453 33 30  
Fax: +36 1 240 4632

**Sverige**

Wyeth AB  
Tel: + 46 8 470 3200  
Fax: + 46 8 730 0666

**Ελλάδα**

Wyeth Hellas A.E.B.E.  
Τηλ: + 30 2 10 99 81 600  
Φαξ: + 30 2 10 99 21 994

**Malta**

Vivian Corporation Ltd.  
Tel: +35621 344610  
Fax: +35621 341087

**United Kingdom**

Wyeth Pharmaceuticals  
Tel: + 44 845 367 0098  
Fax: + 44 1628 414802

**España**

Wyeth Farma S.A.  
Tel:+ 34 91 334 65 65  
Fax: + 34 91 663 65 53

**Nederland**

Wyeth Pharmaceuticals B.V.  
Tel: + 31 23 567 2567  
Fax: +31 23 567 2599

**France**

Wyeth Pharmaceuticals France  
Tél:+ 33 1 41 02 70 00  
Fax: + 33 1 41 02 70 10

**Norge**

Wyeth  
Tlf:+47 40 00 23 40  
Fax: +47 40 00 23 41

**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:

### Introduction

#### Step 1: Setting up for an injection

#### Step 2: Choosing an injection site

#### Step 3: Injecting the Enbrel solution

#### Step 4: Disposing of supplies

### 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.

#### Step 1: Setting up for an injection

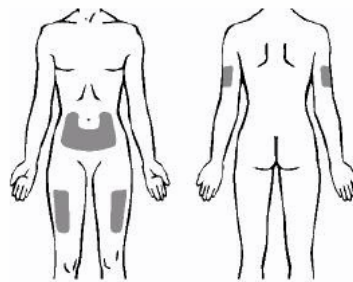
1. Select a clean, well-lit, flat working surface.
2. Take the Enbrel carton containing the pre-filled syringes out of the refrigerator and place it on the flat work surface. Remove one pre-filled syringe and one alcohol swab and place them on the work surface. Do not shake the pre-filled syringe of Enbrel. Place the carton containing any remaining pre-filled syringes back into the refrigerator. Please see [section 5](#) for instructions on how to store Enbrel. If you have any questions about storage, contact your doctor, nurse, or pharmacist for further instructions.
3. **You should allow 15 to 30 minutes for the Enbrel solution in the syringe to reach room temperature. DO NOT** remove the needle cover while allowing it to reach room temperature. Do not warm Enbrel in any other way (for example, do not warm it in a microwave or in hot water).

4. Assemble the additional supplies you will need for your injection. These include an alcohol swab and a cotton ball or gauze.
5. Wash your hands with soap and warm water.
6. Make sure the solution in the pre-filled syringe is clear, colourless or pale yellow, and practically free from visible particles. Otherwise, do not inject the solution. Use a different Enbrel pre-filled syringe, then contact your pharmacist for assistance.

### Step 2: Choosing an injection site

1. The three recommended injection sites for Enbrel using a pre-filled syringe 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 1). If you are self injecting, you should not use the outer area of the upper arms.

Diagram 1.



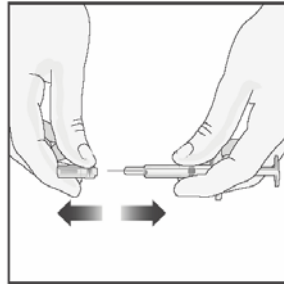
2. A different site should be used for each new injection. Each new injection should be given at least 3 cm from an old site. Do not inject into areas where the skin is tender, bruised, red, or hard. Avoid areas with scars or stretch marks. (It may be helpful to keep notes on the location of the previous injections.)
3. 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”).

### Step 3: Injecting the Enbrel solution

1. 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.
2. Pick up the pre-filled syringe from the flat work surface. Remove the needle cover by firmly pulling it straight off the syringe (see Diagram 2). **Be careful not to bend or twist the cover during removal to avoid damage to the needle.**

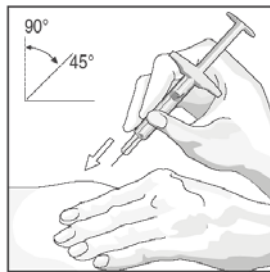
When you remove the needle cover, there may be a drop of liquid at the end of the needle; this is normal. Do not touch the needle or allow it to touch any surface. Do not touch or bump the plunger. Doing so could cause the liquid to leak out.

Diagram 2.



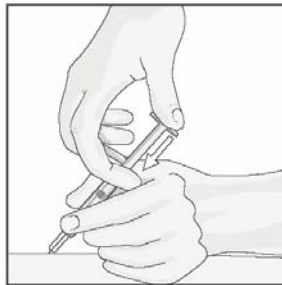
3. When the cleaned area of skin has dried, pinch and hold it firmly with one hand. With the other hand, hold the syringe like a pencil.
4. With a quick, short motion, push the needle all the way into the skin at an angle between  $45^\circ$  and  $90^\circ$  (see Diagram 3). With experience, you will 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 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 stabilise it. Then push the plunger to inject all of the solution at a **slow**, steady rate (see Diagram 4).

Diagram 4



5. 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 a little bleeding at the injection site. You can press a cotton ball or gauze

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over the injection site for 10 seconds. Do not rub the injection site. If needed, you may cover the injection site with a bandage.

**Step 4: Disposing of supplies**

- The pre-filled syringe is for single-use administration only. The syringe and needle should **NEVER** be re-used. **NEVER** re-cap a needle. Dispose of the needle 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.**