MYCLIC®

Pfizer

FIT ENBREL® INTO YOUR LIFE WITH MYCLIC®

A step-by-step guide to using the ENBREL 50 mg pre-filled pen—MYCLIC

Refer to the Package Leaflet for important information you should read before using ENBREL.[1]

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INTRODUCING MYCLIC® (ENBREL® 50 MG SOLUTION FOR INJECTION IN A PRE-FILLED PEN)

The new MYCLIC pen makes it simple to self-inject and this guide makes it easy to learn how.

When you were first trained on proper injection technique using MYCLIC, your doctor or nurse probably made it look simple—and that's because it is. But if the thought of injecting on your own for the first time causes you any anxiety, this booklet is here to help. It may also be reassuring to know that the MYCLIC pre-filled pen has been carefully evaluated in people injecting ENBREL. In this evaluation, ease of performing the injection, ease of learning how to use the pen, confidence in performing the injection correctly, and overall patient satisfaction were all considered better compared to injecting ENBREL using a more traditional syringe.[2]

This brochure is intended to help you feel confident when using MYCLIC to inject ENBREL. It will guide you, step by step, through the self-injection process—and demonstrate how, with practice, injecting ENBREL can become a simple and routine part of your life. This information covers:

1. Preparing for an ENBREL injection
2. Choosing an injection site
3. Injecting the ENBREL solution
4. Disposing of used MYCLIC
5. Additional information such as travelling with ENBREL

Be sure you read all the instructions before beginning.

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SOME IMPORTANT THINGS TO REMEMBER BEFORE YOU START

Here are some tips that will get you off to a good start and help you fit ENBREL® into your life.

Always check the expiry date (month/year) on the carton and on the pen. If the date has passed, do not use the pen and contact your pharmacist for assistance. Store MYCLIC out of sight and reach of children.[1]

Store MYCLIC in a refrigerator between 2°C and 8°C.[1] Do not freeze.[1]

Keep the injection area and injection supplies as clean and germ-free as possible.

Establish a routine; set up specific days and times to inject. It may be helpful to use a diary to keep track of your injection schedule.

Never re-use MYCLIC or other injection-related materials. DO NOT attempt to recap the pen.[1]

Dispose of MYCLIC as instructed by your doctor, nurse or pharmacist.[1]

Before injecting ENBREL:
Refer to the Package Leaflet in the MYCLIC carton for important information you should read before using ENBREL—including information on possible allergic reactions, side effects (serious or other), and under what circumstances ENBREL should not be used.

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HOW TO USE MYCLIC®

The instructions below explain how to use MYCLIC to inject ENBREL®.[1] Please read the instructions carefully and follow them step by step. Your doctor or nurse will show you how to inject ENBREL.

Do not attempt to administer an injection until you are sure that you understand how to use MYCLIC properly. If you have questions about how to inject, please ask your doctor or nurse for help.

This injection should not be mixed with any other medicine.

Step 1: Preparing for an ENBREL injection[1]

- Select a clean, well-lit, flat working surface.[1]
- Gather the items that you will need for your injection, and place them on the chosen surface:[1]

a. One MYCLIC pre-filled pen and one alcohol swab
(Take these from the carton of pens you keep in your refrigerator.)[1]
Do not shake the pen.[1]

b. One cotton-wool ball or gauze.[1]

Diagram 1

- Be sure you remember to check the expiry date (month/year) on MYCLIC®. If the date has passed, do not use the pen and contact your pharmacist for assistance.[1]
- Inspect the solution in the pen by looking through the clear inspection window.[1] The solution should be clear or slightly opalescent, colourless or pale yellow, and may contain small white or almost transparent particles of protein. This appearance is normal for ENBREL®. Do not use the solution if it is discoloured, cloudy, or if particles other than those described above are present. If you are concerned with the appearance of the solution, then contact your pharmacist for assistance.[1]
- **Leave the white needle cap in place and wait approximately 15 to 30 minutes** to allow the ENBREL® solution in the pen to reach room temperature.[1] Do not warm in any other way.[1] **Always leave the pen out of sight and reach of children.[1]**

While waiting for the solution in the pen to reach room temperature, review **Step 2** (on the next page) and choose an injection site.[1]

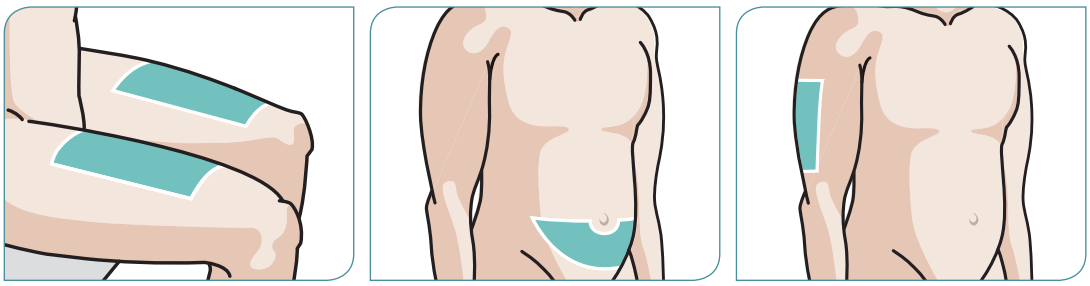
Helpful Hint

Waiting until the solution reaches room temperature may make the injection more comfortable for you.[1]

Step 2: Choosing an injection site[1]

- The recommended injection site is the middle of the front of the thighs. *(See Diagram 2.)*[1] If you prefer, you may alternatively use the stomach area, but make sure you choose a site at least 5 cm away from the belly button (navel).[1] If someone else is giving you the injection, the outer area of the upper arms may also be used.[1]
- Each new injection should be given at least 3 cm from where you last injected.[1] Do not inject into tender, bruised, or hard skin.[1] Avoid scars or stretch marks. (It may be helpful to keep notes on the location of the previous injections.)[1]
- If you have psoriasis, you should try not to inject directly into any raised, thick, red or scaly skin.[1]

Diagram 2



Helpful Hint

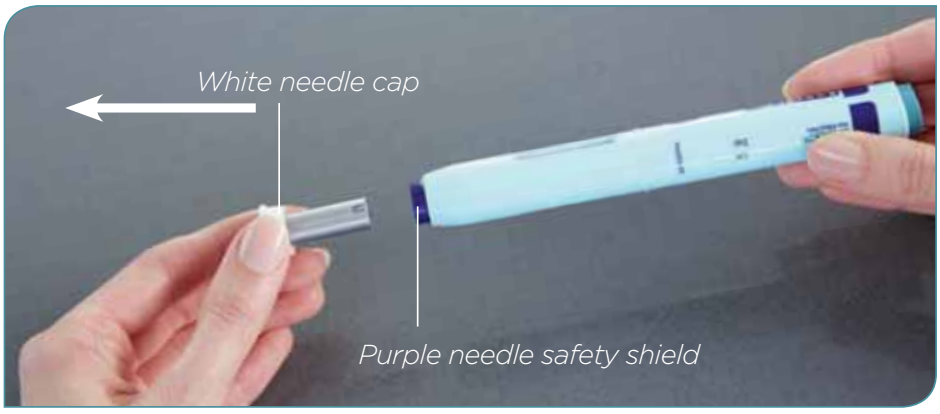
Keep notes on the location of the previous injections.[1]

Step 3: Injecting the ENBREL® solution[1]

After waiting approximately 15 to 30 minutes for the solution in the pen to warm to room temperature, wash your hands with soap and water.[1] Clean the injection site with the alcohol swab using a circular motion, and allow it to dry.[1] Do not touch this area again before injecting.[1]

- Pick up MYCLIC®, and remove the white needle cap by pulling it straight off. *(See Diagram 3.)*[1] To avoid damaging the needle inside MYCLIC, do not bend the white needle cap while you are removing it and do not re-attach it once it has been removed.[1] After you remove the white needle cap, you will see the purple needle safety shield extending slightly from the end of MYCLIC pen.[1] The needle will remain protected inside the pen until the pen is activated. Do not use the pen if it is dropped with the needle cap off.[1]
- Lightly pinching the skin around the injection site between the thumb and index finger of your free hand may make the injection easier and more comfortable.[1]

Diagram 3



Helpful Hint

Once you remove the white needle cap, you should immediately complete your injection.[1]

Step 3: (continued):[1]

› Hold the MYCLIC® pen at a right angle (90°) to the injection site. Push the open end of the pen firmly against the skin so that the purple needle safety shield is pushed completely inside of the pen.[1] A slight depression in the skin will be seen. *(See Diagram 4.)*[1] The pen can only be activated when the purple needle safety shield is completely pushed inside the pen.[1]

Helpful Hint

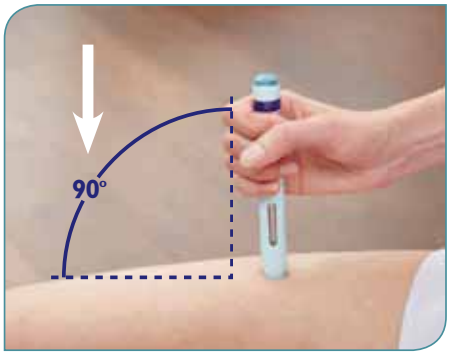
The green activation button will remain locked until the needle shield is completely pushed inside of MYCLIC.[1]

› While pushing the pen firmly against your skin to ensure that the purple needle safety shield is fully depressed inside the pen, press the centre of the green activation button on top of the pen with your thumb to start the injection. *(See Diagram 5.)*[1] On pressing the centre of the button, you will hear a click.[1]

› **Continue to hold MYCLIC firmly against your skin until you hear a second click,** or until 10 seconds after the first click (whichever happens first).[1]

Note: If you are unable to start the injection as described, press the pen more firmly against your skin, then press the green activation button again.[1]

Diagram 4



Purple needle safety shield disappears inside the pen

Diagram 5

Press the centre of the green activation button

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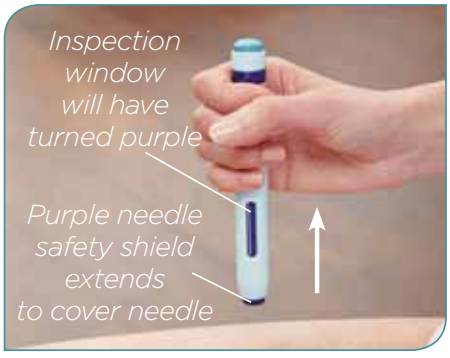
- On hearing the second click (or, if you do not hear a second click, after 10 seconds have passed), your injection will be complete. *(See Diagram 6.)*[1] You may now lift the pen from your skin. *(See Diagram 7.)*[1] As you lift the pen, the purple needle safety shield will automatically extend to cover the needle.[1]
- The pen's inspection window should now be completely purple, confirming that the dose has been injected correctly.[1] If the window is not completely purple, contact your nurse or pharmacist for assistance, since the pen may not have injected the ENBREL® solution completely.[1] Do not try to use the pen again, and do not try to use another pen without consulting your nurse or pharmacist.[1]
- If you notice a spot of blood at the injection site, you should press the cotton wool ball or gauze over the injection site for 10 seconds.[1] Do not rub the injection site.[1]

Helpful Hint

Keep MYCLIC firmly pressed against the injection site to ensure you receive the full dose.[1]

Diagram 6

Diagram 7



Step 4: Disposing of used MYCLIC®[1]

MYCLIC should be used once only. It should never be reused. Do not attempt to recap the pen.[1] Medicines should not be disposed of via wastewater or household waste. Ask your doctor, nurse, or pharmacist how to dispose of medicines that are no longer required.[1] These measures will help to protect the environment.

Travelling with ENBREL®

Remember: ENBREL must be stored between 2°C and 8°C.[1]

ENBREL may be stored at temperatures up to a maximum of 25°C for a single period of up to four weeks; after which, it should not be refrigerated again. ENBREL should be discarded if not used within four weeks of removal from refrigeration. It is recommended that you record the date ENBREL is removed from the refrigerator and the date after which it should be discarded (4 weeks after).[1]

If you are flying, ask the airline or appropriate authorities in advance whether you can take ENBREL on board with you as part of your hand luggage, or whether it can be refrigerated during the flight.

It is recommended that you carry an ENBREL prescription and letter from your doctor, in case you have to explain to customs and airport security why you need to carry MYCLIC. Do not forget to leave copies of the prescription and letter at home in case you lose the originals.

If you have any questions or require further information, please talk with your doctor, nurse, or pharmacist.

NOTES

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References:

1. ENBREL (etanercept) SmPC and Patient Information Leaflet. Available at: www.ema.europa.eu.

2. Müller-Ladner U, Flipo RM, Vincendon P, Brault Y, Kielar D. Comparison of patient satisfaction with two different etanercept delivery systems. *Z Rheumatol*. 2012;71(10):890-899.

ENBREL

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:

ADR Reporting
The Medicines Authority
Post-Licensing Directorate
203 Level 3, Rue D'Argens
GŻR-1368 Gżira
Website: www.medicinesauthority.gov.mt
e-mail: postlicensing.medicinesauthority@gov.mt

Other Contact Information

For any suspected adverse reactions you may also report such events promptly to Pfizer at Pfizer Hellas A.E 243 Messoghion Ave. N.Psychiko, Athens GR-15451, Greece.

Pfizer Hellas Pharmacovigilance Department contact details: +30 210 67 85 908 and +30 210 67 85 808 (24-hour line).

For more information, please contact Pfizer Hellas S.A. Medical Information at +30 210 67 85 800.
Local Representative: Vivian Corporation Ltd.
Tel: +35621 344610

ABBREVIATED SUMMARY OF PRODUCT CHARACTERISTICS. ENBREL 25 MG POWDER AND SOLVENT FOR SOLUTION FOR INJECTION. ENBREL 25 MG SOLUTION FOR INJECTION IN PRE-FILLED SYRINGE. ENBREL 50 MG SOLUTION FOR INJECTION IN PRE-FILLED SYRINGE. ENBREL 50 MG SOLUTION FOR INJECTION IN PRE-FILLED PEN. (ETANERCEPT). THERAPEUTIC INDICATIONS: *Rheumatoid arthritis:* Enbrel in combination with methotrexate is indicated for the treatment of moderate to severe active rheumatoid arthritis in adults when the response to disease-modifying antirheumatic drugs, including methotrexate (unless contraindicated), has been inadequate. Enbrel can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate. Enbrel is also indicated in the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate. Enbrel, alone or in combination with methotrexate, has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function. *Juvenile idiopathic arthritis:* Treatment of 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, or who have proved intolerant of, methotrexate. Treatment of psoriatic arthritis in adolescents from the age of 12 years who have had an inadequate response to, or who have proved intolerant of, methotrexate. Treatment of enthesitis-related arthritis in adolescents from the age of 12 years who have had an inadequate response to, or who have proved intolerant of, conventional therapy. Enbrel has not been studied in children aged less than 2 years. *Psoriatic arthritis:* Treatment of active and progressive psoriatic arthritis in adults when the response to previous disease-modifying antirheumatic drug therapy has been inadequate. Enbrel has been shown to improve physical function in patients with psoriatic arthritis, and to reduce the rate of progression of peripheral joint damage as measured by X ray in patients with polyarticular symmetrical subtypes of the disease. *Axial spondyloarthritis: Ankylosing spondylitis (AS):* Treatment of adults with severe active ankylosing spondylitis who have had an inadequate response to conventional therapy. *Non-radiographic axial spondyloarthritis:* Treatment of adults with severe non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) evidence, who have had an inadequate response to nonsteroidal anti-inflammatory drugs (NSAIDs). *Plaque psoriasis:* Treatment of adults with moderate to severe plaque psoriasis who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapy, including ciclosporin, methotrexate or psoralen and ultraviolet-A light (PUVA). *Paediatric plaque psoriasis:* Treatment of chronic severe plaque psoriasis in children and adolescents from the age of 6 years who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies. **POSOLOGY AND METHOD OF ADMINISTRATION:** Enbrel treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, non-radiographic axial spondyloarthritis, plaque psoriasis or paediatric plaque psoriasis. Patients treated with Enbrel should be given the Patient Alert Card. **POSOLOGY:** *Rheumatoid arthritis:* 25 mg Enbrel administered twice weekly is the recommended dose. Alternatively, 50 mg administered once weekly has been shown to be safe and effective. *Psoriatic arthritis, ankylosing spondylitis and non-radiographic axial spondyloarthritis:* The recommended dose is 25 mg Enbrel administered twice weekly, or 50 mg administered once weekly. For all of the above indications, available data suggest that a clinical response is usually achieved within 12 weeks of treatment. Continued therapy should be carefully reconsidered in a patient not responding within this time period. *Plaque psoriasis:* The recommended dose of Enbrel is 25 mg administered twice weekly or 50 mg administered once weekly. Alternatively, 50 mg given twice weekly may be used for up to 12 weeks followed, if necessary, by a dose of 25 mg twice weekly or 50 mg once weekly. Treatment with Enbrel should continue until remission is achieved, for up to 24 weeks. Continuous therapy beyond 24 weeks may be appropriate for some adult patients. Treatment should be discontinued in patients who show no response after 12 weeks. If re-treatment with Enbrel is indicated, the same guidance on treatment duration should be followed. The dose should be 25 mg twice weekly or 50 mg once weekly. ***Special populations:*** *Renal and hepatic impairment:* No dose adjustment is required. *Older people (≥ 65 years):* No dose adjustment is required. Posology and administration are the same as for adults 18-64 years of age. *Paediatric population:* ***Enbrel 25 mg &50 mg solution for injection in pre-filled syringe, 50 mg solution for injection in pre-filled pen:*** The dosage of Enbrel is based on body weight for paediatric patients. Patients weighing less than 62.5 kg should be accurately dosed on a mg/kg basis using the powder and solvent for solution for injection presentations or the powder for solution for injection presentations (see below for dosing for specific indications). Patients weighing 62.5 kg or more, may be dosed using a fixed-dose pre-filled syringe or pre-filled pen. ***Enbrel 25 mg powder and solvent for solution for injection, Enbrel 25 mg and 50 mg solution for injection in pre-filled syringe:*** *Juvenile idiopathic arthritis*: The recommended dose is 0.4 mg/kg (up to a maximum of 25 mg per dose), given twice weekly as a subcutaneous injection with an interval of 3-4 days between doses or 0.8 mg/kg (up to a maximum of 50 mg per dose) given once weekly. Discontinuation of treatment should be considered in patients who show no response after 4 months. No formal clinical trials have been conducted in children aged 2 to 3 years. However, limited safety data from a patient registry suggest that the safety profile in children from 2 to 3 years of age is similar to that seen in adults and children aged 4 years and older, when dosed every week with 0.8 mg/kg subcutaneously. There is generally no applicable use of Enbrel in children aged below 2 years in the indication juvenile idiopathic arthritis. *Paediatric plaque psoriasis (age 6 years and above):* The recommended dose is 0.8 mg/kg (up to a maximum of 50 mg per dose) once weekly for up to 24 weeks. Treatment should be discontinued in patients who show no response after 12 weeks. If re-treatment with Enbrel is indicated, the above guidance on treatment duration should be followed. The dose should be 0.8 mg/kg (up to a maximum of 50 mg per dose) once weekly. There is generally no applicable use of Enbrel in children aged below 6 years in the indication plaque psoriasis. **METHOD OF ADMINISTRATION:** Enbrel is administered by subcutaneous injection. ***Enbrel 25 mg powder and solvent for solution for injection:*** Enbrel powder for solution must be reconstituted in 1 ml of solvent before use. **CONTRAINDICATIONS:** Hypersensitivity to the active substance or to any of the excipients. Sepsis or risk of sepsis. Treatment with Enbrel should not be initiated in patients with active infections, including chronic or localised infections. **SPECIAL WARNINGS AND PRECAUTIONS FOR USE:** *Infections:* Patients should be evaluated for infections before, during, and after treatment with Enbrel, taking into consideration that the mean elimination half-life of etanercept is approximately 70 hours (range 7 to 300 hours). Serious infections, sepsis, tuberculosis, and opportunistic infections, including invasive fungal infections, listeriosis and legionellosis, have been reported with the use of Enbrel. These infections were due to bacteria, mycobacteria, fungi, viruses and parasites (including protozoa). In some cases, particular fungal and other opportunistic infections have not been recognised, resulting in delay of appropriate treatment and sometimes death. In evaluating patients for infections, the patient's risk for relevant opportunistic infections (e.g., exposure to endemic mycoses) should be considered. Patients who develop a new infection while undergoing treatment with Enbrel should be monitored closely. Administration of Enbrel should be discontinued if a patient develops a serious infection. The safety and efficacy of Enbrel in patients with chronic infections have not been evaluated. Physicians should exercise caution when considering the use of Enbrel in patients with a history of recurring or chronic infections or with underlying conditions that may predispose patients to infections, such as advanced or poorly controlled diabetes. *Tuberculosis:* Cases of active tuberculosis, including miliary tuberculosis and tuberculosis with extra-pulmonary location, have been reported in patients treated with Enbrel. Before starting treatment with Enbrel, all patients must be evaluated for both active and inactive ('latent') tuberculosis. This evaluation should include

a detailed medical history with personal history of tuberculosis or possible previous contact with tuberculosis and previous and/or current immunosuppressive therapy. Appropriate screening tests, i.e., tuberculin skin test and chest X-ray, should be performed in all patients (local recommendations may apply). It is recommended that the conduct of these tests should be recorded in the patient's alert card. Prescribers are reminded of the risk of false negative tuberculin skin test results, especially in patients who are severely ill or immunocompromised. If active tuberculosis is diagnosed, Enbrel therapy must not be initiated. If inactive ('latent') tuberculosis is diagnosed, treatment for latent tuberculosis must be started with anti-tuberculosis therapy before the initiation of Enbrel, and in accordance with local recommendations. In this situation, the benefit/risk balance of Enbrel therapy should be very carefully considered. All patients should be informed to seek medical advice if signs/symptoms suggestive of tuberculosis (e.g., persistent cough, wasting/weight loss, low-grade fever) appear during or after Enbrel treatment. *Hepatitis B virus reactivation:* Reactivation of hepatitis B in patients who were previously infected with the hepatitis B virus (HBV) and had received concomitant TNF-antagonists, including Enbrel, has been reported. This includes reports of reactivation of hepatitis B in patients who were anti-HBc positive but HBsAg negative. Patients should be tested for HBV infection before initiating treatment with Enbrel. For patients who test positive for HBV infection, consultation with a physician with expertise in the treatment of hepatitis B is recommended. Caution should be exercised when administering Enbrel in patients previously infected with HBV. These patients should be monitored for signs and symptoms of active HBV infection throughout therapy and for several weeks following termination of therapy. Adequate data from treating patients infected with HBV with anti-viral therapy in conjunction with TNF-antagonist therapy are not available. In patients who develop HBV infection, Enbrel should be stopped and effective anti-viral therapy with appropriate supportive treatment should be initiated. *Worsening of hepatitis C:* There have been reports of worsening of hepatitis C in patients receiving Enbrel. Enbrel should be used with caution in patients with a history of hepatitis C. *Concurrent treatment with anakinra:* Concurrent administration of Enbrel and anakinra has been associated with an increased risk of serious infections and neutropenia compared to Enbrel alone. This combination has not demonstrated increased clinical benefit. Thus, the combined use of Enbrel and anakinra is not recommended. *Concurrent treatment with abatacept:* In clinical studies, concurrent administration of abatacept and Enbrel resulted in increased incidences of serious adverse events. This combination has not demonstrated increased clinical benefit; such use is not recommended. *Allergic reactions:* Allergic reactions associated with Enbrel administration have been reported commonly. Allergic reactions have included angioedema and urticaria; serious reactions have occurred. If any serious allergic or anaphylactic reaction occurs, Enbrel therapy should be discontinued immediately and appropriate therapy initiated. ***Enbrel 25 mg & 50 mg solution for injection in pre-filled syringe, 50 mg solution for injection in pre-filled syringe:*** The needle cover of the pre-filled syringe contains latex (dry natural rubber) that may cause hypersensitivity reactions when handled by, or when Enbrel is administered to, persons with known or possible latex sensitivity. *Immunosuppression:* The possibility exists for TNF-antagonists, including Enbrel, to affect host defences against infections and malignancies since TNF mediates inflammation and modulates cellular immune responses. In a study of 49 adult patients with rheumatoid arthritis treated with Enbrel, there was no evidence of depression of delayed-type hypersensitivity, depression of immunoglobulin levels, or change in enumeration of effector cell populations. Two juvenile idiopathic arthritis patients developed varicella infection and signs and symptoms of aseptic meningitis, which resolved without sequelae. Patients with a significant exposure to varicella virus should temporarily discontinue Enbrel therapy and be considered for prophylactic treatment with Varicella Zoster Immune Globulin. The safety and efficacy of Enbrel in patients with immunosuppression have not been evaluated. *Malignancies and lymphoproliferative disorders: Solid and haematopoietic malignancies (excluding skin cancers):* Reports of various malignancies (including breast and lung carcinoma and lymphoma) have been received in the postmarketing period. In the controlled portions of clinical trials of TNF-antagonists, more cases of lymphoma have been observed among patients receiving a TNF-antagonist compared with control patients. However, the occurrence was rare, and the follow-up period of placebo patients was shorter than for patients receiving TNF-antagonist therapy. In the postmarketing setting, cases of leukaemia have been reported in patients treated with TNF-antagonists. There is an increased background risk for lymphoma and leukaemia in rheumatoid arthritis patients with long-standing, highly active, inflammatory disease, which complicates risk estimation. Based on current knowledge, a possible risk for the development of lymphomas, leukaemia or other haematopoietic or solid malignancies in patients treated with a TNF-antagonist cannot be excluded. Caution should be exercised when considering TNF-antagonist therapy for patients with a history of malignancy or when considering continuing treatment in patients who develop a malignancy. Malignancies, some fatal, have been reported among children, adolescents and young adults (up to 22 years of age) treated with TNF-antagonists (initiation of therapy ≤ 18 years of age), including Enbrel, in the postmarketing setting. Approximately half the cases were lymphomas. The other cases represented a variety of different malignancies and included rare malignancies typically associated with immunosuppression. A risk for the development of malignancies in children and adolescents treated with TNF-antagonists cannot be excluded. *Skin cancers:* Melanoma and non-melanoma skin cancer (NMSC) have been reported in patients treated with TNF-antagonists, including Enbrel. Postmarketing cases of Merkel cell carcinoma have been reported very infrequently in patients treated with Enbrel. Periodic skin examination is recommended for all patients, particularly those with risk factors for skin cancer. Combining the results of controlled clinical trials, more cases of NMSC were observed in patients receiving Enbrel compared with control patients, particularly in patients with psoriasis. *Vaccinations:* Live vaccines should not be given concurrently with Enbrel. No data are available on the secondary transmission of infection by live vaccines in patients receiving Enbrel. In a double-blind, placebo-controlled, randomised clinical study in adult patients with psoriatic arthritis, 184 patients also received a multivalent pneumococcal polysaccharide vaccine at week 4. In this study, most psoriatic arthritis patients receiving Enbrel were able to mount effective B-cell immune response to pneumococcal polysaccharide vaccine, but titres in aggregate were moderately lower, and few patients had two-fold rises in titres compared to patients not receiving Enbrel. The clinical significance of this is unknown. *Autoantibody formation:* Treatment with Enbrel may result in the formation of autoimmune antibodies. *Haematologic reactions:* Rare cases of pancytopenia and very rare cases of aplastic anaemia, some with fatal outcome, have been reported in patients treated with Enbrel. Caution should be exercised in patients being treated with Enbrel who have a previous history of blood dyscrasias. All patients and parents/caregivers should be advised that if the patient develops signs and symptoms suggestive of blood dyscrasias or infections (e.g., persistent fever, sore throat, bruising, bleeding, paleness) whilst on Enbrel, they should seek immediate medical advice. Such patients should be investigated urgently, including full blood count; if blood dyscrasias are confirmed, Enbrel should be discontinued. *Neurological disorders:* There have been rare reports of CNS demyelinating disorders in patients treated with Enbrel. Additionally, there have been very rare reports of peripheral demyelinating polyneuropathies (including Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, demyelinating polyneuropathy, and multifocal motor neuropathy). Although no clinical trials have been performed evaluating Enbrel therapy in patients with multiple sclerosis, clinical trials of other TNF antagonists in patients with multiple sclerosis have shown increases in disease activity. A careful risk/benefit evaluation, including a neurologic assessment, is recommended when prescribing Enbrel to patients with pre-existing or recent onset of demyelinating disease, or to those who are considered to have an increased risk of developing demyelinating disease. *Combination therapy:* In a controlled clinical trial of two years duration in rheumatoid arthritis patients, the combination of Enbrel and methotrexate did not result in unexpected safety findings, and the safety profile of Enbrel when given in combination with methotrexate was similar to the profiles reported in studies of Enbrel and methotrexate alone. Long-term studies to assess the safety of the combination are ongoing. The long-term safety of Enbrel in combination with other disease-modifying antirheumatic drugs (DMARD) has not been established. The use of Enbrel in combination with other systemic therapies or phototherapy for the treatment of psoriasis has not been studied. *Renal and hepatic impairment:* Based on pharmacokinetic data, no dose adjustment is needed in patients with renal or hepatic impairment; clinical experience in such patients is limited. *Congestive heart failure:* Physicians should use caution when using Enbrel in patients who have congestive heart failure (CHF). There have been postmarketing reports of worsening of CHF, with and without identifiable precipitating factors, in patients taking Enbrel. Two large clinical trials evaluating the use of Enbrel in the treatment of CHF were terminated early due to lack of efficacy. Although not conclusive, data from one of these trials suggest a possible tendency toward worsening CHF in those patients assigned to Enbrel treatment. *Alcoholic hepatitis:* In a phase II randomised placebo-controlled study of 48 hospitalised patients treated with Enbrel or placebo for moderate to severe alcoholic hepatitis, Enbrel was not efficacious, and the mortality rate in patients treated with Enbrel was significantly higher after 6 months. Consequently, Enbrel should not be used in patients for the treatment of alcoholic hepatitis. Physicians should use caution when using Enbrel in patients who also have moderate to severe alcoholic hepatitis. *Wegener's granulomatosis:* A placebo-controlled trial, in which 89 adult patients were treated with Enbrel in addition to standard therapy (including cyclophosphamide or methotrexate, and glucocorticoids) for a median duration of 25 months, has not shown Enbrel to be an effective treatment for Wegener's

granulomatosis. The incidence of non-cutaneous malignancies of various types was significantly higher in patients treated with Enbrel than in the control group. Enbrel is not recommended for the treatment of Wegener's granulomatosis. *Hypoglycaemia in patients treated for diabetes:* There have been reports of hypoglycaemia following initiation of Enbrel in patients receiving medication for diabetes, necessitating a reduction in anti-diabetic medication in some of these patients. *Special populations: Older people (≥ 65 years):* In the Phase 3 studies in rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis, no overall differences in adverse events, serious adverse events, and serious infections in patients age 65 or older who received Enbrel were observed compared with younger patients. However, caution should be exercised when treating the elderly and particular attention paid with respect to occurrence of infections. *Paediatric population:* Vaccinations: It is recommended that paediatric patients, if possible, be brought up to date with all immunisations in agreement with current immunisation guidelines prior to initiating Enbrel therapy (see Vaccinations, above). Inflammatory bowel disease (IBD) and uveitis in patients with juvenile idiopathic arthritis (JIA): There have been reports of IBD and uveitis in JIA patients being treated with Enbrel. **INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION:** *Concurrent treatment with anakinra:* Adult patients treated with Enbrel and anakinra were observed to have a higher rate of serious infection when compared with patients treated with either Enbrel or anakinra alone (historical data). In addition, in a double-blind, placebo-controlled trial in adult patients receiving background methotrexate, patients treated with Enbrel and anakinra were observed to have a higher rate of serious infections (7%) and neutropenia than patients treated with Enbrel. The combination Enbrel and anakinra has not demonstrated increased clinical benefit, and is therefore not recommended. *Concurrent treatment with abatacept:* In clinical studies, concurrent administration of abatacept and Enbrel resulted in increased incidences of serious adverse events. This combination has not demonstrated increased clinical benefit; such use is not recommended. *Concurrent treatment with sulfasalazine:* In a clinical study of adult patients who were receiving established doses of sulfasalazine, to which Enbrel was added, patients in the combination group experienced a statistically significant decrease in mean white blood cell counts in comparison to groups treated with Enbrel or sulfasalazine alone. The clinical significance of this interaction is unknown. Physicians should use caution when considering combination therapy with sulfasalazine. *Non-interactions:* In clinical trials, no interactions have been observed when Enbrel was administered with glucocorticoids, salicylates (except sulfasalazine), nonsteroidal anti-inflammatory drugs (NSAIDs), analgesics, or methotrexate. No clinically significant pharmacokinetic drug-drug interactions were observed in studies with methotrexate, digoxin or warfarin. **FERTILITY, PREGNANCY AND LACTATION:** *Women of childbearing potential:* Women of childbearing potential should be advised to use appropriate contraception to avoid becoming pregnant during Enbrel therapy and for three weeks after discontinuation of therapy. *Pregnancy:* Developmental toxicity studies performed in rats and rabbits have revealed no evidence of harm to the foetus or neonatal rat due to etanercept. There are no studies of Enbrel in pregnant women. Thus, Enbrel is not recommended during pregnancy. Etanercept crosses the placenta and has been detected in the serum of infants born to female patients treated with Enbrel during pregnancy. The clinical impact of this is unknown, however, infants may be at increased risk of infection. Administration of live vaccines to infants for 16 weeks after the mother's last dose of Enbrel is generally not recommended. *Breast-feeding:* Etanercept has been reported to be excreted in human milk following subcutaneous administration. In lactating rats following subcutaneous administration, etanercept was excreted in the milk and detected in the serum of pups. Because immunoglobulins, in common with many medicinal products, can be excreted in human milk, a decision must be made whether to discontinue breast-feeding or to discontinue Enbrel therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman. Fertility: Preclinical data about peri- and postnatal toxicity of etanercept and of effects of etanercept on fertility and general reproductive performance are not available. **UNDESIRABLE EFFECTS:** *Summary of the safety profile:* The most commonly reported adverse reactions are injection site reactions (such as pain, swelling, itching, reddening and bleeding at the puncture site), infections (such as upper respiratory infections, bronchitis, bladder infections and skin infections), allergic reactions, development of autoantibodies, itching, and fever. Serious adverse reactions have also been reported for Enbrel. TNF-antagonists, such as Enbrel, affect the immune system and their use may affect the body's defenses against infection and cancer. Serious infections affect fewer than 1 in 100 patients treated with Enbrel. Reports have included fatal and life-threatening infections and sepsis. Various malignancies have also been reported with use of Enbrel, including cancers of the breast, lung, skin and lymph glands (lymphoma). Serious haematological, neurological and autoimmune reactions have also been reported. These include rare reports of pancytopenia and very rare reports of aplastic anaemia. Central and peripheral demyelinating events have been seen rarely and very rarely, respectively, with Enbrel use. There have been rare reports of lupus, lupus-related conditions, and vasculitis. *Tabulated list of adverse reactions:* The following list of adverse reactions is based on experience from clinical trials in adults and on postmarketing experience. Within the organ system classes, adverse reactions are listed under headings of frequency (number of patients expected to experience the reaction), using the following categories: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1000 to <1/100); rare (≥1/10,000 to <1/1000); very rare (<1/10,000); not known (cannot be estimated from the available data). *Infections and infestations:* Very common: Infections (including upper respiratory tract infections, bronchitis, cystitis, skin infections)*, Uncommon: Serious infections (including pneumonia, cellulitis, septic arthritis, sepsis and parasitic infection)*, Rare: Tuberculosis, opportunistic infections (including invasive fungal, protozoal, bacterial, atypical mycobacterial, viral infections and Legionella)*, Not known: Listeria, hepatitis B reactivation, *Neoplasms benign, malignant and unspecified (including cysts and polyps):* Uncommon: Non-melanoma skin cancers*, Rare: Lymphoma, melanoma, Not known: Leukaemia, Merkel cell carcinoma, *Blood and lymphatic system disorders:* Uncommon: Thrombocytopenia, Rare: Anaemia, leukopenia, neutropenia, pancytopenia*, Very rare: Aplastic anaemia*, *Immune system disorders:* Common: Allergic reactions, autoantibody formation*, Uncommon: Systemic vasculitis (including anti-neutrophilic cytoplasmic antibody positive vasculitis), Rare: Serious allergic/anaphylactic reactions (including angioedema, bronchospasm), sarcoidosis, Not known: Macrophage activation syndrome*, worsening of symptoms of dermatomyositis, *Nervous system disorders:* Rare: Seizures, CNS demyelinating events suggestive of multiple sclerosis or localised demyelinating conditions, such as optic neuritis and transverse myelitis, Very rare: Peripheral demyelinating events, including Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, demyelinating polyneuropathy, and multifocal motor neuropathy. *Eye disorders:* Uncommon: Uveitis, scleritis, *Cardiac disorders:* Rare: Worsening of congestive heart failure, *Respiratory, thoracic and mediastinal disorders:* Uncommon: Interstitial lung disease (including pneumonitis and pulmonary fibrosis)*, *Hepatobiliary disorders:* Rare: Elevated liver enzymes, autoimmune hepatitis, *Skin and subcutaneous tissue disorders:* Common: Pruritus, Uncommon: Angioedema, urticaria, rash, psoriasiform rash, psoriasis (including new onset or worsening and pustular, primarily palms and soles), Rare: Cutaneous vasculitis (including leukocytoclastic vasculitis), Stevens-Johnson syndrome, erythema multiforme, Very rare: Toxic epidermal necrolysis, *Musculoskeletal and connective tissue disorders:* Rare: Subacute cutaneous lupus erythematosus, discoid lupus erythematosus, lupus-like syndrome, *General disorders and administration site conditions:* Very common: Injection site reactions (including bleeding, bruising, erythema, itching, pain, swelling)*, Common: Fever * see Description of selected adverse reactions, below. *Description of selected adverse reactions: Malignancies and lymphoproliferative disorders:* One hundred and twenty-nine (129) new malignancies of various types were observed in 4,114 rheumatoid arthritis

patients treated in clinical trials with Enbrel for up to approximately 6 years, including 231 patients treated with Enbrel in combination with methotrexate in the 2-year active-controlled study. The observed rates and incidences in these clinical trials were similar to those expected for the population studied. A total of 2 malignancies were reported in clinical studies of approximately 2 years duration involving 240 Enbrel-treated psoriatic arthritis patients. In clinical studies conducted for more than 2 years with 351 ankylosing spondylitis patients, 6 malignancies were reported in Enbrel-treated patients. In a group of 2,711 plaque psoriasis patients treated with Enbrel in double-blind and open-label studies of up to 2.5 years, 30 malignancies and 43 nonmelanoma skin cancers were reported. In a group of 7,416 patients treated with Enbrel in rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and psoriasis clinical trials, 18 lymphomas were reported. Reports of various malignancies (including breast and lung carcinoma and lymphoma) have also been received in the postmarketing period. *Injection site reactions:* Compared to placebo, patients with rheumatic diseases treated with Enbrel had a significantly higher incidence of injection site reactions (36% vs. 9%). Injection site reactions usually occurred in the first month. Mean duration was approximately 3 to 5 days. No treatment was given for the majority of injection site reactions in the Enbrel treatment groups, and the majority of patients who were given treatment received topical preparations, such as corticosteroids, or oral antihistamines. Additionally, some patients developed recall injection site reactions characterised by a skin reaction at the most recent site of injection, along with the simultaneous appearance of injection site reactions at previous injection sites. These reactions were generally transient and did not recur with treatment. In controlled trials in patients with plaque psoriasis, approximately 13.6% of patients treated with Enbrel developed injection site reactions compared with 3.4% of placebo-treated patients during the first 12 weeks of treatment. *Serious infections:* In placebo-controlled trials, no increase in the incidence of serious infections (fatal, life-threatening, or requiring hospitalisation or intravenous antibiotics) was observed. Serious infections occurred in 6.3% of rheumatoid arthritis patients treated with Enbrel for up to 48 months. These included abscess (at various sites), bacteraemia, bronchitis, bursitis, cellulitis, cholecystitis, diarrhoea, diverticulitis, endocarditis (suspected), gastroenteritis, hepatitis B, herpes zoster, leg ulcer, mouth infection, osteomyelitis, otitis, peritonitis, pneumonia, pyelonephritis, sepsis, septic arthritis, sinusitis, skin infection, skin ulcer, urinary tract infection, vasculitis, and wound infection. In the 2-year active-controlled study where patients were treated with either Enbrel alone, methotrexate alone or Enbrel in combination with methotrexate, the rates of serious infections were similar among the treatment groups. However, it cannot be excluded that the combination of Enbrel with methotrexate could be associated with an increase in the rate of infections. There were no differences in rates of infection among patients treated with Enbrel and those treated with placebo for plaque psoriasis in placebo-controlled trials of up to 24 weeks duration. Serious infections experienced by Enbrel-treated patients included cellulitis, gastroenteritis, pneumonia, cholecystitis, osteomyelitis, gastritis, appendicitis, *Streptococcal* fasciitis, myositis, septic shock, diverticulitis and abscess. In the double-blind and open-label psoriatic arthritis trials, 1 patient reported a serious infection (pneumonia). Serious and fatal infections have been reported during use of Enbrel; reported pathogens include bacteria, mycobacteria (including tuberculosis), viruses and fungi. Some have occurred within a few weeks after initiating treatment with Enbrel in patients who have underlying conditions (e.g., diabetes, congestive heart failure, history of active or chronic infections) in addition to their rheumatoid arthritis. Enbrel treatment may increase mortality in patients with established sepsis. Opportunistic infections have been reported in association with Enbrel, including invasive fungal, parasitic (including protozoal), viral (including herpes zoster), bacterial (including *Listeria* and *Legionella*), and atypical mycobacterial infections. In a pooled data set of clinical trials, the overall incidence of opportunistic infections was 0.09% for the 15,402 subjects who received Enbrel. The exposure-adjusted rate was 0.06 events per 100 patient-years. In postmarketing experience, approximately half of all of the case reports of opportunistic infections worldwide were invasive fungal infections. The most commonly reported invasive fungal infections included *Candida*, *Pneumocystis*, *Aspergillus* and *Histoplasma*. Invasive fungal infections accounted for more than half of the fatalities amongst patients who developed opportunistic infections. The majority of the reports with a fatal outcome were in patients with *Pneumocystis* pneumonia, unspecified systemic fungal infections, and aspergillosis. *Autoantibodies:* Adult patients had serum samples tested for autoantibodies at multiple timepoints. Of the rheumatoid arthritis patients evaluated for antinuclear antibodies (ANA), the percentage of patients who developed new positive ANA (≥1:40) was higher in patients treated with Enbrel (11%) than in placebo-treated patients (5%). The percentage of patients who developed new positive anti-double-stranded DNA antibodies was also higher by radioimmunoassay (15% of patients treated with Enbrel compared to 4% of placebo-treated patients) and by *Crithidia luciliae* assay (3% of patients treated with Enbrel compared to none of placebo-treated patients). The proportion of patients treated with Enbrel who developed anticardiolipin antibodies was similarly increased compared to placebo-treated patients. The impact of long-term treatment with Enbrel on the development of autoimmune diseases is unknown. There have been rare reports of patients, including rheumatoid factor positive patients, who have developed other autoantibodies in conjunction with a lupus-like syndrome or rashes that are compatible with subacute cutaneous lupus or discoid lupus by clinical presentation and biopsy. *Pancytopenia and aplastic anaemia:* There have been postmarketing reports of pancytopenia and aplastic anaemia, some of which had fatal outcomes. *Interstitial lung disease:* There have been postmarketing reports of interstitial lung disease (including pneumonitis and pulmonary fibrosis), some of which had fatal outcomes. *Concurrent treatment with anakinra:* In studies when adult patients received concurrent treatment with Enbrel plus anakinra, a higher rate of serious infections compared to Enbrel alone was observed and 2% of patients (3/139) developed neutropenia (absolute neutrophil count < 1000/mm^3). While neutropenic, one patient developed cellulitis that resolved after hospitalisation. *Paediatric population:* Undesirable effects in paediatric patients with juvenile idiopathic arthritis: In general, the adverse events in paediatric patients with juvenile idiopathic arthritis were similar in frequency and type to those seen in adult patients. Differences from adults and other special considerations are discussed in the following paragraphs. The types of infections seen in clinical trials in juvenile idiopathic arthritis patients aged 2 to 18 years were generally mild to moderate and consistent with those commonly seen in outpatient paediatric populations. Severe adverse events reported included varicella with signs and symptoms of aseptic meningitis, which resolved without sequelae, appendicitis, gastroenteritis, depression/personality disorder, cutaneous ulcer, oesophagitis/gastritis, group A streptococcal septic shock, type I diabetes mellitus, and soft tissue and post-operative wound infection. In one study in children with juvenile idiopathic arthritis aged 4 to 17 years, 43 of 69 (62%) children experienced an infection while receiving Enbrel during 3 months of the study (part 1, open-label), and the frequency and severity of infections was similar in 58 patients completing 12 months of open-label extension therapy. The types and proportion of adverse events in juvenile idiopathic arthritis patients were similar to those seen in trials of Enbrel in adult patients with rheumatoid arthritis, and the majority were mild. Several adverse events were reported more commonly in 69 juvenile idiopathic arthritis patients receiving 3 months of Enbrel compared to the 349 adult rheumatoid arthritis patients. These included headache (19% of patients, 1.7 events per patient year), nausea (9%, 1.0 event per patient year), abdominal pain (19%, 0.74 events per patient year), and vomiting (13%, 0.74 events per patient year). There were 4 reports of macrophage activation syndrome in juvenile idiopathic arthritis clinical trials. There have been reports of inflammatory bowel disease and uveitis in JIA patients being treated with Enbrel from post-marketing sources, including a very small number of cases indicating a positive rechallenge. Undesirable effects in paediatric patients with plaque psoriasis: In a 48-week study in 211 children aged 4 to 17 years with paediatric plaque psoriasis, the adverse events reported were similar to those seen in previous studies in adults with plaque psoriasis.

SUPPLY CLASSIFICATION POM. **MARKETING AUTHORISATION HOLDER:** Pfizer Limited, Ramsgate Road, Sandwich, Kent CT13 9NJ, United Kingdom. **LOCAL REPRESENTATIVE OF THE MARKETING AUTHORISATION HOLDER IN MALTA:** Vivian Corporation Ltd, 29, Sanitas Building Tower Street, Msida MSD1824, Malta Tel: + 35621 344610 **MARKETING AUTHORISATION NUMBER(S)**: Enbrel 25 mg powder and solvent for solution for injection: EU/1/99/126/003, Enbrel 25 mg solution for injection in pre-filled syringe: EU/1/99/126/013, Enbrel 50 mg solution for injection in pre-filled syringe: EU/1/99/126/017. Enbrel 50 mg solution for injection in pre-filled pen: EU/1/99/126/020. **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION:** Date of first authorisation: 03 February 2000, Date of last renewal: 03 February 2010. **DATE OF REVISION OF THE TEXT:** 12/2014. For additional information please refer to the Summary of Products Characteristics. For any suspected adverse reactions please report such events in accordance with the national spontaneous reporting system to the Medicines Authority Post-Licensing Directorate, 203, Level 3, Rue D'Argens, Gzira GZR 1368, Malta, or at http://www.medicinesauthority.gov.mt/adrportal or else to the local representative Vivian Corporation Ltd., Tel: +35621 344610.

IMPORTANT SAFETY INFORMATION. Serious infections, including sepsis and tuberculosis, have been reported with the use of etanercept. Some of these infections have been fatal. These infections were due to bacteria, mycobacteria, fungi viruses and parasites (including protozoa). Opportunistic infections have also been reported including invasive fungal (*Candida, Pneumocystis, Aspergillus,* and *Histoplasma*), parasitic (including protozoal), viral (including herpes zoster), bacterial (including Listeria and Legionella) and atypical mycobacterial infections. Patients who develop a new infection while undergoing treatment with etanercept should be monitored closely. Administration of etanercept should be discontinued if a patient develops a serious infection. Caution should be exercised when considering the use of etanercept in patients with a history of recurring or chronic infections or with underlying conditions which may predispose patients to infections. Treatment with ETANERCEPT (ENBREL) should not be initiated in patients with serious active infections, including chronic or localized infections. Patients with RA appear to have an increased rate of TB infection. Before initiation of therapy with ETANERCEPT (ENBREL), any patient at increased risk for TB should be evaluated for active or latent infection. Prophylaxis of latent TB infection should be initiated prior to therapy with ETANERCEPT (ENBREL). Some patients who tested negative for latent tuberculosis prior to receiving ETANERCEPT (ENBREL) have developed active tuberculosis. Physicians should monitor patients receiving ETANERCEPT (ENBREL) for signs and symptoms of active tuberculosis, including patients who tested negative for latent tuberculosis infection. Applicable local guidelines should be consulted. - Reports of malignancies affecting various sites have been received in the postmarketing period. In the controlled portions of clinical trials of TNFantagonists, more cases of lymphoma have been observed among patients receiving a TNF-antagonist compared with control patients. However, the occurrence was rare, and the follow-up period of placebo patients was shorter than for patients receiving TNF-antagonist therapy. Furthermore, there is an increased background lymphoma risk in rheumatoid arthritis patients with longstanding, highly active, inflammatory disease, which complicates the risk estimation. Post hoc analyses of rheumatoid arthritis clinical trials with ETANERCEPT (ENBREL) have neither confirmed nor excluded an increased risk for malignancies. Malignancies (particularly Hodgkin's and non-Hodgkin's lymphomas), some fatal, have been reported among children and adolescents who received treatment with TNF-antagonists, including ETANERCEPT (ENBREL). Most of the patients were receiving concomitant immunosuppressants. Based on current knowledge, a possible risk for the development of lymphomas or other hematopoietic or solid malignancies in patients treated with a TNF-antagonist cannot be excluded. - Melanoma and non-melanoma skin cancer (NMSC) have been reported in patients treated with TNF-antagonists, including ETANERCEPT (ENBREL). Postmarketing cases of Merkel cell carcinoma have been reported very infrequently in patients treated with ETANERCEPT (ENBREL). Periodic skin examination is recommended for all patients who are at increased risk for skin cancer. Combining the results of controlled portions of clinical trials of ETANERCEPT (ENBREL), more cases of NMSC were observed in patients receiving ETANERCEPT (ENBREL) compared with control patients, particularly in patients with psoriasis. - Do not start ETANERCEPT (ENBREL) in patients with hypersensitivity to ETANERCEPT (ENBREL) or its components. Allergic reactions associated with ETANERCEPT (ENBREL) administration have been reported. If any serious allergic or anaphylactic reaction occurs, discontinue administration of ETANERCEPT (ENBREL) immediately. There have been rare reports of CNS demyelinating disorders in patients treated with ETANERCEPT (ENBREL). Additionally, there have been very rare reports of peripheral demyelinating polyneuropathies (including Guillain-Barré syndrome). A careful risk/benefit evaluation, including a neurological assessment, is recommended when prescribing Etanercept therapy to patients with pre-existing or recent onset of demyelinating disease, or to those who are considered to have an increased risk of developing demyelinating disease. Rare cases of pancytopenia and very rare cases of aplastic anemia, some with fatal outcome, have been reported in patients treated with ETANERCEPT (ENBREL). Caution should be exercised in patients being treated with ETANERCEPT (ENBREL) who have a previous history of blood dyscrasias. All patients should be advised that if they develop signs and symptoms suggestive of blood dyscrasias or infections (e.g., persistent fever, sore throat, bruising, bleeding, paleness) whilst on etanercept, they should seek immediate medical advice. Such patients should be evaluated urgently, including full blood count; if blood dyscrasias are confirmed, etanercept should be discontinued. Reactivation of hepatitis B in patients who were previously infected with the hepatitis B virus (HBV) and had received concomitant anti-TNF agents including etanercept has been reported. The majority of these reports have occurred in patients concomitantly receiving other medications that suppress the immune system, which may also contribute to HBV reactivation. Patients at risk for HBV infection should be evaluated for prior evidence of HBV infection before initiating anti-TNF therapy Caution should be exercised when administering etanercept in patients previously infected with HBV. These patients should be monitored for signs and symptoms of active HBV infection. There have been reports of worsening of hepatitis C in patients receiving ETANERCEPT (ENBREL), although a causal relationship with ETANERCEPT (ENBREL) has not been established. The use of ETANERCEPT (ENBREL) in patients for the treatment of alcoholic hepatitis is not recommended. Physicians should use caution when using ETANERCEPT (ENBREL) in patients who also have moderate to severe alcoholic hepatitis. Patients in controlled clinical studies treated with ETANERCEPT (ENBREL) had a significantly higher incidence of injection site reactions (erythema and/or itching, pain, or swelling) compared with placebo-treated patients. The frequency of injection site reactions was greatest in the first month and subsequently decreased in frequency. Some patients who experienced injection site reactions also experienced reactions at previous injection sites. There have been post marketing reports of worsening of congestive heart failure, with and without identifiable precipitating factors, in patients taking ETANERCEPT (ENBREL). Physicians should use caution when using ETANERCEPT (ENBREL) in patients who also have CHF. Live vaccines should not be given concurrently with ETANERCEPT (ENBREL). Treatment with ETANERCEPT (ENBREL) may be associated with the formation of autoimmune antibodies. There have been reports of hypoglycemia following initiation of ETANERCEPT (ENBREL) in patients receiving medication for diabetes, necessitating a reduction in anti-diabetic medication in some of these patients. Women of childbearing potential should be advised to use appropriate contraception to avoid becoming pregnant during Enbrel therapy and for three weeks after discontinuation of therapy. There are no studies of Enbrel in pregnant women, thus, Enbrel is not recommended during pregnancy. The safe use of ETANERCEPT (ENBREL) during lactation has not been established. In general, the adverse events in pediatric patients were similar in frequency and type to those seen in adult patients. Infection was the most common adverse event reported in pediatric patients taking ETANERCEPT (ENBREL) and occurred at an incidence similar to placebo. If possible, bring pediatric patients up to date with immunizations according to current local guidelines before beginning therapy with ETANERCEPT (ENBREL).

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