The European Agency for the Evaluation of Medicinal Products
Evaluation of Medicines for Human Use

London, 3 October 2000
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REVISED EMEA PUBLIC STATEMENT ON ETANERCEPT (ENBREL) – SERIOUS HEMATOLOGICAL REACTIONS AND DEMYELINATION DISORDERS -

The European Medicines Evaluation Agency's (EMEA) scientific committee, the Committee for Proprietary Medicinal Products (CPMP) has been made aware of 10 case reports of serious blood dyscrasias, some with a fatal outcome, in patients with rheumatoid arthritis treated with etanercept (Enbrel).

Etanercept (Enbrel)[1] is a recombinant human tumour necrosis factor receptor that binds to and renders TNF biologically inactive. Enbrel is indicated in the treatment of active rheumatoid arthritis in adults when the response to disease modifying antirheumatic drugs, including methotrexate (unless contraindicated) has been inadequate and the treatment of active polyarticular-course juvenile chronic arthritis in children aged 4 to 17 years who have an inadequate response to, or who have proved intolerant of, methotrexate.

Since first marketing (USA, November 1998) an estimated 80,000 patients have been treated with the product world-wide but only a limited number is currently treated with this medicinal product within the EU (approx. 5500).

These 10 reports of serious blood dyscrasias, from world-wide post marketing experience, include 3 cases of aplastic anaemia and 7 cases of pancytopenia. Five (5) of these 10 cases had a fatal outcome due to sepsis. In the majority of these cases, there was a close temporal relationship between the start of treatment with etanercept and the occurrence of haematological disorders (range 2 weeks to 5 months). Since the clinical experience with etanercept is still limited as this product has only recently been marketed, onset after this period cannot be ruled out. Recent or concomitant exposure to other anti-rheumatic medicines known or suspected to have myelosuppressant effects, such as methotrexate, leflunomide, 6-mercaptopurine, cyclophosphamide and azathioprine was reported in some patients who subsequently developed pancytopenia; some patients had no clear past history of haematological abnormalities.

Following a review of the above information, the EMEA wishes to draw attention to the following:

- **Cases of pancytopenia and aplastic anaemia, some with fatal outcome, have been reported rarely (i.e. less than 1 case out of 1,000 patients treated with the product) and very rarely (i.e. less than 1:10,000), respectively, in patients with rheumatoid arthritis treated with Enbrel.**
- **Caution should be exercised in patients with a previous history of blood dyscrasias being treated with Enbrel.**
- **All patients should be informed that if they develop 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.**

As an urgent measure, the prescribing and patient information has been modified through a rapid procedure at the request of the marketing authorisation holder. The EMEA thought it necessary to provide this new information to the public. The complete revised product information is available in the European Public Assessment Report of Enbrel published on the EMEA website.

[1] The European Commission granted marketing authorisation for the European Union to Wyeth Europa Ltd., U.K. on 3 February 2000 for the medicinal product Enbrel 25mg powder and solvent for solution for injection, which contains the active substance etanercept. Enbrel 25mg powder and solvent for solution for injection is made available in all Member States.

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UPDATE ON DEMYELINATION DISORDERS

The European Medicines Evaluation Agency's (EMEA) scientific committee, the Committee for Proprietary Medicinal Products (CPMP) has been made aware of 14 reports of demyelination disease in patients treated with etanercept (Enbrel).

The causal relationship between the onset of the neurological disorders and the administration of etanercept is unclear but some of the data present in the reports indicate a temporal association between starting etanercept and the onset of neurological disorders. Moreover, although no clinical trials have been performed evaluating etanercept therapy in patients with MS, two published studies investigating the effects of two other TNF inhibitors concluded that an inhibition of TNF in patients with established MS was likely to cause an exacerbation of their disease.

Following a review of the above information, the EMEA wishes to draw attention to the following:

- **A careful risk/benefit evaluation is recommended when prescribing Enbrel to patients with pre-existing or recent onset of CNS demyelinating disease.**
- **Patients treated or likely to be treated with Enbrel with a current or previous history of a demyelinating disease (such as multiple sclerosis or optic neuritis) should inform their doctor.**

The prescribing and patient information will be modified through a normal procedure at the request of the marketing authorisation holder.

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PROVISIONAL CHANGES INTRODUCED
TO INFORMATION FOR PATIENTS AND PRESCRIBERS

Enbrel 25mg powder and solvent for solution for injection

(Changes are underlined)

INFORMATION TO PATIENTS (PACKAGE LEAFLET):

2. BEFORE YOU INJECT ENBREL

Take special care with Enbrel:

- If you or your child are about to have any major surgery or develop a new infection. Your doctor may wish to monitor your treatment.
- Advise your doctor if you or your child have a history of recurrent infections or suffer from diabetes or other conditions that increase the risk of infection.
- There have been very rare reports of pronounced lowering of red and white blood cells and of blood platelets (possibly due to failure of the bone marrow) in patients treated with Enbrel. Seek medical advice immediately if you have any symptoms such as persistent fever, sore throat, bruising, bleeding or paleness. Such symptoms may point out to the existence of potentially life-threatening blood cell disorders which may require discontinuation of Enbrel.
- Some vaccines, such as oral polio vaccine, should not be given while receiving Enbrel. Please check with your doctor before you or your child receive any vaccines.
- If possible, children should be up to date with all vaccinations before receiving Enbrel.

4. POSSIBLE SIDE EFFECTS

Less frequently, serious infections that have occurred in adults while taking Enbrel, include kidney or urinary infection, bronchitis, joint inflammation or infection, localised infections in the abdomen or legs, tissue and wound infection, bone marrow infection, pneumonia, shingles, mouth infection, skin infection, bowel inflammation, bursitis, endocarditis (suspected), gastroenteritis, peritonitis, skin ulcer, vasculitis, and blood poisoning. Patients who have other medical problems, which increase the risk of infection, may rarely develop serious infections including fatal sepsis, while taking Enbrel. Other serious side effects include malignancies, heart failure, heart attack, stroke, low blood pressure, gall bladder inflammation, inflammation of the pancreas, gastrointestinal bleeding, shortness of breath, or depression. These side effects have occurred at a similar rate in patients with rheumatoid arthritis not taking Enbrel. Other serious side effects include low blood platelet count, low red blood cell count, low white blood cell count, combined low platelet, red and white cell count (possibly due to failure of the bone marrow) (see also Take special care with Enbrel).

INFORMATION TO PRESCRIBERS (SUMMARY OF PRODUCT CHARACTERISTICS):

4.4 Special warnings and special precautions for use

Haematologic reactions
Rare cases of pancytopenia and very rare cases of aplastic anaemia, some with fatal outcome, have been reported in patients with rheumatoid arthritis treated with Enbrel. Caution should be exercised in patients being treated with 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 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.

4.8 Undesirable effects

Postmarketing reports
The following table of suspected undesirable effects is based on postmarketing reports:
Uncommon: Thrombocytopenia
Rare: Anaemia, leukopenia, pancytopenia
Very rare: Aplastic anaemia

Some cases of pancytopenia and aplastic anaemia have had fatal outcomes (see section 4.4 – Special warnings and special precautions for use).