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Wyeth

4th February 2003

IMPORTANT SAFETY INFORMATION

Increased risk of serious infection and neutropenia in patients treated concurrently with anakinra and Enbrel® (etanercept).

Concurrent administration of Enbrel and anakinra is not recommended.

Dear Ms Arthur,

Following discussions with the Irish Medicines Board (IMB) and other EU regulatory agencies, Wyeth Ltd wishes to notify you of important new safety information regarding the use of Enbrel® (etanercept)[1] in combination with anakinra.

In a recent clinical trial patients with rheumatoid arthritis who received concurrent treatment with anakinra and Enbrel showed a higher incidence of serious infection and of neutropenia than patients receiving Enbrel alone and higher than that previously observed for anakinra alone. No therapeutic benefit of the combination treatment over Enbrel alone was observed in the controlled study.

Enbrel 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. Enbrel is indicated in the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate. In this population Enbrel has been shown to also slow progression of disease-associated structural damage as measured by X-ray. Enbrel is indicated in 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. Enbrel is also indicated in the treatment of active and progressive psoriatic arthritis in adults when the response to previous disease modifying antirheumatic drug therapy has been inadequate.

John Wyeth & Brother Limited
Registered in England No. 135937
Registered Office: Huntercombe Lane South
Taplow, Maidenhead, Berkshire, SL6 0PH
Registered in Dublin No. E900939

Incorporating: Wyeth Vaccines
Wyeth Biotechnology

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The above-mentioned clinical trial was a 24-week, randomized, controlled trial, conducted in 242 patients with rheumatoid arthritis who had not previously been treated with biologic agents and who were taking background methotrexate. The objective was to compare the efficacy and safety of Enbrel 25 mg biweekly alone with Enbrel plus anakinra 100 mg daily. The results of this study demonstrated an incidence of serious infection of 7% and the occurrence of neutropenia in the combination group. The incidence of infection and of neutropenia was higher than in the Enbrel alone group. These findings were also observed in another small open-label trial where anakinra was added to patients already being treated with Enbrel.[2] No therapeutic benefit of the combination treatment over Enbrel alone was observed in the controlled study.[3] Following a review of the above information, Wyeth wishes to draw attention to the following:

- The concurrent administration of Enbrel with anakinra is not a licensed use of Enbrel.

- The concurrent administration of Enbrel and anakinra has been associated with an increased risk of serious infections, an increased risk of neutropenia and no additional benefit compared to Enbrel alone. Thus, the combined use of Enbrel and anakinra is not recommended.

This information will be incorporated in the Summary of Product Characteristics (i.e. prescribing information).

Yours sincerely,

Dr Allison Jeynes–Ellis MBChB, MFPM
Medical Director

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Any suspected adverse drug reactions (ADRs) should be notified to the company and/or the IMB in the usual way.

Should you have any questions or require additional information concerning use of Enbrel, please contact: Wyeth Pharmaceuticals, M50 Business Park, Ballymount Road Upper, Walkinstown, Dublin 12 Tel: 01 670 9200.

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

[2] Safety of Combination Therapy with Anakinra and Etanercept in Patients with Rheumatoid Arthritis. ACR 2001 *M Schiff, K Bulpitt, A Weaver, M Genovese, et al. Thousand Oaks, Los Angeles, Stanford, Denver, Dallas, Birmingham, Boston and Grand Rapids*

[3] Data on file Amgen Inc.

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