The European Agency for the Evaluation of Medicinal Products
Post-authorisation evaluation of medicines for human use

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EMEA PUBLIC STATEMENT
Increased risk of serious infection and neutropenia in patients treated concurrently with Kineret (anakinra) and Enbrel (etanercept)

The European Medicines Evaluation Agency (EMEA) and its scientific committee (CPMP) have been made aware of important new safety information regarding the use of Kineret (anakinra) in combination with Enbrel (etanercept). In a recently completed clinical trial sponsored by Amgen Inc. patients with rheumatoid arthritis who received concurrent Kineret (anakinra) and Enbrel (etanercept) showed a higher incidence of serious infection and of neutropenia than patients receiving Enbrel alone and higher than observed in previous trials where Kineret was used alone.

Kineret (anakinra)[1] is a recombinant, non-glycosylated form of the human interleukin-1 receptor antagonist (IL-1ra) and is indicated for the treatment of the signs and symptoms of rheumatoid arthritis in combination with methotrexate, in patients with an inadequate response to methotrexate alone.
Enbrel (etanercept)[2] is a tumour necrosis factor-α (TNFα) inhibitor. Enbrel is indicated in the treatment of active rheumatoid arthritis in adults, active juvenile arthritis in children (4-17 years) and active and progressive psoriatic arthritis in adults when the response to disease-modifying antirheumatic drugs (DMARDs) has been inadequate. Enbrel is also indicated in the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate.

The concurrent use of Kineret and Enbrel is not authorised.
A 24-week randomised, controlled trial was 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 Kineret 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 and higher than observed in previous trials where Kineret was used alone. These findings were also observed in another small open-label trial where anakinra was added to Enbrel treatment. No therapeutic benefit of the combination treatment over etanercept alone was observed in the controlled study.
The above-mentioned information does not affect the benefit/risk balance of the respective products when used separately.

[1] Date of Marketing Authorisation: 08 March 2002 – Marketing Authorisation Holder: Amgen Europe B.V – Kineret is available in the following countries: Austria, Denmark, Finland, Germany, Greece, Ireland, Netherlands, Iceland, Norway, Portugal, Sweden and UK.

[2] Date of Marketing Authorisation: 03 February 2000 – Marketing Authorisation Holder: Wyeth Europa Ltd – Enbrel is available in the following countries: Austria, Belgium, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Italy, Luxemburg, Netherlands, Norway, Portugal, Spain, Sweden and UK.

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The EMEA wishes to point out the following important safety information to physicians:

- The concurrent administration of Enbrel with Kineret is not a licenced use for Kineret or for Enbrel.

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

- The safety and efficacy of Kineret used in combination with other TNF antagonists has not been established and their combined use is therefore not recommended.

Information for patients:

Patients under concurrent treatment with Kineret and Enbrel (and other TNF antagonists) should contact their treating physician.

The changes to the product information of Enbrel and Kineret have been approved by the CPMP on 23 january 2003 through a type II variation (see annexes 1 and 2 for relevant changes). The revised Summary of Product Characteristics (SPCs) are being forwarded to the European Commission for implementation.

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ANNEX 1

KINERET: CHANGES TO INFORMATION FOR PRESCRIBERS

Kineret 100 mg/0.67 ml (150 mg/ml) Solution for injection

4.4 Special warnings and special precautions for use

[…]

Concurrent Kineret and TNF antagonist treatment

Concurrent administration of Kineret and etanercept has been associated with an increased risk of serious infections and neutropenia compared to etanercept alone. This treatment combination has not demonstrated increased clinical benefit.
The concurrent administration of Kineret and etanercept or other TNF antagonists is not recommended (see section 4.5 and 4.8).

4.5 Interaction with other medicinal products and other forms of interaction

[…]

Concurrent Kineret and TNF antagonist treatment
In a clinical trial with patients receiving background methotrexate, patients treated with Kineret and etanercept were observed to have a higher rate of serious infection (7 %) and neutropenia than patients treated with etanercept alone and higher than observed in previous trials where Kineret was used alone. Concurrent Kineret and etanercept treatment has not demonstrated increased clinical benefit and is therefore not recommended.

The safety and efficacy of Kineret administered concurrently withTNF antagonists other than etanercept has not been established. In the absence of such data the concurrent administration of Kineret and other TNF antagonists is also not recommended.(see section 4.4 and 4.8).

[…]

4.8 Undesirable effects

[…]

Serious infections

[…]

In studies where patients received concurrent Kineret and etanercept treatment, a higher rate of serious infections compared to etanercept alone were observed (see 4.4 and 4.5).

Neutropenia

[…]

In studies where patients received concurrent Kineret and etanercept treatment, 2% of patients (3/139) developed ANC < $1.0x10^9$L. While neutropenic, one patient developed cellulitis that resolved after hospitalisation (see 4.4 and 4.5).

ANNEX 2

ENBREL: CHANGES TO INFORMATION FOR PRESCRIBERS

25 mg powder and solvent for solution for injection, 25 mg powder for solution for injection

[…]

4.4 Special warnings and special precautions for use

Concurrent Enbrel and anakinra treatment
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 (see sections 4.5 and 4.8).

[…]

4.5 Interaction with other medicinal products and other forms of interaction

[…]

Concurrent Enbrel and anakinra treatment
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 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 (see sections 4.4 and 4.8). The combination Enbrel and anakinra has not demonstrated increased clinical benefit and is therefore not recommended.

[…]

4.8 Undesirable effects

[…]

Concurrent Enbrel and anakinra treatment
In studies where patients received concurrent treatment with Enbrel plus anakinra, a higher rate of serious infections compared to etanercept 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 (see sections 4.4 and 4.5).

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