



European Medicines Agency

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## **SCIENTIFIC CONCLUSIONS**

### **RAPTIVA**

International Nonproprietary Name:  
efalizumab

**Procedure No. EMA/H/542/A20/28**

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK  
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 86 68  
E-mail: [mail@emea.europa.eu](mailto:mail@emea.europa.eu) <http://www.emea.europa.eu>

## SCIENTIFIC CONCLUSIONS AND GROUNDS FOR THE SUSPENSION OF RAPTIVA PRESENTED BY THE EMEA

Efalizumab (RAPTIVA) is a recombinant humanized monoclonal antibody that binds specifically to the CD11 a subunit of lymphocyte function-associated antigen-1 (LFA-1), a leukocyte cell surface protein.

Raptiva was authorised in the EU on 20 September 2004. It is indicated for the *“treatment of adult patients with moderate to severe chronic plaque psoriasis who have failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies including ciclosporin, methotrexate and PUVA.”*

Recently four (three confirmed and one suspected) cases of, progressive multifocal leukoencephalopathy (PML) in psoriatic patients under long-term treatment with efalizumab have been identified prompting a re-evaluation of the benefit-risk. Two confirmed cases were fatal and the one suspected case as well.

Efalizumab was the first biological approved for the treatment of moderate to severe psoriasis in 2004 in so-called “high-need” patients, i.e. those who have failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies. The indication was granted in this last line therapy on the grounds of a limited efficacy and lack of long term safety data.

Further to the initial Marketing Authorisation safety issues have arisen leading to the addition of a number of warnings into the Summary of Product Characteristics (SPC) such as aseptic meningitis, immune mediated haemolytic anaemia, antibody development with vaccinations, interstitial pneumonitis, arthritis, erythema multiforme, inflammatory polyradiculoneuropathy Miller Fisher syndrome, facial palsy and Bells palsy and severe infections, malignancies during long-term use, including serious (fatal) events such as opportunistic infections and Guillain Barré syndrome (GBS). Recently, the MAH notified the EMEA about three confirmed cases of PML and one suggestive case of PML, received for patients using efalizumab for more than 3 years, as well as 3 cases of encephalopathy and 5 cases of encephalitis.

At the December 2008 CHMP meeting, the Committee agreed to convene the Scientific Advisory Group on clinical neurosciences (SAG-CNS) with additional experts on the treatment of psoriasis to discuss the benefits and risks of efalizumab and its place in therapy.

The SAG meeting was held in January 2009 and the group looked at all of the available data on the benefits and risks of Raptiva. The experts were concerned that the margin of benefits over risks for Raptiva had narrowed since the medicine’s approval, but agreed that despite a modest efficacy and increased risk reported to date efalizumab still represents a useful treatment option albeit with a restricted role in the treatment of moderate and severe psoriasis and with limited evidence to document the actual response rate in non-responders to previous systemic treatments.

In view of the above the European Commission initiated a procedure under Article 20 of Regulation (EC) No 726/2004. The European Commission requested the Committee on 16 January 2009 to assess the above concerns and its impact on the benefit/risk balance for Raptiva, and to give its opinion on measures necessary to ensure the safe and effective use of Raptiva and on whether the marketing authorisation for this product should be maintained, varied, suspended or withdrawn.

At the January 2009 CHMP meeting, it was considered that there were uncertainties with the benefit/risk of Raptiva and the CHMP requested the MAH to submit further data on the above-mentioned safety concerns. The overall assessment of these data confirmed the previous safety concerns of Raptiva without identifying any subgroups with a potentially more favourable benefit/risk balance.

The CHMP reviewed all the available data submitted by the MAH to address the increased safety concerns and its impact on the benefit-risk and came to the following conclusions.

### **Efficacy**

Based on the five phase III clinical trials submitted at the time of the Marketing authorisation and the additional data provided since then, the Committee considers that the efficacy of efalizumab in psoriasis is modest.

Also, as acknowledged by the MAH, it is not possible to define a psoriasis patient population that exclusively benefits of efalizumab and not to other therapies in psoriasis.

Although severe psoriasis is a serious disease with a potentially negative impact on the patient's social life, it is not life threatening.

### **Safety**

As discussed above the recent cases of PML are of concerns. Recently, four cases were reported by the MAH; of these reported cases, three were confirmed with two of them leading to the patients death.

To address these safety issues, the MAH has proposed additional risk minimisation activities including restriction of continuous use to 2 years, excluding non-responders at 3 months, cautionary use in the elderly, intensive monitoring, contraindication of concurrent use of immunosuppressive and educational programs for physicians and patients.

It is questionable whether these risk minimisations are useful. Several issues are already covered in the current SPC i.e. Raptiva is not recommended in combination with other immunosuppressive anti-psoriasis products and should be initiated by a dermatologist. Frequent monitoring for infections is already recommended. For PML it is questionable whether frequent monitoring aimed at early detection of PML will be effective and it is rare that the sequel of PML is reversed if diagnosed. These limit the value of frequent monitoring for PML. Exclusion of non-responders after 3 months is in fact common practice i.e. if no effect is observed treatment will not be continued. Restriction of use by maximizing the duration of treatment up to 2 years is based on the four individual PML cases. However this can not be considered as evidence to recommend the limitation of treatment to 2 years. Besides it is highly unlikely that the treatment is interrupted after 2 years if the therapy is still efficacious and alternatives are not available and more importantly it does not address the other risks. Hence, the additional risk minimisation measures, as proposed by the MAH, are not considered appropriate to ensure the safe use of Raptiva and thus do not change the current benefit/risk substantially.

Additional options suggested were the restriction of the indication to last resort patients i.e. non-responders to TNF alpha blockers and patients for which TNF alpha blocker are contra-indicated. Data to support this approach is currently missing.

Response rates in non-responders to TNF alpha are the same if not less as for the normal psoriasis population. In absence of supportive data, it is impossible to identify up front a psoriasis population who responds to efalizumab.

Moreover, there are no arguments that the risk in such refractory patients is different. On the contrary, non-responsiveness to TNF alpha blockers suggests that the immune-system in these patients is different which raises the question whether these patients are not more vulnerable for developing 'immunological' adverse events. In addition, these patients would already have received other immunosuppressive treatments before, which might have altered their immune systems. The point is that the immune system of these TNF alpha blocker resistant patients is different from the one in the unrestricted population.

Therefore, restricting the indication to this population is not considered as an option, as the benefit at best is the same as for the unrestricted population, but potentially with a higher risk. It is also noted that Raptiva is not free from cardiovascular and tuberculosis risks and switching to efalizumab because of these contra-indication for the other biologicals would lead to a selection of an at risk population with efalizumab.

### **Benefit/Risk Balance**

The efficacy of Raptiva in psoriasis is modest.

The new safety signals that have emerged (especially PML) together with the known risk of opportunistic infections do compromise the benefit/risk ratio. Since the grant of the Marketing Authorisation, the safety issues have arisen leading to the addition of a number of warnings into the SPC such as aseptic meningitis, immune mediated haemolytic anaemia, antibody development with vaccinations, interstitial pneumonitis, arthritis, erythema multiforme, inflammatory polyradiculoneuropathy Miller Fisher syndrome, facial palsy and Bells palsy and severe infections, malignancies during long-term use, including serious (fatal) events such as opportunistic infections and Guillain Barré syndrome (GBS). In addition the MAH recently notified the EMEA about 3 cases of encephalopathy and 5 cases of encephalitis.

Furthermore, based on a comparative evaluation of serious adverse events, it appears that Raptiva has an unfavourable safety profile as compared to the other biologicals with respect to fatal reports, fatal infections neoplasm and neurological disorder.

It is questioned by the CHMP whether a psoriasis population can be identified that exclusively benefits from efalizumab. As indicated by the experts there might be a small group of patients who could benefit from Raptiva. However the CHMP considered that no further risk minimisation measures would be effective for this group. Moreover it might be that this group of patients naturally would be at higher risk.

Therefore on the basis of the above, the CHMP concluded that the benefit/risk of Raptiva is considered negative.

### **Overall Conclusion**

The MAH has proposed additional risk minimisation measures including restriction of use by restriction of the duration of treatment, promoting rotational treatment and frequent monitoring. It is questionable whether a restriction in duration of use prevents the occurrence of PML in users.

Since the time of approval several additional warnings and serious adverse reactions have been included in the product information and it is not considered appropriate to add further precautions.

Hence, considering that moderate to severe psoriasis is not a life threatening disease, the efficacy of efalizumab is modest, the safety profile is of concern and includes fatal reports of PML, encephalopathy, encephalitis and the availability of alternative treatments, the CHMP recommends a suspension of the marketing authorisation of Raptiva (efalizumab) for the treatment of adult patients with moderate to severe chronic plaque psoriasis.

## GROUNDINGS FOR SUSPENSION PRESENTED BY THE EMEA

The Committee reviewed all available information on the benefits and risks of Raptiva including all studies that have been completed and post-marketing data.

The Committee considered that the efficacy of Raptiva in the treatment of psoriasis is modest. The Committee considered that although the mechanism of action of efalizumab distinguishes itself from the other biologicals this property as such is not sufficient to justify the use of Raptiva.

The Committee is of the opinion that the safety profile of Raptiva is of concern considering the recent cases of PML. Furthermore since the time of approval several additional warnings and serious adverse reactions have been included in the product information and further risk minimisation is not considered effective.

The Committee concluded, in view of the available data, that the risks associated with the use of Raptiva as *treatment of adult patients with moderate to severe chronic plaque psoriasis who have failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies including ciclosporin, methotrexate and PUVA* outweigh the benefits. In addition, the Committee considered that the current and proposed risk minimisation activities were not adequate to reduce the risks to an acceptable level or predict which patients may be at risk.

The Committee considered that in the more limited indication as proposed by the MAH both data on efficacy and safety are lacking and therefore no conclusions can be drawn on the benefit-risk ratio in this patient population.

The Committee, as a consequence, concluded that the benefit/risk balance of Raptiva is not positive under the approved conditions of use.

The CHMP has therefore recommended the suspension of the Marketing Authorisation for Raptiva until the MAH is able to identify a patient population in which the clinical benefits outweigh its risks.