MERCK SERONO

November 2008

Direct Healthcare Professional Communication on the association of efalizumab (Raptiva®) with progressive multifocal leukoencephalopathy (PML)

IMPORTANT SAFETY INFORMATION

Dear Health Care Professional,

Following discussions with EU regulatory agencies, including the Irish Medicines Board (IMB), Merck Serono wishes to inform you of new safety data regarding Raptiva (efalizumab).

Raptiva® is an immunosuppressive, humanized monoclonal antibody indicated for:

- treatment of adult patients with moderate to severe chronic plaque psoriasis who have failed to respond to, or who have a contraindication to, or who have a contraindication to, or are intolerant to other systemic therapies including ciclosporin, methotrexate and PUVA.

Summary

- In September 2008, a case of progressive multifocal leukoencephalopathy (PML) was reported in a patient with plaque psoriasis receiving efalizumab (Raptiva) in the post-marketing setting.
- In this case Raptiva had been given as monotherapy for approximately 4 years.
- The case underlines the importance of:
  - continued clinical vigilance;
  - prompt discontinuation of Raptiva when PML is suspected with subsequent appropriate evaluation, including magnetic resonance imaging (MRI) scan and lumbar puncture.
- The content of this letter has been agreed with the European Authorities.

Bedfont Cross, Stanwell Road,
Feltham, Middlesex
TW14 8NX
United Kingdom
Phone +44 (0)20 8818 7200
Fax +44 (0)20 8818 7267
www.merckserono.net

Merck Serono Ltd. Reg. 990823
Serono Ltd. Reg. 1192915
Both registered in England and Wales
Trading as Merck Serono

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Further information on the safety concern

Progressive Multifocal Leukoencephalopathy (PML) is a rare, progressive and demyelinating disease of the central nervous system that usually leads to death or severe disability. PML is caused by activation of JC virus, a polyoma virus that resides in latent form in up to 80% of healthy adults. JC virus usually remain latent, typically only causing PML in immunocompromised patients. The factors leading to activation of the latent infection are not fully understood.

There has been one confirmed case of PML and one case with symptoms suggestive of PML in patients receiving Raptiva.

The recent case of PML has been reported in a 70-year-old man who received RAPTIVA for longer than 4 years for treatment of plaque psoriasis. He was not receiving other systemic immunosuppressants concomitantly to Raptiva. The patient also suffered from coronary artery disease and hyperlipidemia. PML was diagnosed based on the detection of JC viral DNA in the CSF, clinical symptoms, and MRI findings. The patient died about two months after his first neurological symptoms started.

The second case refers to a patient who developed progressive degenerative neurological symptoms suggestive of PML; however, a final diagnosis was not made and PML was not confirmed.

These cases emphasise the importance of clinical vigilance in the management of patients treated with Raptiva.

The overall exposure to date, since RAPTIVA was first approved in the United States in October 2003, is estimated at approximately 47'000 patient-years worldwide, of which approximately 15'000 patient-years correspond to the exposure in the European Union

The absolute risk of PML in patients treated with Raptiva cannot be precisely estimated.

Further information on recommendations to healthcare professionals

If a patient develops PML, Raptiva must be permanently discontinued.

Raptiva must be prescribed in compliance with the Summary of Product Characteristics (SPC).

Patients must be monitored at regular intervals for any new or worsening neurological symptoms or signs that may be suggestive of PML (such as impaired cognition, visual disturbances, hemiparesis, altered mental state or behavioural changes). If PML is suspected, further dosing must be suspended until PML has been excluded.

The clinician should evaluate the patient to determine if the symptoms are indicative of neurological dysfunction and, if so, whether these symptoms are possibly suggestive of PML. If any doubt exists, further evaluation, including Magnetic Resonance Imaging (MRI) scan preferably with contrast, cerebrospinal fluid (CSF) testing for JC viral DNA and repeat neurological assessment, should be considered.

Patients should also be advised to inform their partner or caregivers about their treatment, since they may notice symptoms that the patient is not aware of.

Call for reporting

Healthcare professionals should report any suspected adverse reactions associated with the use of Raptiva to the Irish Medicines Board (IMB), in the usual way (www.imb.ie). Adverse events should also be reported to Merck Serono ltd. (+44 (0)20 8818 7373, medinfo.uk@merckserono.net) or to Merck Serono Global Drug Safety Department (GlobalDrugSafety@merckserono.net).

Communication information

If you have further questions on this issue, please contact Medical Information, Merck Serono ltd., Bedfont Cross, Stanwell Road, Feltham, Middlesex TW14 8BR [+44 (0)20 8818 7373, medinfo.uk@merckserono.net)

Yours sincerely,

Dr Gillian Shepherd, MD,MRCP
Director Health and Clinical Excellence