



18th February 2008
P212828

Reports of Progressive Multifocal Leukoencephalopathy (PML) in CellCept[®] (mycophenolate mofetil) treated patients

Dear Health Care Professional.

In agreement with the EMEA, F.Hoffmann-La Roche wishes to inform you of new safety information regarding CellCept[®] (mycophenolate mofetil).

- **Isolated cases of progressive multifocal leukoencephalopathy (PML) have been reported in patients receiving CellCept[®]. The case reports have been associated with confounding factors in particular the nature of the underlying disease, concomitant immunosuppression and the latency between the use of CellCept[®] and the onset of PML. However, based on the temporal relationship observed in some cases, the contributory role of CellCept[®] cannot be excluded.**
- **The Summary of Product Characteristics of CellCept[®] has been updated to include this new information.**
- **Physicians should consider PML in the differential diagnosis in patients reporting neurological symptoms following treatment with CellCept[®] and appropriate specialist referral investigation and management should be considered as clinically indicated. Consideration should be given to reducing the total immunosuppression in patients who develop PML. In transplant patients, however, reduced immunosuppression may place the graft at risk.**

Progressive Multifocal Leukoencephalopathy (PML) is a rare, progressive, demyelinating disease of the central nervous system (CNS) that usually leads to death or severe disability. PML is caused by the reactivation of the JC virus, a polyomavirus that resides in latent form in 70 – 90% of the adult population worldwide. JC virus usually remains latent, typically only causing PML in immunocompromised patients. The factors leading to activation of the latent infection are not fully understood although abnormalities in T-cells have been described as important for reactivation of JC virus and PML. Patients usually present with focal CNS abnormalities and radiographic evidence of white matter disease without mass effect.

PML has been described in transplant patients involving different immunosuppressant medicines. 75% of all the PML cases reported in transplant recipients presented subacutely; hemiparesis, apathy, and confusion were the most frequent presenting features. PML should be considered in any transplant recipient who develops central neurological symptoms.

PML has also been reported in other immunocompromised patients, including HIV-positive patients, cancer patients, and patients with autoimmune disease including systemic lupus erythematosus (SLE). The incidence of PML in autoimmune diseases is not known, however, there are a number of cases reported in the literature. PML has been reported in patients with SLE receiving prednisone, azathioprine, cyclophosphamide and other immunosuppressants.

CellCept[®] and PML

The data related to the case reports of PML in CellCept[®] treated patients has been reviewed by the CHMP.

CellCept[®] (mycophenolate mofetil), which has been on the market for over 10 years, is an immunosuppressive agent indicated in combination with ciclosporin and corticosteroids for the



prophylaxis of acute transplant rejection in adults receiving allogeneic renal, cardiac or hepatic transplants, and in children and adolescents (2-18 years) receiving renal transplants.

Isolated cases of PML have been described in kidney, heart and lung transplant patients, and in SLE patients, receiving CellCept®. In the EU CellCept® is not authorised for the treatment of SLE. Transplant patients were male (aged 33-62 years) and were taking concomitant immunosuppressants (e.g. tacrolimus, basiliximab, prednisone and cyclosporine). The patients involved in the SLE reports were females aged 40-53 years and had longstanding SLE. SLE patients were taking concomitant medicines including ciclosporin, cyclophosphamide and steroids. Diagnoses were confirmed by detection of JC virus in the cerebrospinal fluid and/or brain biopsy. Case outcomes varied from resolution, to improvement or death.

PML should be considered in the differential diagnosis in patients taking CellCept® who develop neurological symptoms, and appropriate specialist referral for investigation and management should be considered. Consideration should be given to reducing the total immunosuppression in patients who develop PML. In transplant patients, however, reduced immunosuppression may place the graft at risk. Apart from reducing the total immunosuppression, there are no interventions that can reliably prevent PML, or adequately treat PML if it develops.

Roche will continue to monitor the safety of CellCept® through established reporting mechanisms and notify regulatory authorities of any serious adverse events. You can assist us in monitoring the safety of CellCept® by reporting adverse reactions to us. Please provide as much information as possible, including information about medical history, any concomitant medication, onset and treatment dates.

You can assist us in monitoring the safety of CellCept® by reporting adverse reactions to us to Roche UK Drug Safety Centre on 01707 367554.

Should you have any questions or require additional information regarding the use of CellCept®, please contact medical information on 0800 328 1629

A handwritten signature in black ink, appearing to read "Michelle Rashford".

Michelle Rashford
Medical Director

Attachment:

Text of the revised Product Information (with changes made visible) as adopted at the January 2008 CHMP plenary meeting

Text of the revised Product Information

4.4 Special warnings and precautions for use

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Oversuppression of the immune system increases the susceptibility to infection including opportunistic infections, fatal infections and sepsis (see section 4.8).

Cases of Progressive Multifocal Leukoencephalopathy (PML), sometimes fatal, have been reported in CellCept treated patients. The reported cases generally had risk factors for PML, including immunosuppressant therapies and impairment of immune function. In immunosuppressed patients, physicians should consider PML in the differential diagnosis in patients reporting neurological symptoms and consultation with a Neurologist should be considered as clinically indicated. Consideration should be given to reducing the total immunosuppression in patients who develop PML. In transplant patients, however, reduced immunosuppression may place the graft at risk.

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4.8 Undesirable effects

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Disorders related to immunosuppression: serious life-threatening infections including meningitis, endocarditis, tuberculosis and atypical mycobacterial infection. Cases of Progressive Multifocal Leukoencephalopathy (PML), sometimes fatal, have been reported in CellCept treated patients. The reported cases generally had risk factors for PML, including immunosuppressant therapies and impairment of immune function.