Date: 12 December 2014

Mycophenolate mofetil (CellCept®): new warnings about the risks of hypogammaglobulinaemia and bronchiectasis.

Dear Healthcare Professional

F. Hoffmann-La Roche Ltd. in agreement with the European Medicines Agency and the Medicines Authority would like to inform you of important safety information regarding the use of mycophenolate mofetil (CellCept®). The active pharmacological form of mycophenolate mofetil is mycophenolic acid, therefore the new warnings regarding the risks of hypogammaglobulinaemia and bronchiectasis also apply to products that contain mycophenolic acid as their active ingredient.

Summary of the safety concern and recommendations

Hypogammaglobulinaemia

- Hypogammaglobulinaemia associated with recurrent infections has been reported in patients receiving mycophenolate mofetil in combination with other immunosuppressants.
- Patients who develop recurrent infections should have their serum immunoglobulins measured.
- In cases of sustained, clinically relevant hypogammaglobulinaemia, appropriate clinical action should be considered. In some of the reported cases, switching mycophenolate mofetil to an alternative immunosuppressant resulted in serum IgG levels returning to normal.

Bronchiectasis

- There have been published reports of bronchiectasis in patients who received mycophenolate mofetil in combination with other immunosuppressants.
- Patients who develop persistent pulmonary symptoms, such as cough and dyspnea, should be investigated promptly.
- In some of the confirmed cases of bronchiectasis, switching mycophenolate mofetil to another immunosuppressant resulted in improvement in respiratory symptoms.

Further background information to this safety update

Mycophenolate mofetil is a prodrug that is completely converted to the active pharmacological form mycophenolic acid (MPA), which has potent cytostatic effects on both B- and T-lymphocytes.

A review of case reports and published studies showed that mycophenolate mofetil in combination with other immunosuppressants can cause hypogammaglobulinaemia and bronchiectasis. Because

MPA is the active pharmacological form of mycophenolate mofetil, these risks also apply to all products that contain MPA as their active ingredient.

Patients who developed bronchiectasis usually presented with a persistent productive cough and, in some cases, recurrent upper airway infection. The diagnosis was confirmed by high resolution computed tomography of the chest. The onset of respiratory symptoms varied from a few months to several years after starting mycophenolate mofetil. Because of this relatively long latency period, it is not possible to reliably estimate the incidence of bronchiectasis from short-term clinical trials. The risk of bronchiectasis may be linked to hypogammaglobulinaemia or to a direct effect of MPA on the lung.

In addition to causing bronchiectasis, there have also been isolated reports of interstitial lung disease, some of which were fatal. Therefore, clinicians are advised to consider the possibility of these conditions as part of a differential diagnosis in patients with persistent pulmonary symptoms.

Hypogammaglobulinaemia may present as recurrent infections. Because serum immunoglobulin levels were not routinely measured in clinical trials the incidence of hypogammaglobulinaemia is not known.

Call for reporting

Healthcare professionals should report any serious adverse events suspected to be associated with the use of CellCept® (mycophenolate mofetil) according to national reporting requirements.

Please report suspected adverse events to the Medicines Authority; ADR report forms can be downloaded from www.medicinesauthority.gov.mt/adrportal and sent to postlicensing.medicinesauthority@gov.mt or sent to ADR reporting 201, level 3, Rue d'Argens Gzira/GZR 1368.

In addition adverse events should also be reported to Roche Products Ltd. Please contact Roche Drug Safety Centre by emailing welwyn.uk_dsc@roche.com or calling +44(0)1707 367554.

Company contact point

Should you have any questions or require additional information regarding the use of CellCept® (mycophenolate mofetil) please contact Roche Medical Information by phone on +44(0)800 328 1629 or via e-mail medinfo.uk@roche.com

Yours sincerely

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