Heredia, May 19th, 2015

Direct Healthcare Professional Communication

Association of MabThera (rituximab) with Toxic Epidermal Necrolysis and Stevens-Johnson-Syndrome

Dear Healthcare Provider,

F. Hoffmann-La Roche Ltd. would like to inform you of important new safety information on the use of MabThera (rituximab):
Summary

- In patients with autoimmune diseases, severe skin reactions such as Toxic Epidermal Necrolysis (TEN) and Stevens- Johnson Syndrome (SJS) with fatal outcome have been reported very rarely with MabThera in the post -marketing setting.

- In patients with haematological malignancies, information on severe bullous skin reactions including fatal cases of Toxic Epidermal Necrolysis and Stevens-Johnson Syndrome, which have been reported rarely in the post marketing setting, are already included in the MabThera product information.

- For autoimmune and oncology indications, in case of the occurrence of severe skin reactions, MabThera treatment should be discontinued. The decision to re-administer MabThera must be carefully assessed based on the individual patient`s benefit–risk profile.

Further information on the safety concern

The cases of Toxic Epidermal Necrolysis and Stevens- Johnson Syndrome in autoimmune patients have been reported with either first time use or with later infusions. Some of the cases occurred on the day of dosing or within a few days of dosing. In other cases, the event occurred weeks or up to four months after the dose.

Four of the cases in autoimmune patients had a close association in time to MabThera dosing

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(starting on the day of dosing or the next day), of which one case of Toxic Epidermal Necrolysis had a fatal outcome.

In several of the cases in autoimmune patients, treatments known to be possibly associated with Toxic Epidermal Necrolysis and Stevens- Johnson Syndrome were given concomitantly with MabThera therapy.

The mechanism of these reactions remains unknown.

The "Warnings and Precautions" and the "Undesirable Effects" sections of the prescribing/product information for MabThera have been updated to reflect the new safety information, as follows:

2.4 Warnings and Precautions
2.4.1 General
Skin reactions
Severe skin reactions such as Toxic Epidermal Necrolysis and Stevens - Johnson syndrome, some with fatal outcome, have been reported (see section 2.6.2 Post marketing). In case of such an event with a suspected relationship to MabThera/Rituxan, treatment should be permanently discontinued.

2.6 Undesirable Effects
2.6.2 Post Marketing
Skin and appendages:
Severe bullous skin reactions including some fatal cases of toxic epidermal necrolysis and Stevens - Johnson syndrome have been reported rarely.

Recent analysis of the cases of Toxic Epidermal Necrolysis and Stevens- Johnson Syndrome reported in patients with haematological malignancies was consistent with the information already provided in the Undesirable Effects section of the MabThera product information, which states severe bullous skin reactions including fatal cases of Toxic Epidermal Necrolysis have been reported rarely.

Further information
Full prescribing and adverse event information for MabThera® with this new information will be presented soon.

Call for reporting
Health care professionals should report any serious adverse events suspected to be associated with the use of MabThera® to: cac.farmacovigilancia@roche.com or +506-2298-1500 / US toll free 1-888-670-4123.

Company contact point

Should you have any questions regarding the use of MabThera® (capecitabine), please feel free to contact us under the below address: cac.medical_info@roche.com.
Roche Servicios, S. A.

Should you have any questions or require additional information regarding the use of Xeloda®, please contact: cac.medical_info@roche.com

To report an adverse event of Xeloda® or any other Roche product, please contact: cac.farmacovigilancia@roche.com

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