Heredia, February 10th, 2015

Subject: Direct Healthcare Professional Communication

IMPORTANT SAFETY UPDATE OF PRESCRIBING INFORMATION FOR XELODA® (CAPECITABINE)

Dear Healthcare Provider,

F. Hoffmann-La Roche Ltd (hereafter referred to as Roche) would like to inform you about new recommendations concerning the treatment of patients with dihydropyrimidine dehydrogenase (DPD) deficiency with Xeloda (capecitabine).

Summary

- Contraindications

  This section has been updated to remove the following information:

  "As with other fluoropyrimidines, Xeloda is contraindicated in patients with known dihydropyrimidine dehydrogenase (DPD) deficiency".

  This information has been removed because currently available screening tests for DPD activity are unreliable and such a contraindication could result in withholding an effective drug from patients who may not have reduced levels of DPD. Additionally, it is recognised that DPD deficiency poses a spectrum of risk from minimal risk to the potential for serious adverse events, dependent upon the actual degree of DPD impairment.

- Warnings and Precautions

  This section has been updated based on evidence from post-marketing reports and published literature.

Roche Servicios S. A. Apartado Postal 3438-1000 San José. Costa Rica Dirección Médica Tel. + 506 2298-1500 Fax + 506 2298-1606 e-mail: cac.farmacogilancia@roche.com

Patients with complete or near complete absence of DPD activity have the greatest risk of life-threatening or fatal toxicity; no dose has been proven safe for such patients who should not be treated with Xeloda.

For patients with partial DPD deficiency and where the benefits of treatment are considered to outweigh the risks, these patients must be treated with extreme caution, initially with substantial dose reduction and frequent monitoring.

Roche is working closely with health authorities to update the product information. Once approved by the health authorities, the revised Xeloda product information will be available on insert version December 2014.

Further information on the background of the new recommendations

DPD enzymatic activity tests are currently unreliable. Patients are not routinely screened for either genetic variants (DPYD polymorphisms or DPD enzymatic activity) prior to treatment. DPD deficiency poses a spectrum of risk from minimal risk to the potential for serious toxicity and fatal outcome.

The current contraindication effectively excludes patients with any degree of DPD deficiency and could result in withholding an effective drug from patients in whom Xeloda treatment could be used with appropriate dose adjustment.

Therefore, the absolute Contraindication to patients with known DPD deficiency is removed in order not to deprive eligible patients unnecessarily from the benefits of Xeloda treatment.

However, the Warnings and Precaution section has been updated based on evidence from post marketing reports and published literature which recognises that DPD deficiency can occur at differing levels of impaired DPD activity with an associated spectrum of risk.

Update of Warnings and Precautions related to DPD deficiency:

Rarely, unexpected, severe toxicity (e.g. stomatitis, diarrhea, mucosal inflammation, neutropenia and neurotoxicity) associated with 5-FU has been attributed to a deficiency of DPD activity. Patients with low or absent DPD activity, an enzyme involved in fluorouracil degradation, are at increased risk for severe, life-threatening, or fatal adverse reactions caused by fluorouracil.

Patients with certain homozygous or certain compound heterozygous mutations in the DPYD gene locus that cause complete or near complete absence of DPD activity, have the highest risk of life-threatening or fatal toxicity and must not be treated with Xeloda. No dose has been proven safe for patients with complete absence of DPD activity.

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For patients with partial DPD deficiency where the benefits of Xeloda are considered to outweigh the risks (taking into account the suitability of an alternative non-fluoropyrimidine chemotherapeutic regimen), these patients must be treated with extreme caution, initially with a substantial dose reduction and frequent subsequent monitoring and dose adjustment according to toxicity .

In patients with unrecognized DPD deficiency treated with capecitabine, life-threatening toxicities manifesting as acute overdose may occur. In the event of grade 2-4 acute toxicity, treatment must be discontinued immediately. Permanent discontinuation should be considered based on clinical assessment of the onset, duration and severity of the observed toxicities.

Therapeutic indications

Xeloda® is indicated for

- Xeloda in combination with docetaxel is indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of cytotoxic chemotherapy. Previous therapy should have included an anthracycline. Xeloda is also indicated as monotherapy for the treatment of patients with locally advanced or metastatic breast cancer after failure of a taxane and an anthracycline-containing chemotherapy regimen or for whom further anthracycline therapy is not indicated.
- Colorectal cancer:
  Xeloda is indicated as adjuvant treatment of patients with colon cancer.
  Xeloda is indicated as first-line treatment of patients with metastatic colorectal cancer.
- Gastric Cancer:
  Xeloda is indicated as first-line treatment of patients with advanced gastric cancer.

Xeloda® is contraindicated in patients who have:

- Hypersensitivity to capecitabine or to any of its components
- Patents with a history of severe and unexpected reactions to fluoropyrimidine therapy or with a known hypersensitivity to fluorouracil
- Concomitant administration with sorivudine or its chemically related analogues; such as brivudine

Further information

Full prescribing and adverse event information for Xeloda® 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 Xeloda® to: cac.farmacovigilancia@roche.com or +506-2298-1500 / US toll free 1-888-670-4123.

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Company contact point

Should you have any questions regarding the use of Xeloda® (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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