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

Dear Healthcare Provider,

F. Hoffmann-La Roche Ltd representation office in Armenia (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 recognized 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.

Patients with complete or near complete absence of DPD activity have the greatest risk of life-

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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 within 8 months at www.pharm.am website.

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.

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

- The treatment of locally advanced or metastatic breast cancer in combination with docetaxel after failure of cytotoxic therapy of which one must have included an anthracycline.
- The treatment of locally advanced or metastatic breast cancer as monotherapy after failure of a taxane and an anthracycline-containing chemotherapy regimen or for whom further anthracycline therapy is not indicated.
- The adjuvant treatment of patients with colon cancer
- The treatment of patients with metastatic colorectal cancer
- First-line treatment of patients with advanced esophogastric cancer

Xeloda® is contraindicated in patients who have:

- Hypersensitivity to capecitabine or to any of its components
- Patients 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® can be found in the currently authorized product information available via

Call for reporting

According to the Article 17 of the RA Law “On Drugs” “Prophylactic establishments, pharmacies and establishments and organizations engaged in drug realization and use should immediately notify the body authorized by the Government about all cases of unknown side effects”

In Republic of Armenia drug safety monitoring is conducted by “Scientific centre of drug and medical technology expertise after acad. E. Gabrileyan” JSC MoH.

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Should you have any questions or require additional information regarding the use of Xeloda (capecitabine) please feel free to contact via following details:

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signature