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Bandra Kurla Complex, Bandra (E),
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19-May-2020

Product: Capecitabine Tablets I.P. [150mg and 500mg]

Direct Healthcare Professional Communication

5-Fluorouracil (i.v.), Capecitabine and Tegafur containing products: Pre-treatment testing to identify DPD-deficient patients at increased risk of severe toxicity

Dear Healthcare Professional,

Marketing authorization holders of medicines containing 5-fluorouracil i.v. (5-FU), Capecitabine or tegafur, in agreement with the European Medicines Agency (EMA) would like to inform you of the following:

Summary

- **Patients with partial or complete dihydropyrimidine dehydrogenase (DPD) deficiency are at increased risk of severe toxicity during treatment with fluoropyrimidines (5-FU, capecitabine, tegafur).**
- **Phenotype and/or genotype testing before initiation of treatment with fluoropyrimidines is recommended.**
- **Treatment with 5-FU, capecitabine or tegafur-containing medicinal products is contraindicated in patients with known complete DPD deficiency.**
- **Consider a reduced starting dose in patients with identified partial DPD deficiency.**
- **Therapeutic drug monitoring (TDM) of fluorouracil may improve clinical outcomes in patients receiving continuous 5-fluorouracil infusions**

Background on the safety concern

Fluoropyrimidines consist of a group of cancer medicines including 5-fluouracil (5-FU) and its prodrugs capecitabine and tegafur, with different presentations:

- Parenteral 5-FU: a component of the standard therapy for a variety of malignancies, including colorectal, pancreatic, gastric, breast and head and neck cancer, mostly used in combination with other anticancer agents;
- Capecitabine: an oral prodrug of 5-FU, indicated for the treatment of colorectal, gastric and breast cancer;
- Tegafur: an oral prodrug of 5-FU, available <as mono therapy or> in combination with two modulators of 5-FU metabolism, gimeracil, and oteracil for the treatment of gastric cancer.

Dihydropyrimidine dehydrogenase (DPD) is the rate limiting enzyme in the catabolism of 5-FU. DPD activity is subject to a wide variability. Complete DPD deficiency is rare (0.01-0.5% of Caucasians). Partial DPD deficiency is estimated to affect 3-9% of the Caucasian population.

Impaired DPD enzyme function leads to an increased risk for severe or life-threatening toxicity in patients treated with 5-FU or its prodrugs. Despite negative test results for DPD deficiency, severe toxicity may still occur.

- Patients with complete DPD deficiency are at high risk of life-threatening or fatal toxicity and must not be treated with fluoropyrimidines.
- Patients with partial DPD deficiency are at increased risk of severe and potentially life-threatening toxicity. A reduced starting dose should be considered to limit the risk of severe toxicity. Subsequent doses may be increased in the absence of serious toxicity, as the efficacy of a reduced dose has not been established.

Pre-treatment testing of DPD activity

To identify patients at risk for severe toxicity, pre-treatment testing for DPD deficiency is recommended, despite uncertainties regarding optimal testing methodology.

Both genotyping of the DPD coding gene (DPYD) and phenotyping by measurement of blood uracil levels are acceptable methods.

Genotyping

Four DPYD genotype variants (c.1905+1G>A, c.1679T>G, c.2846A>T and c.1236G>A/HapB3) are associated with an increased risk of severe toxicity. Other rare DPYD genotype variants may also be associated with increased risk of severe toxicity.

Phenotyping

DPD deficiency is associated with elevated pre-treatment plasma uracil levels. A blood uracil level ≥ 16 ng/ml and < 150 ng/ml is indicative of partial DPD deficiency, while a blood uracil level ≥ 150 ng/ml is indicative of complete DPD deficiency.

Therapeutic drug monitoring (TDM) in patients treated with 5-FU (i.v.)

Complementary to upfront DPD testing, TDM of fluorouracil may improve clinical outcomes in patients treated with intravenous 5-FU. The target AUC is supposed to be between 20 and 30mg x h/L.

Call for reporting

Suspected severe and life-threatening toxicity of capecitabine, 5-fluorouracil or tegafur-containing medicinal products should be reported to us on at +91-98201 63752 or india.drugsafety@roche.com.

Additionally, All suspected Adverse Event / Special Situations and Other Case Type Reports* / Product Complaints (with or without AE) associated with the use of a Roche medicinal product should be reported to india.drugsafety@roche.com".
*Pregnancy/Breastfeeding, use in Pediatric/Elderly population, Lack of Efficacy, Overdose, Misuse, Abuse, Off Label Use, Medication Error (including Intercepted Medication Error and Potential Medication Error), Occupational Exposure, data related to a Suspected Transmission of an Infectious Agent via a Medicinal Product (STIAMP), Drug Interaction, Falsified Medicinal Products (whether suspected or confirmed) and suspected AEs from class action lawsuits.

Company contact point

Should you have any questions or require additional information regarding the use of Xeloda® (Capecitabine Tablets I.P. 150mg and 500mg) please feel free to contact us at +91-8879021826 or india.medinfo@roche.com

Yours sincerely,
Roche Products (India) Pvt. Ltd.

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