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 authorisation holders of medicines containing 5-fluorouracil i.v. (5-FU), capecitabine or tegafur, in agreement with the European Medicines Agency, 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-fluorouracil (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 monotherapy 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 of 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 of 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.

National Clinical guidelines addressing DPD genotyping or phenotyping should be considered.>

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 continuous intravenous 5-FU. The target AUC is supposed to be between 20 and 30 mg x h/L.

Call for reporting
Suspected severe and life-threatening toxicity of capecitabine, 5-fluorouracil or tegafur-containing medicinal products should be reported in accordance with the national spontaneous reporting system.

Health care professionals should report any adverse events suspected to be associated with the use of Xeloda® (capecitabine) at: cac.farmacovigilancia@roche.com

Company contact point

Should you have any questions regarding the use of Xeloda ® capecitabine, please feel free to contact us at: cac.medical_info@roche.com

Sincerely,

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Local Safety Responsible
Roche Servicios S.A.

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