Sandoz Office, Riyadh
P.O. Box 16032, Riyadh 11464
Kingdom of Saudi Arabia
Phone: +966 11 265 8101
Fax: +966 11 265 8139

Direct Healthcare Professional Communication

27-Jul-2020

5-Fluorouracil (i.v.) capecitabine 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, in agreement with the European Medicines Agency and the Saudi Food and Drug Authority (SFDA), 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).**
- **Phenotype and/or genotype testing before initiation of treatment with fluoropyrimidines is recommended.**
- **Treatment with 5-FU, capecitabine-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, 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;

Sandoz Office, Riyadh
P.O. Box 16032, Riyadh 11464
Kingdom of Saudi Arabia
Phone: +966 11 265 8101
Fax: +966 11 265 8139

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.

Sandoz Office, Riyadh
P.O. Box 16032, Riyadh 11464
Kingdom of Saudi Arabia
Phone: +966 11 265 8101
Fax: +966 11 265 8139

Call for reporting

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

Patient Safety Department Novartis Saudi Limited - Saudi Arabia -.
Toll Free Number: 8001240078
Phone: +966112658100
Fax: +966112658107
Email: adverse.events@novartis.com
Website: http://report.novartis.com/

Saudi Food and Drug Authority National Pharmacovigilance Center
Unified Contact Center: 19999
Toll Free Number: 80024900000
Email: npc.drug@sfda.gov.sa
Website: https://ade.sfda.gov.sa

Should you have any questions, please do not hesitate to contact us. We will keep you informed as further information becomes available.