06 April 2023

Capecitabine: Pre-treatment testing to identify DPD-deficient patients at increased risk of severe toxicity.

Dear Healthcare Professional,

Sudair Pharma Company, in agreement with 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 capecitabine.**
- **Phenotype and/or genotype testing before initiation of treatment with capecitabine is recommended.**
- **Treatment with capecitabine is contraindicated in patients with known complete DPD deficiency.**
- **Consider a reduced starting dose in patients with identified partial DPD deficiency.**

Further information on the safety concern and the recommendations

Capecitabine: an oral prodrug of 5-FU, indicated for the treatment of colorectal, gastric and breast 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 Capecitabine. 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 Capecitabine.
- 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.

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.

Call for reporting

Suspected severe and life-threatening toxicity of capecitabine, 5-fluorouracil or tegafur-containing medicinal products should be reported using the below national reporting channels of Saudi Food and Drug Authority (SFDA);

SFDA call center: 19999
Email: npc.drug@sfda.gov.sa
Website: https://ade.sfda.gov.sa

Company contacts point

If you need further information and also to report any adverse events, please contact Sudair Pharma Company through the below details;
Sudair Pharma Company;

Email: pharmacovigilance@sudairpharma.com

Online: https://sudairpharma.com/report-a-side-effect/

Tel: 920001432 ext. 107

Mobile: 0546030507