SAFETY ALERT

DRAP SAFTEY ALERT NO. 36

Safety Alert of Risk of Potentially Life-threatening Toxicity with Fluorouracil and Capecitabine in Di-hydropyrimidine Dehydrogenase (DPD) Deficient Patients.

Date: 26th of October, 2023.

Target Audience:

- Manufacturers and importers of Fluorouracil and Capecitabine;
- Healthcare professionals; and
- Patients, consumers or caregivers.

Background:

The Therapeutic Goods Administration (TGA) of Australia in Sep-2022 and the Medicine and Health Product Agency (MHRA) in October, 2020 issued updates regarding the use of fluorouracil, capecitabine and flucytosine. These updates included a new warning about the potential for severe and life-threatening toxicity in patients with a partial di-hydropyrimidine dehydrogenase (DPD) deficiency. Previously, these medications were contraindicated for patients with known complete DPD deficiency. Reports of adverse events suggested a link between DPD deficiency and toxicities, although DPD deficiency testing was often not performed in affected patients. Healthcare professionals were advised to consider DPD deficiency testing before initiating therapy and to reduce the starting dose if partial DPD deficiency is detected. Similar recommendations were made by the MHRA, referencing a European safety review, which emphasized the importance of DPD deficiency testing prior to treatment initiation. *Testing is not required for topical fluorouracil formulations due to minimal systemic absorption*. The PRAC of the EMA in March 2020 also recommended pre-treatment testing for DPD deficiency before administering fluorouracil via injection or infusion. Lack of DPD enzyme can lead to the accumulation of fluorouracil in the blood, resulting in severe and life-threatening adverse reactions. Patients with complete DPD deficiency should not be given these medications, and a reduced starting dose is recommended for patients with partial DPD deficiency.

Action in Pakistan:

The case was discussed in the 2nd meeting of PRAEC-DRAP wherein it was decided to Co-opt experts in Oncology as per Rule 9 (5) of the Pharmacovigilance Rules, 2022 to assess the case of

testing of DPD deficiency in patients before initiation of treatment with Fluorouracil and Capecitabine and submit their reports in the next meeting of PRAEC. Two expert members of oncology were selected from the leading hospitals in Pakistan.

Accordingly, the PRAEC in its 3rd meeting held on the 8th of September, 2023 decided as per Rule 10(1)(h)(ii) of the Pharmacovigilance Rules, 2022 and in light of comments of co-opted experts to update contraindications in patients with known complete absence of di-hydro pyrimidine dehydrogenase (DPD) activity. Likewise, the PRAEC as per Rule 10(1)(h)(iv) of the Pharmacovigilance Rules, 2022 decided to update the warning and precaution section of prescribing information by including information about the importance of testing for DPD deficiency before initiation of the treatment with Fluorouracil and Capecitabine. Include information about the reduced starting dose in partial DPD deficiency, followed by enhanced monitoring for toxicities.

Therapeutic Goods Affected.

Name: **Fluorouracil** is indicated alone or in combination with other medicines to treat various cancers such as malignant tumours, particularly of the breast, colon or rectum. Also, it is applied to the skin for actinic keratosis and dermal warts. The recommendations are related to system fluorouracil not topical.

Capecitabine is indicated for the treatment of certain types of colon, colorectal, oesophagogastric and breast cancer

Advice for patients.

Patients should inform healthcare professionals if he/she or their family members have a history of complete or partial DPD deficiency. Patients should also promptly notify healthcare professionals about fluoropyrimidines-related toxicity, including for example stomatitis, diarrhoea, mucosal inflammation, neutropenia, and neurotoxicity.

Advice for healthcare professionals.

Healthcare professionals are informed that patients with complete or partial DPD deficiency are at increased risk of severe and fatal toxicity during treatment with medicines containing 5-fluorouracil (intravenous) and capecitabin. Therefore, healthcare professionals are advised not to treat patients with known complete DPD deficiency with these medicines. Likewise, in patients with partial DPD deficiency, a reduced starting dose should be considered. All patients need to be monitored for toxicity particularly during the first cycle of treatment or after a dose increase.

Guidelines for reporting Adverse Drug Reactions (ADRs):

Both healthcare professionals and patients are requested to report any suspected adverse drug reaction (ADRs) with fluorouracil and capecitabine to the National Pharmacovigilance Centre (NPC), Drug Regulatory Authority of Pakistan through the Med Vigilance E-Reporting System available on the DRAP website. Similarly, ADRs can also be reported through Med Safety App which is available for download from the App Store (for iOS devices) and Google Play (for Android devices).

References:

- Minutes of 3rd meeting of Pharmacovigilance Risk Assessment Expert Committee.
- Fluorouracil and capecitabine - DPD deficiency of TGA website.
- 5-Fluorouracil (intravenous), capecitabine, tegafur: MHR-UK recommended DPD testing before initiation to identify patients at increased risk of severe and fatal toxicity.
- PRAC-EMA recommendation.

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