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 and the <National Competent Authority>, 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 treatement 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 *<to be filled nationally>*.

Company contact point

<Contact point details for access to further information, including relevant website address(es), telephone numbers and a postal address>

Annexes

<Link/reference to other available relevant information, such as information on the website of a competent authority>

DHPC COMMUNICATION PLAN	
Medicinal product(s)/active substance(s)	capecitabine-containing medicinal products 5-fluorouracil-containing medicinal products (i.v.) tegafur containing medicinal products (including combinations)
Marketing authorisation holder(s)	All MAHs of capecitabine-containing medicinal products, 5-fluorouracil-containing medicinal products (i.v.) and tegafur containing medicinal products (including combinations)
Safety concern and purpose of the communication	Increased risk of severe and life-threatening toxicity in patients with partial or complete DPD deficiency To inform HPCs about the risks associated with DPD deficiency and the updated recommendations on pre-treatment DPD testing. To inform about the possibility of TDM for products containing 5-fluorouracil (i.v.)
DHPC recipients	Healthcare professionals who may prescribe (oncologists) or dispense (hospital pharmacists; pharmacists involved in the preparation of cytostatic drugs) capecitabine, tegafur (incl. combinations) and 5-fluorouracil-containing medicinal products (i.v.) – [*details to be confirmed, upon discussions with national competent authorities (NCAs) in countries where the product is currently being marketed*] Dissemination mechanism: [*to be agreed with national competent authorities*] Other recipients: [*Details on distribution list to be agreed with national competent authorities*]
Member States where the DHPC will be distributed	All EU countries where the products are marketed.

Timetable	Date
DHPC and communication plan (in English) agreed by PRAC	12.03.2020
DHPC and communication plan (in English) agreed by CHMP	30.04.2020
Submission of translated DHPCs to all national competent authorities (NCA) for review	7 days after adoption of CHMP Opinion
Agreement of translations by national competent authorities	14 days after submission to NCAs
Dissemination of DHPC	14 days after agreement of translation