Medicines containing 5-fluorouracil (i.v.): In patients with moderate or severe renal impairment, phenotyping for dihydropyrimidine dehydrogenase (DPD) deficiency by measuring blood uracil levels should be interpreted with caution

Dear healthcare professional,

The marketing authorisation holders of medicines containing 5-fluorouracil i.v. (5-FU), in agreement with <the European Medicines Agency> and the <National Competent Authority> would like to inform you of the following:

Summary

- **In patients with moderate or severe renal impairment, blood uracil levels used for dihydropyrimidine dehydrogenase (DPD) phenotyping should be interpreted with caution, as impaired kidney function can lead to increased uracil blood levels.**

- **Consequently, there is an increased risk for incorrect diagnosis of DPD deficiency, which may result in underdosing of 5-FU, leading to reduced treatment efficacy.**

Background on the safety concern

Parenteral 5-fluorouracil (5-FU) is part of the standard therapy for various malignancies, including colorectal, pancreatic, gastric, breast, and head and neck cancer. It is mostly used in combination with other anticancer agents.

The rate-limiting enzyme in the catabolism of 5-FU is dihydropyrimidine dehydrogenase (DPD). As a result, patients with impaired DPD enzyme function are at increased risk of severe or life-threatening toxicity when treated with 5-FU or one of its prodrugs, phenotyping and/or genotyping before initiation of treatment is recommended.

To identify these patients, pre-treatment testing for DPD deficiency is recommended, despite uncertainties regarding optimal testing methodology.

• Patients with complete DPD deficiency are at high risk of life-threatening or fatal toxicity and must not be treated with 5-FU or other fluoropyrimidines (capecitabine, tegafur).

• Patients with partial DPD deficiency are at increased risk of severe and potentially life--threatening toxicity. To limit the risk of severe toxicity, a reduced starting dose should be considered. Subsequent doses may be increased in the absence of serious toxicity, as the efficacy of a reduced dose has not been established.

If blood uracil levels are used to determine the DPD phenotype, the phenotype result must be interpreted with caution in patients with moderate or severe renal impairment, as renal impairment can lead to increased blood uracil levels. This could result in an incorrect diagnosis of DPD deficiency and consequently underdosing of 5-FU or other fluoropyrimidines in these patients. <National guidelines should be taken into account when choosing the appropriate approach to determine DPD activity.>

[Further information may be added according to the national context as applicable.]

Call for reporting

<A reminder of the need and how to report adverse reaction in accordance with the national spontaneous reporting system m including the details (e.g. name, postal address, fax number, website address) and how to access the national spontaneous reporting system >

Company contact point

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

DHPC COMMUNICATION PLAN	
Medicinal product(s)/active substance(s)	5-fluorouracil-containing medicinal products (i.v. application)
Marketing authorisation holder(s)	All MAHs of 5-fluorouracil-containing medicinal products (i.v. application) All concerned marketing authorisation holders in each Member State are strongly encouraged to collaborate, so that a single DHPC is prepared and circulated in each Member State.
Safety concern and purpose of the communication	Inform HCPs about a restriction of use of dihydropyrimidine dehydrogenase (DPD) deficiency phenotyping by measurement of blood uracil levels in patients with impaired kidney function.
DHPC recipients	Healthcare professionals who may prescribe (oncologists and haematologists) or dispense (hospital pharmacists; pharmacists involved in the preparation of cytostatic drugs) or are involved in the testing of uracil levels. The target group should be further defined at national level, in agreement with the respective national competent authority.
Member States where the DHPC will be distributed	Member states where fluorouracil (i.v. application) is marketed and where measurement of uracil levels is used for detection of DPD deficiency. Final decision on distributing the DHPC will be made by the respective NCA.

Timetable	Date
DHPC and communication plan (in English) agreed by PRAC	05/09/2024
DHPC and communication plan (in English) agreed by CMDh	19/09/2024
Submission of translated DHPCs to the national competent authorities for review	26/09/2024
Agreement of translations by national competent authorities	10/10/2024
Dissemination of DHPC	24/10/2024