PLEASE READ

IMPORTANT MEDICINE SAFETY INFORMATION

APPROVED BY THE HPRA

An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

Direct Healthcare Professional Communication

24th October 2024

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 Accord Healthcare Ireland Ltd and Pfizer healthcare Ireland, in agreement with the European Medicines Agency (EMA) and the Health Products Regulatory Authority (HPRA) 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, and 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.

Call for reporting

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, website: www.hpra.ie. Reports of suspected adverse reactions can also be made to the marketing authorisation holders, see contact details below.

Company contact points

This information is being provided jointly by the following marketing authorisation holders. If you have any questions, please use the below contact details for further information.

Marketing Authorisation Holder	**Product Name**	**Email**	**Telephone**
Accord Healthcare Ireland Ltd.	Fluorouracil 50 mg/ml Solution for Injection or Infusion PA 2315/091/001	medinfo@accord-healthcare.com	+44 (0) 1271385257
Pfizer Healthcare Ireland	Fluorouracil 25 mg/ml Solution for Injection or Infusion PA 0822/223/001	EUMEDINFO@pfizer.com or RegAffairsInfo@pfizer.com	1800 633 363 (toll free) or +44 (0) 1304 616161

Yours faithfully,

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