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Direct Healthcare Professional Communication (DHPC)

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,

Accord Healthcare Ireland Limited, Accord Healthcare S.L.U, Central Procurement and Supplies Unit, JV Healthcare Limited, Remedica Limited in agreement with the European Medicines Agency and the Malta Medicines 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 treatment 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 and Clinical guidelines addressing DPD genotyping or phenotyping should be considered as applicable.

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

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 reminded to continue to report suspected adverse reactions associated with fluorouracil, capecitabine and tegafur-containing products in accordance with the national spontaneous reporting system. Report forms can be downloaded from www.medicinesauthority.gov.mt/adrportal and posted to Post-licensing directorate, Medicines Authority, Sir Temi Żammit Buildings, Malta Life Sciences Park, San Ġwann SĠN 3000, Malta or sent by email to postlicensing.medicinesauthority@gov.mt.

Company contact point

Company	Product Name	Email	Phone
Accord Healthcare Ireland Limited	Fluorouracil 50mg/ml Solution for Injection or Infusion (5ml vial)	Kunal_more@accord-healthcare.com jackie_roberts@accord-healthcare.com	+44 02088631427 +44 01271385347
	Fluorouracil 50mg/ml Solution for Injection or Infusion (10ml vial)		
	Fluorouracil 50mg/ml Solution for Injection or Infusion (20ml vial)		
	Fluorouracil 50mg/ml Solution for Injection or Infusion (50ml vial)		
	Fluorouracil 50mg/ml Solution for Injection or Infusion (100ml vial)		
Accord Healthcare S.L.U.	Capecitabine Accord	Kunal_more@accord-healthcare.com jackie_roberts@accord-healthcare.com	+44 02088631427 +44 01271385347
Central Procurement and Supplies Unit	Capecitabine Mylan Tablet, film coated 500mg	Info.cpsu@gov.mt	+356 23439150
JV Healthcare Limited	Fluorouracil 50mg/ml Solution for injection or infusion	Alexandra.grima@jvpharma.eu	+356 21437551
	Fluorouracil Teva Solution for Infusion 5g/100ml		
Remedica Limited	Kapetral Tablet, film coated 150mg	a.vasiliou@remedica.com.cy drugsafety@remedica.com.cy	+357 25553000
	Kapetral Tablet, film coated 500mg		

Yours faithfully,

Post Licensing Directorate

Medicines Authority

Disclaimer

This Direct Healthcare Professional Communication has been submitted to you on behalf of Accord Healthcare Ireland Limited, Accord Healthcare S.L.U, Central Procurement and Supplies Unit, JV Healthcare Limited and Remedica Limited

Annexes

The summary of product characteristics can be found on the website of the Malta Medicines Authorityor the European Medicines Agency:
www.medicinesauthority.gov.mt/medicinesdatabase
www.ema.europa.eu