27 May 2020
Ref: RXUKESTP00025

Direct Healthcare Professional Communication

5-Fluorouracil (i.v.), Capecitabine and Tegafur containing products:
Pre-treatment testing to identify DPD-deficient patients at increased risk of severe and fatal toxicity

Dear Healthcare Professional,

The Marketing Authorisation Holders of medicines containing 5-fluorouracil i.v. (5-FU), capecitabine or tegafur, in agreement with the European Medicines Agency and the Medicines and Healthcare products Regulatory Agency (MHRA) would like to inform you of the following:

Summary

- **Patients with partial or complete dihydropyrimidine dehydrogenase (DPD) deficiency are at increased risk of severe and fatal 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-FU 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 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 for 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 for 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.
Applicable 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.

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 intravenous 5-FU. The target AUC is between 20 and 30mg x h/L.

Call for reporting
Please continue to report suspected adverse drug reactions (ADRs) to the MHRA through the Yellow Card Scheme.

During the coronavirus pandemic, please report suspected side effects electronically. You can report side effects via:

- the Yellow Card website https://www.gov.uk/yellowcard
- the free Yellow Card app available from the Apple App Store or Google Play Store
- some clinical IT systems (EMIS/SystmOne/Vision/MiDatabank) for healthcare professionals

If there is no online access to report a suspected side effect to the Yellow Card Scheme, call 0800 731 6789 for free, Monday to Friday between 9am and 5pm. You can leave a message outside of these hours.

Please report:
- all suspected ADRs that are serious or result in harm. Serious reactions are those that are fatal, life-threatening, disabling or incapacitating, those that cause a congenital abnormality or result in hospitalisation, and those that are considered medically significant for any other reason
- all suspected ADRs associated with new drugs and vaccines identified by the black triangle▼

When reporting please provide as much information as possible, including information about medical history, any concomitant medication, onset, treatment dates, and product brand name.

Company contact point

Alternatively, suspected adverse reactions may also be reported to the Marketing Authorisation Holders or their authorised distributor using the details provided below. If you have further questions or require additional information, please contact:

Company	Product name	Email	Phone	Fax
Accord Healthcare Limited	Fluorouracil 50mg/ml solution for injection/infusion Capecitabine 150mg film-coated tablet Capecitabine 300mg film-coated tablet Capecitabine 500mg film-coated tablet	Additional information and suspected adverse reactions: medinfo@accord-healthcare.com	Additional information and suspected adverse reactions: +44 (0)1271 385257	+44 (0) 1271 346106
Cipla (Eu) Limited	Xelcip - Capecitabine 150mg film-coated tablet - Capecitabine 500mg film-coated tablet	Additional information and suspected adverse reactions: Drugsafety@cipla.com	Additional information and suspected adverse reactions: +44 (0)800 0472144	N/A
Dr. Reddy's Laboratories (UK) Ltd.	Capecitabine Dr. Reddys 150mg Film-Coated Tablets Capecitabine Dr. Reddys 500mg Film-Coated Tablets	Additional information and suspected adverse reactions: drreddys@EU.ProPharmaGroup.com	Additional information and suspected adverse reactions: +44 (0)1748 828873	+44 (0) 1748 828801
Generics [UK] Limited (Mylan)	Capecitabine 150mg film-coated tablet Capecitabine 500mg film-coated tablet	Additional information: info@mylan.co.uk Suspected adverse reactions: ukpharmacovigilance@mylan.com	Additional information: +44 (0)1707 853 000 (option 1) Suspected adverse reactions: +44 (0)1707 853 000 (option 1)	N/A
Glenmark Pharmaceuticals Europe Limited	Capecitabine 150mg film-coated tablet Capecitabine 500mg film-coated tablet	Additional information and suspected adverse reactions: Medical_information@glenmarkpharma.com	Additional information: +44 (0)800 458 0383	+44 (0)1923 251137
Hospira UK Ltd	Fluorouracil 25mg/ml solution for injection Fluorouracil 50mg/ml solution for injection	Suspected adverse reactions: GBR.AEReporting@pfizer.com	Additional information: +44 (0)1304	+44 (0)1304 656221

			616161	
Medac Gesellschaft Für Klinische Spezialpräparate Mbh (Wedel)	Fluorouracil 25mg/ml solution for injection Fluorouracil 50mg/ml solution for injection	Additional information and suspected adverse reactions: info@medacpharma.co.uk	Additional information and suspected adverse reactions: +44 (0)1786 458086	+44 (0)1786 458032
Morningside Healthcare Ltd	Capecitabine 150mg film-coated tablet Capecitabine 500mg film-coated tablet	Additional information and suspected adverse reactions: medicalenquiry@morningsidehealthcare.com	Additional information and suspected adverse reactions: +44 (0)116 478 0322	N/A
Nordic Group B.V.	Teysuno - Tegafur 15mg/ gimeracil 4.35mg /oteracil 11.8 mg hard capsule - Tegafur 20 mg/ gimeracil 5.8 mg / oteracil 15.8 mg hard capsule	Additional information and suspected adverse reactions: pv@nordicpharma.co.uk	Additional information and suspected adverse reactions: +44 (0) 800 121 8924	+44 (0) 44 1748 828801
Roche Products Limited	Xeloda - Capecitabine 150mg film-coated tablets - Capecitabine 500mg film-coated tablets	Additional Information: medinfo.uk@roche.com Suspected adverse reactions: welwyn.uk_dsc@roche.com	Additional information: +44 (0)800 328 1629 Suspected adverse reactions: +44 (0)1707 367554	N/A
Sandoz Ltd	Capecitabine 150mg film-coated tablet Capecitabine 500mg film-coated tablet	Additional information: Sandozgb@EU.propharmagroup.com Suspected adverse reactions: www.report.novartis.com or uk.patientsafety@novartis.com	Additional information: +44 (0)1276 698 101	N/A
Waverley Pharma Limited	Capecitabine 150mg film-coated tablet Capecitabine 500mg film-coated tablet	Additional information and suspected adverse reactions: Safety.uk@lambda-cro.com	Additional information and suspected adverse reactions: +44(0)208 9013370	N/A
Zentiva Pharma UK Limited	Capecitabine 150mg film-coated tablet Capecitabine 500mg film-coated tablet	Additional information: UKMedInfo@zentiva.com	Additional information: +44 (0)800 090	N/A

		Suspected adverse reactions: PV-United-Kingdom@zentiva.com	2408 Suspected adverse reactions: +44 (0)800 090 2408	

Annexes: The Summary of Product Characteristics for capecitabine, 5-fluorouracil or tegafur-containing medicinal products is available either via The European Medicines Agency website at https://www.ema.europa.eu/en, via the MHRA website at https://www.gov.uk/guidance/find-product-information-about-medicines or via the Electronic Medicines Compendium at https://www.medicines.org.uk/emc , and this will be updated after Commission Decision.

This Direct Healthcare Professional Communication is provided to you by: Accord Healthcare Limited, Cipla (Eu) Limited, Dr. Reddy's Laboratories (UK) Ltd, Generics [UK] Limited, Glenmark Pharmaceuticals Europe Limited, Hospira UK Ltd, Medac Gesellschaft Für Klinische Spezialpräparate Mbh (Wedel), Morningside Healthcare Ltd, Nordic Group B.V., Roche Products Limited, Sandoz Ltd, Waverley Pharma Limited and Zentiva Pharma UK Limited.