Fluorouracil, capecitabine, tegafur and flucytosine: EMA recommends DPD testing prior to treatment

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Information on Fluorouracil and Fluorouracil pro-drugs

- Capecitabin, tegafur and flucytosine are pro-drugs of fluorouracil, meaning that they are converted into fluorouracil into the body
- Fluorouracil, given by injection or infusion, capecitabine and tegafur, taken by mouth, are used to treat various cancers. They act by blocking the growth of cancer cells and therefore, by interfering with enzymes involved in making new DNA
- Fluorouracil, given as cream, can be applied to the skin to treat skin conditions such as keratosis and dermal warts
- Flucytosine is a fluorouracil pro-drug, which can be given by injection or by mouth and it is used as antifungal treatment.

In Malta products authorised through various licensing procedures, can be found in Annex I

Information from the EMA about performing DPD tests before starting treatment with fluorouracil and its pro-drugs

Following a review carried out by the Pharmacovigilance Risk Assessment Committee (PRAC), the EMA has issued its recommendations on testing for the lack of the enzyme dihydropyrimidine dehydrogenase (DPD) when using fluoruracil and its prodrugs. These recommendations are not applicable to fluorouracil medicines given as cream to treat skin conditions, such as actinic keratosis and warts, since only a very small amount of the medicine is absorbed through the skin.

DPD is an enzyme needed to break down fluorouracil and its pro-drugs capecitabine, tegafur and flucytosine. A significant proportion of the general population has a deficiency of DPD[1], which results in an accumulation of fluorouracil and its pro-drugs following treatment. The accumulation of fluorouracil and its pro-drugs in the blood, may result in severe and life-threatening side effects, such as neutropenia (low levels of neutrophils, a type of white blood cells needed to fight infection), neurotoxicity (damage to the nervous system), severe diarrhoea and stomatitis (inflammation of the lining of the mouth).

[1] Up to 9% of the Caucasian population have low levels of a working DPD enzyme, and up to 0.5% completely lack the enzyme

Patients can be testes for DPD deficiency either by measuring the level of uracil (a substance broken down by DPD) or by checking the presence of mutations in the gene for DPD. The EMA's recommendations are:

- Before starting cancer treatment with fluorouracil, capecitabine and tegafur, patients should be tested for lack of DPD enzyme
- For patients who should start antifungal treatment for severe fungal infection with flucytosine, testing is not required to avoid delayed treatment
- Fluorouracil medicines must not be given to patients who completely lack of the DPD enzyme
- For patients with partial deficiency, the doctor may consider starting cancer treatment at lower doses than normal or stopping flucytosine treatment if severe side effects occur.

The CHMP opinion will now be forwarded to the European Commission, which will issue a final legally binding decision applicable in all EU Member States in due course.

In Malta

For Healthcare Professionals

Fluorouracil, capecitabine and tegafur

- Phenotype and/or genotype testing is recommended before starting treatment with fluoropyrimidines (fluorouracil, capecitabine, tegafur), since patients with partial or complete DPD deficiency are at increased risk of severe toxicity during treatment
- Treatment with fluorouracil, capecitabine or tegafur-containing medicines is contraindicated in patients with known complete DPD deficiency
- A reduced starting dose should be considered in patients with identified partial DPD deficiency
- Therapeutic drug monitoring of fluorouracil may improve clinical outcomes in patients receiving continuous fluorouracil infusions.

Flucytosine

- To avoid delay in starting flucytosine therapy, pre-treatment testing for DPD is not required
- Treatment with flucytosine is contraindicated in patients with known complete DPD deficiency due to the risk of life-threatening toxicity
- Consideration to stopping treatment with flucytosine should be given if toxicity occurs. Testing for DPD activity may be considered if toxicity is confirmed or suspected

Two DHPC letters, one for flucytosine and one for fluorouracil, capecitabine and tegafur will be disseminated to HCPs in Malta in due course. Archived DHPC letters are available online at http://www.medicinesauthority.gov.mt/dhpc

Advice for Patients

Treatment with fluorouracil, capecitabine or tegafur

- Before starting cancer treatment with fluorouracil given by injection or infusion (drip), capecitabine or tegafur, your doctor should do a test to check whether you have a working DPD enzyme

- If you have a known complete lack of DPD, you will not be given these treatments as they will increase the risk of severe and life-threatening side effects
- If you have a partial DPD deficiency, your doctor may start treatment at low doses, which can be increased if there are no serious side effects
- If you know that you have a partial DPD deficiency or if you have a family member who has partial or complete DPD deficiency, talk to your doctor or pharmacist before taking these medicines
- If you are using fluorouracil applied to the skin for conditions such as actinic keratosis and warts you do not need a DPD test, as the level of fluorouracil absorbed through the skin into the body is very low
- If you have any questions about your treatment or about DPD testing, talk to your doctor or pharmacist.

Treatment with flucytosine

- Flucytosine is a medicine related to fluorouracil that is used to treat severe yeast and fungal infections, including some forms of meningitis (inflammation of the membranes that surround the brain and spinal cord)
- As flucytosine may have to be given urgently, pre-treatment DPD testing (which may take up to one week) is not required in order to avoid any delay in starting therapy
- If you have a known complete DPD deficiency you must not be given flucytosine, due to the risk of life-threatening side effects
- In case of side effects, your doctor may consider stopping treatment with flucytosine. Your doctor may also consider testing DPD activity, since the risk of severe side effects is higher in patients with a low DPD activity
- If you have any questions about your treatment or about DPD testing, speak to your doctor

For more information, visit the European Medicines Agency's Fluorouracil and fluorouracil related substances (capecitabine, tegafur and flucytosine) containing medicinal products referral page

Reporting Adverse Drug Reactions

Healthcare professionals and patients are encouraged to maintain vigilance on Fluorouracil and fluorouracil related substances containing medicinal products. Suspected Adverse Drug Reactions (side effects) may be reported using the Medicines Authority Form and sending it to Sir Temi Żammit Buildings, Malta Life Sciences Park, San Ġwann SĠN 3000 or online to **http://www.medicinesauthority.gov.mt/adrportal** or to the marketing authorisation holder or their local representatives.

Post-Licensing Directorate
Medicines Authority

Healthcare professionals and patients are encouraged to regularly check the Medicines Authority website for product safety updates as these are issued on an ongoing basis.

Annex I

Active Ingredients	Product Name	Pharmaceutical Form	Classifcation	Authorisation Number	MAH/license holder
FLUOROURACIL 50 milligram(s)/millilitre	Fluorouracil 50mg/ml Solution for Injection or Infusion (5ml vial)	Solution for infusion or injection	POM	MA1269/02601	Accord Healthcare Ireland Ltd
FLUOROURACIL 50 milligram(s)/millilitre	Fluorouracil 50mg/ml Solution for Injection or Infusion (10ml vial)	Solution for infusion or injection	POM	MA1269/02602	Accord Healthcare Ireland Ltd
FLUOROURACIL 50 milligram(s)/millilitre	Fluorouracil 50mg/ml Solution for Injection or Infusion (20ml vial)	Solution for infusion or injection	POM	MA1269/02603	Accord Healthcare Ireland Ltd
FLUOROURACIL 50 milligram(s)/millilitre	Fluorouracil 50mg/ml Solution for Injection or Infusion (50ml vial)	Solution for infusion or injection	POM	MA1269/02604	Accord Healthcare Ireland Ltd
FLUOROURACIL 50 milligram(s)/millilitre	Fluorouracil 50mg/ml Solution for Injection or Infusion (100ml vial)	Solution for infusion or injection	POM	MA1269/02605	Accord Healthcare Ireland Ltd
CAPECITABINE 500 milligram(s)	Capecitabine Mylan Tablet, film coated 500mg	Film-coated tablet	POM	AA565/17901	Central Procurement & Supplies Unit
FLUOROURACIL 50 milligram(s)/millilitre	Fluorouracil 50mg/ml Solution for injection or infusion	Solution for injection/infusion	POM	PI770/06703A	JV Healthcare Limited
FLUOROURACIL 50 milligram(s)/millilitre	Fluorouracil Teva Solution for Infusion 5g/100ml	Solution for infusion	POM	AA770/06702	JV Healthcare Limited
CAPECITABINE 500 milligram(s)	Capecitabine Pharmacare 500mg Film-coated Tablet	Film-coated tablet	POM	AA1033/01202	Pharmacare Premium Limited
CAPECITABINE 150 milligram(s)	Capecitabine Pharmacare 150mg Film-coated tablets	Film-coated tablet	POM	AA1033/01201	Pharmacare Premium Limited
CAPECITABINE 150 milligram(s)	Kapetral Tablet, film coated 150mg	FILM-COATED TABLET	POM	AA084/11201	Remedica Limited
CAPECITABINE 500 milligram(s)	Kapetral Tablet, film coated 500mg	Film-coated tablet	POM	AA084/11202	Remedica Limited

Feedback Form

The Medicines Authority thanks you for the time taken to read this safety circular. The dissemination of safety circulars is an important process whereby Regulatory Authorities can communicate important issues with respect to the safety of medicines, in order to protect and enhance public health

The Medicines Authority kindly invites your anonymous feedback about the regulatory action being communicated. This may be returned by folding this formt (address side up), stapling the ends and then posting (no stamp required)

Feedback:

We thank you for your interest and look forward to hearing your opinion.

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Pharmacovigilance Section

Post-Licensing Directorate

Medicines Authority

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