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EMA recommendations on DPD testing prior to treatment with fluorouracil, capecitabine, tegafur and flucytosine

On 30 April 2020, EMA recommended that patients should be tested for the lack of the enzyme dihydropyrimidine dehydrogenase (DPD) before starting cancer treatment with fluorouracil given by injection or infusion (drip) or with the related medicines, capecitabine and tegafur.

As treatment for severe fungal infections with flucytosine (another medicine related to fluorouracil) should not be delayed, testing patients for DPD deficiency before they start treatment is not required

Patient who completely lack DPD must not be given any fluorouracil medicines. 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.

These recommendations do not apply to fluorouracil medicines used on the skin for conditions such as actinic keratosis and warts, as only very low levels of the medicine are absorbed through the skin.

A significant proportion of the general population has a deficiency of DPD,[1] which is needed to break down fluorouracil and the related medicines capecitabine, tegafur and flucytosine. As a result, following treatment with these medicines, fluorouracil can build up in their blood, leading to 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).

Patients can be tested for DPD deficiency by measuring the level of uracil (a substance broken down by DPD) in the blood, or by checking for the presence of certain mutations (changes) in the gene for DPD. Relevant clinical guidelines should be taken into consideration.

Information 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.

[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.

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- 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.

Information for healthcare professionals

Fluorouracil, capecitabine and tegafur

- Patients with partial or complete DPD deficiency are at increased risk of severe toxicity during treatment with fluoropyrimidines (fluorouracil, capecitabine, tegafur). Phenotype and/or genotype testing is therefore recommended before starting treatment with fluoropyrimidines.
- 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

- Pre-treatment testing for DPD deficiency is not required, in order to avoid delay in starting treatment with flucytosine.
- Treatment with flucytosine is contraindicated in patients with known complete DPD deficiency due to the risk of life-threatening toxicity.
- In case of drug toxicity, consideration should be given to stopping treatment with flucytosine. Determination of DPD activity may be considered where drug toxicity is confirmed or suspected.

Two direct healthcare professional communications (one DHPC for fluorouracil, capecitabine and tegafur, and a separate one for flucytosine) have been sent to healthcare professionals prescribing, dispensing or administering the medicines. The DHPCs have also been published on a dedicated page on the EMA website.

More about the medicine

The review concerns fluorouracil medicines given by injection or applied to the skin as well as medicines containing capecitabine and tegafur taken by mouth (so-called fluorouracil prodrugs), which are converted to fluorouracil in the body. It also includes the antifungal medicine flucytosine which is given by injection or by mouth and some of which is converted into fluorouracil in the body.

Fluorouracil given by injection or infusion and its prodrug medicines are used to treat various cancers. They work by interfering with enzymes involved in making new DNA, thereby blocking the growth of cancer cells.

Fluorouracil applied to the skin is used for various skin conditions such as actinic keratosis and dermal warts.

Capecitabine has been authorised through EMA with the brand name Xeloda as well as various generic medicines. A medicine containing tegafur has been authorised through EMA with the brand name Teysuno.

Some tegafur- and capecitabine-containing medicines have also been authorised at national level, as have all fluorouracil and flucytosine medicines.

More about the procedure

The review was initiated March 2019 at the request of the French Medicines Agency (ANSM), under Article 31 of Directive 2001/83/EC.

The review was first carried out by the Pharmacovigilance Risk Assessment Committee (PRAC), the Committee responsible for the evaluation of safety issues for human medicines, which made a set of recommendations.

The PRAC recommendations were sent to the Committee for Medicinal Products for Human Use (CHMP), responsible for questions concerning medicines for human use, which adopted the Agency's opinion. The CHMP opinion was forwarded to the European Commission, which issued final legally binding decisions for the medicines concerned between 3 July and 7 July 2020 that are applicable in all EU Member States.