



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

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## New testing and treatment recommendations for fluorouracil, capecitabine, tegafur and flucytosine

EMA's safety committee (PRAC) has recommended that patients should be tested for the lack of an enzyme called dihydropyrimidine dehydrogenase (DPD) before starting cancer treatment with medicines containing fluorouracil given by injection or infusion (drip) and the related medicines capecitabine and tegafur, which are converted to fluorouracil in the body.

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.

No pre-treatment testing is needed for patients treated with topical fluorouracil (applied to the skin to treat various skin conditions).

Lack of a working DPD enzyme,<sup>1</sup> which is needed to break down fluorouracil, causes fluorouracil to build up in the blood. This may lead 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 body's nervous system), severe diarrhoea and stomatitis (inflammation of the lining of the mouth).

The PRAC assessed the available data and recommended the following measures to ensure the safe use of fluorouracil and fluorouracil-related medicines:

### Fluorouracil, capecitabine and tegafur

Testing of patients for DPD deficiency is recommended before starting treatment with fluorouracil injection or infusion, capecitabine and tegafur. This can be done 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 which are associated with an increased risk of severe side effects. Relevant clinical guidelines should be taken into consideration.

Patients with a known complete DPD deficiency must not be given fluorouracil injection or infusion, capecitabine or tegafur, as a complete lack of working DPD puts them at higher risk of severe and life-threatening side effects.

For patients with a partial DPD deficiency, a reduced starting dose of these medicines should be considered; since the effectiveness of a reduced dose has not been established, following doses may

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<sup>1</sup> Up to 8% of the Caucasian population have low levels of a working DPD enzyme, and up to 0.5% completely lack the enzyme.



be increased if there are no serious side effects. Regular monitoring of fluorouracil blood levels in patients receiving fluorouracil by continuous infusion could improve treatment outcome.

Pre-treatment testing or dose adjustments based on DPD activity are not needed for patients using topical fluorouracil. This is because the level of fluorouracil absorbed through the skin into the body is extremely low, and the safety of topical fluorouracil is not expected to change in patients with partial or complete DPD deficiency.

### **Flucytosine**

Flucytosine 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). To avoid any delay in starting therapy, pre-treatment testing for DPD deficiency is not required.

Patients with a known complete DPD deficiency must not be given flucytosine, due to the risk of life-threatening side effects.

Patients with a partial DPD deficiency are also at increased risk of severe side effects. In case of side effects, the treating doctor should consider stopping treatment with flucytosine. Testing of DPD activity may also be considered, since the risk of severe side effects is higher in patients with a low DPD activity.

The prescribing information for doctors and patients will be updated to include the above recommendations.

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### **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.

Medicines containing capecitabine and tegafur have been authorised through EMA and are marketed as Xeloda, Taysuno as well as various generic medicines containing capecitabine.

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

### **More about the procedure**

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

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

The PRAC recommendations will now be sent to the Committee for Medicinal Products for Human Use (CHMP), responsible for questions concerning medicines for human use, which will adopt the Agency's opinion.