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EMA starts review on screening patients before treatment with fluorouracil, capecitabine, tegafur and flucytosine

EMA has started a review of medicines containing fluorouracil (also known as 5-fluorouracil or 5-FU) and the related medicines capecitabine, tegafur and flucytosine, which are converted to fluorouracil in the body. The review will examine existing screening methods and their value in identifying patients at increased risk of severe side effects.

Fluorouracil (given by injection), capecitabine and tegafur are cancer medicines, whereas topical (applied to the skin) fluorouracil is used for various skin conditions and flucytosine is a medicine used in severe fungal infections.

It is known that some patients lack a working enzyme called dihydropyrimidine dehydrogenase (DPD) which is needed to break down fluorouracil.[1] Prescribers may be unaware that their patients lack working DPD, and if these patients are given fluorouracil or related substances, their bodies cannot break fluorouracil down, resulting in its build-up in the blood.

Build-up of high levels of fluorouracil seen with some of these medicines can 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). Patients with a complete deficiency of DPD should therefore not be given fluorouracil, or medicines that can form it in the body.

The product information for most of these medicines states that they should not be used in patients with complete DPD deficiency. Genetic testing for DPD deficiency is recommended for most medicines used in the treatment of cancer, but systematic screening for DPD deficiency before starting treatment is not mandatory. In addition, new data on genetic testing and other DPD screening methods were recently published which may impact current recommendations.

EMA will now assess the available data in relation to existing screening methods to detect DPD deficiency and recommend whether any changes are needed to the way these medicines are used in order to ensure their safe use.

Patients who have concerns about their medicines should consult their doctor and should not stop taking their medicines without seeking medical advice.

[1] Up to 8% of the population have low levels of a working DPD enzyme, and up to 0.5% of the population completely lack the enzyme.

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More about the medicines

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 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, Teysuno and various generic medicines containing capecitabine. More information about these medicines can be found on the EMA website.

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

More about the procedure

This review has been initiated at the request of the French Medicines Agency (ANSM), under Article 31 of Directive 2001/83/EC.

The review is being carried out by the Pharmacovigilance Risk Assessment Committee (PRAC), the Committee responsible for the evaluation of safety issues for human medicines, which will make a set of recommendations. The PRAC recommendations will then be forwarded to the Committee for Medicinal Products for Human Use (CHMP), responsible for questions concerning medicines for human use, which will adopt an opinion. The final stage of the review procedure is the adoption by the European Commission of a legally binding decision applicable in all EU Member States.