Direct Healthcare Professional Communication

2/6/2020

Flucytosine: Updated recommendations for the use in patients with dihydropyrimidine dehydrogenase (DPD) deficiency

Dear Healthcare Professional,

The Central Procurement and Supplies Unit in agreement with the European Medicines Agency and the Medicines Authority, would like to inform you of the following:

Summary

- **Treatment with flucytosine is contraindicated in patients with known complete dihydropyrimidine dehydrogenase (DPD) deficiency due to the risk of life-threatening toxicity.**
- **Patients with a partial DPD deficiency are also at increased risk of severe toxicity.**
- **Determination of DPD activity may be considered where drug toxicity is confirmed or suspected.**
- **In case of drug toxicity, consideration should be given to stopping treatment with flucytosine.**
- **Pre-treatment testing for DPD deficiency is however not required in order to avoid delay in antimycotic therapy.**

Background on the safety concern

Flucytosine is an antimycotic indicated for the treatment of systemic yeast and fungal infections caused by sensitive organisms: such infections include cryptococcosis, candidiasis, chromomycosis and infections due to *ansenula (Pichia)* spp. Flucytosine is a 5-fluorouracil (5-FU) prodrug. Relevant systemic exposure of 5-FU has been observed in patients treated with flucytosine.

The rate-limiting enzyme in the catabolism of 5-FU is dihydropyrimidine dehydrogenase (DPD). 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 3-8% of the Caucasian population.

In patients treated with systemic 5-FU or its prodrugs, impaired DPD enzyme function leads to an increased risk of severe or life-threatening toxicity (stomatitis, mucosal inflammation, diarrhoea, neutropenia, or neurotoxicity). In patients with deficiency in DPD enzyme, the risk of severe drug toxicity is increased, with the level of toxicity correlating with the extent of DPD deficiency. Patients with complete DPD deficiency are at higher risk of developing life-threatening or fatal toxicity, and in such conditions treatment with flucytosine is contraindicated.

Determination of DPD activity can be considered when there is a confirmed or suspected drug toxicity. In case of suspected drug toxicity, consideration should be given to stopping the treatment with flucytosine.

Pre-treatment testing for DPD deficiency is, however, not required in order to avoid delay in antimycotic therapy.

Call for reporting

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are reminded to continue to report suspected adverse reactions associated with flucytosine-containing products in accordance with the national spontaneous reporting system. Report forms can be downloaded from www.medicinesauthority.gov.mt/adrportal and posted to Post-licensing directorate, Medicines Authority, Sir Temi Żammit Buildings, Malta Life Sciences Park, San Ġwann SĠN 3000, Malta or sent by email to postlicensing.medicinesauthority@gov.mt.

Company contact point

Authorisation Holder	Product Name	Email	Contact number
Central Procurement and Supplies Unit, San Gwann Malta SGN 3000	Ancotil Solution for Infusion 2.5g/250ml	Info.cpsu@gov.mt	+356 23439150