Direct Healthcare Professional Communication

19 May 2020

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

Dear Healthcare Professional,

Mylan, in agreement with the European Medicines Agency and the Medicines and Healthcare products Regulatory Agency (MHRA), 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 asked to report any suspected adverse reactions to Mylan on +44 (0) 800 1218267 or UKPharmacovigilance@mylan.com

Please continue to report suspected adverse drug reactions (ADRs) to the MHRA through the Yellow Card Scheme.

During the coronavirus pandemic, please report suspected side effects electronically. You can report side effects via:

- the Yellow Card website https://www.gov.uk/yellowcard
- the free Yellow Card app available from the Apple App Store or Google Play Store
- some clinical IT systems (EMIS/SystmOne/Vision/MiDatabank) for healthcare professionals

If there is no online access to report a suspected side effect to the Yellow Card Scheme, call 0800 731 6789 for free, Monday to Friday between 9am and 5pm. You can leave a message outside of these hours.

Please report:

- all suspected ADRs that are serious or result in harm. Serious reactions are those that are fatal, life-threatening, disabling or incapacitating, those that cause a congenital abnormality or result in hospitalisation, and those that are considered medically significant for any other reason
- all suspected ADRs associated with new drugs and vaccines identified by the black triangle▼
- When reporting please provide as much information as possible, including information about medical history, any concomitant medication, onset, treatment dates, and product brand name"

Company contact point

For further information please contact:

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Annexes

Not applicable.

Signed: **Balwant Heer** – Global Head PSRM & EEA QPPV

Balwant Heer

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