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 <National Competent 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

<A reminder of the need and how to report adverse reactions in accordance with the national spontaneous reporting system, including the details (e.g. name, postal address, fax number, website address) on how to access the national spontaneous reporting system>

<For biological medicinal products, also include a reminder to report the product name and batch details>.

<Mention if product is subject to additional monitoring and the reason why>

Company contact point

<Contact point details for access to further information, including relevant website address(es), telephone numbers and a postal address>

Annexes

<Link/reference to other available relevant information, such as information on the website of a competent authority>.

DHPC COMMUNICATION PLAN	
Medicinal product(s)/active substance(s)	Flucytosine
Marketing authorisation holder(s)	All MAHs of flucytosine-containing medicinal products
Safety concern and purpose of the communication	Increased risk of severe and life-threating toxicity in patients with partial or complete DPD deficiency To inform HPCs about the risks associated with DPD deficiency, the contraindication of flucytosine in patients with complete DPD deficiency and the updated recommendations for fluorouracil monitoring.
DHPC recipients	Healthcare professionals who may prescribe (infectious disease specialists) or dispense (hospital pharmacists) flucytosine – [*details to be confirmed, upon discussions with national competent authorities (NCAs) in countries where the product is currently being marketed* Dissemination mechanism: [*to be agreed with national competent authorities*] Other recipients: [*Details on distribution list to be agreed with national competent authorities*]
Member States where the DHPC will be distributed	All EU countries where the product is marketed. In MS where flucytosine is already contraindicated in patients with known complete DPD deficiency dissemination will be decided on a national level.

Timetable	Date
DHPC and communication plan (in English) agreed by PRAC	12.03.2020
DHPC and communication plan (in English) agreed by CHMP	30.04.2020
Submission of translated DHPCs to all national competent authorities (NCA) for review	7 days after adoption of CHMP opinion
Agreement of translations by national competent authorities	14 days after submission to NCAs
Dissemination of DHPC	14 days after agreement of translation

Strategy for post-communication phase:	Date
In relation to the DHPC: The marketing authorisation holder will coordinate and observe the dissemination of the Direct Healthcare Professional Communication and will inform the corresponding competent authorities of any difficulties identified (e.g. problems related to the list of recipients or the timing and mechanism of	In accordance to national timelines for dissemination and in agreement with NCAs

Strategy for post-communication phase:	Date
dissemination). Appropriate action will be discussed with the national competent authority as needed to correct the situation	