15 March 2019
EMA/PRAC/165648/2019

PRAC List of questions

To be addressed by the marketing authorisation holder(s) for fluorouracil and fluorouracil related substances (capecitabine, tegafur and flucytosine) containing medicinal products

Referral under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data

Procedure number: EMEA/H/A-31/1481

Xeloda EMEA/H/A-31/1481/C/000316/0085
Teysuno EMEA/H/A-31/1481/C/001242/0040
Capecitabine Accord EMEA/H/A-31/1481/C/002386/0032
Capecitabine medac EMEA/H/A-31/1481/C/002568/0021
Capecitabine Teva EMEA/H/A-31/1481/C/002362/0031
Ecansya EMEA/H/A-31/1481/C/002605/0023

INN/active substances: capecitabine, fluorouracil, tegafur, flucytosine

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1. Background

Dihydropyrimidine dehydrogenase (DPD) is the rate limiting step of the catabolism of 5-fluorouracil (5-FU), and has a pivotal role in 5-FU (and related substances) elimination patterns. Treatment of patients with DPD deficiency with fluorouracil or fluorouracil related substances can therefore result in severe and fatal toxicity. At the moment, although DPD deficiency is an identified risk for the use of these products and genetic testing is recommended for DPD deficiency for medicines used in oncological indications, no upfront screening for DPD deficiency is mandated before treatment initiation.

Based on recent publications providing new information on DPD screening methods, the French medicines agency (ANSM) considers that the product information of systemic fluorouracil and its prodrugs (capecitabine and tegafur) does not reflect current evidence and notified PRAC about a referral under Article 31 of Directive 2001/83/EC to review available screening tests to detect DPD deficiency.

Based on the fact that the risk of systemic exposure of 5-fluorouracil after administration of topical formulation or after metabolism of flucytosine cannot be completely excluded, the PRAC further agreed during its March 2019 plenary meeting to extend the scope to include these products in the review.

As part of this review, the PRAC considers it necessary to perform a EudraVigilance analysis of reports of DPD deficiency related toxicity with fluorouracil and fluorouracil related substances capecitabine, tegafur and flucytosine containing medicinal products. The data to perform this analysis will be provided by EMA and will be evaluated by PRAC together with the responses to the list of questions provided by the MAHs. This EudraVigilance analysis will be provided to all MAHs together with the preliminary assessment reports.

In addition, and at the request of the PRAC, the EMA will perform a literature review of any new publication in relation to the screening of DPD deficiency in patients treated with fluorouracil products and related substances.

PRAC may also liaise with relevant stakeholders as part of the procedure.

2. Questions

The marketing authorisation holders (MAHs) are requested to address the following questions:

Question 1

Please provide the marketing status and patient exposure for the year 2018 of your product(s) in the different EU MS (including UK), Iceland and Norway and cumulative patient exposure in the whole European Economic Area (EEA). This should include data from completed and ongoing studies and all post-marketing sources.

For the estimation of the number of exposed patients with 5-FU a DDD of 100 mg should be used. For the estimation of the number of exposed patients with capecitabine a DDD of 3 g should be used. For the topical products assume one sold unit per patient.

Patient exposure should be expressed in number of patients and patient treatment years.

Question 2

Please provide for your product(s) the most recent data on the following:

a) Frequency of partial and full DPD deficiency in the EU population (including UK), Iceland and Norway.

b) Prevalence of serious and fatal toxicity in patients with DPD deficiency treated with 5-FU and related substances containing products in the EU population (including UK), Iceland and Norway. If available, provide the analysis for full and partial DPD deficiency.

c) Prevalence of serious and fatal toxicity in patients with normal DPD activity treated with 5-FU and related substances containing substances in the EU population (including UK), Iceland and Norway.

Question 3

The MAHs should provide a brief summary on clinical consequences of partial and full DPD deficiency taking into account the implemented dosing regimen and the time association (onset of the toxicity) and the use of their product(s).

Question 4

The MAHs should provide an up-to-date review of the clinical data investigating the gene encoding DPD (DPYD) genotyping and identification of DPYD variants known to be associated with decreased DPD activity and the reliability of the translation of genotyping into the phenotype of each clinically relevant variant. Specificity, sensitivity and predictive values of upfront genotyping for predicting toxicity should be reported for each clinically relevant variant. The MAHs should further elaborate on current and new clinical recommendations based on genotyping. More specifically, the MAHs should discuss all available information regarding any dose recommendations based on DPYD gene activity scores including discussion on efficacy of modified treatment.

Question 5.

The MAHs should provide an up-to-date review of the clinical data investigating DPD phenotyping for detection of patients at increased risk for toxicities. More specifically, but not limited to, an evaluation of the reliability and predictive value of the analytical methods to measure uracilaemia (U) and dihydrouracilaemia/uracilaemia ratio (UH2/U) should be included. The MAHs should further discuss relevant cut-off values of U and UH2/U and the associated clinical consequences (reduction of the dose, discontinuation of treatment) and the impact on efficacy of treatment. The MAHs should further elaborate on the current evidence to support an up-front phenotyping in all patients and discuss clinical recommendations. More specifically, the MAHs should discuss all available information regarding any dose recommendations based on phenotyping cut-off values.

Question 6

Based on the discussions on questions 4 and 5, the MAHs should provide an up-to-date review of clinical data investigating the advantages of DPD combined methods (genotyping + phenotyping) for detection of patients at increased risk for toxicities.

Question 7

The MAHs should provide an up-to-date overview and comparison of the data available on the feasibility of genotyping, phenotyping, and combined methods (genotyping + phenotyping) for detection of patients at increased risk for toxicities in the EU. In this context, please provide information on the number/rate of patients screened for DPD deficiency by genotyping, phenotyping or both per EU member states, if available.

Question 8

MAHs of topical products and flucytosine should provide information on the systemic bioavailability of 5-fluorouracil, the maximum 5-fluorouracil plasma concentration observed and discuss the risk for systemic toxicities taking into account DPD deficiency

a) in the approved indication.

b) in off-label use. Please specify the off-label use (indication, dose, treatment duration).

Question 9

In the view of the above, the MAHs should provide a critical discussion of the publication of FUSAFE project and the final recommendations published by the INCA (French Institute of Cancer) in December 2018.[1]

Question 10

Please discuss whether the available data warrant any variation of the product information in regard to mandatory requirement of upfront DPD detection (genotyping, phenotyping or combined approach), update of the RMP or further measures.

[1] DPD deficiency screening with a view to preventing some severe toxicities occurring with treatments including fluoropyrimidines (5-fluorouracil or capecitabine)