NOTIFICATION TO THE PRAC/EMA SECRETARIAT OF A REFERRAL UNDER ARTICLE 31 OF DIRECTIVE 2001/83/EC
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This notification is a referral under Article 31 of Directive 2001/83/EC to the PRAC made by France (ANSM):

Product names in the referring member states	XELODA capecitabine-containing medicinal products 5-fluorouracil-containing medicinal products (i.v. application) TEYSUNO Tegafur containing medicinal products
Active substances	Capecitabine 5-fluorouracil Tegafur
Pharmaceutical forms	Capecitabine : all 5-fluorouracil : Solution for Injection or Infusion Tegafur: all
Strengths	All
Routes of Administration	Capecitabine : all 5-fluorouracil : i.v. application Tegafur: all
Marketing Authorisation Holders	Various

Background

5-fluorouracil (5-FU), capecitabine and tegafur are fluoropyrimidines, and capecitabine and tegafur are prodrugs of the moiety 5-FU.

Fluoropyrimidines are pyrimidine analogues and antineoplastic agents which act as an antimetabolite to uracil. They are enzymatically activated to deoxy-fluorouracil monophosphate.

5-FU inhibits the activity of thymidilate synthase and thus deoxythymidine monophosphate synthesis through complex formation. This results in phase-specific DNA-synthesis inhibition. Furthermore, deoxy-fluoronucleosides inhibit de novo synthesis of pyrimidine nucleotides.

By the above mechanisms 5-FU interferes with cell division and growth, acting thus mainly on tissues with rapid cell division, such as the bone marrow, epithelium of the gastrointestinal tract and oral mucosa.

5-FU has cytotoxic and immunosuppressive properties.

Capecitabine is orally administered and indicated for the treatment of malignancies such as colon cancer, metastatic colorectal cancer, gastric cancer, advanced or metastatic breast cancer.

5-FU (solution for injection or infusion) is indicated for the treatment of malignancies such as gastrointestinal neoplasm malignant (including gastric, colon, pancreatic cancer, oesophageal cancer, advanced colorectal, rectal cancer etc.), head and neck cancer, epidermoid cancer, breast cancer,

malignant respiratory tract neoplasm (including bronchial cancer, lung cancer etc.), liver tumour, cervix carcinoma, bladder cancer, ovarian cancer, prostate cancer, uterine carcinoma.

Tegafur is orally administrated with gimeracil and oteracil and indicated for gastric cancer in combination with cisplatin.

DPD deficiency is a key aspect of the benefit-risk ratio of 5-FU and its prodrugs

The enzyme dihydropyrimidine dehydrogenase (DPD) is the rate limiting step of 5-FU catabolism, and has a pivotal role in 5-FU (and prodrugs) elimination patterns. Treatment of patients with DPD deficiency with fluoropyrimidines can therefore result in severe and fatal toxicity. In the literature, it is reported that about 30-40% of severe toxicities and 60-70% of treatment related toxicities could be attributed to diminished DPD activity.

In the Caucasian population, approximately 3-5% has a partial DPD deficiency and 0.01-0.5% is fully DPD deficient. The estimate prevalence of patient experiencing a serious toxicity is between 15-30%, and the estimate prevalence of patient experiencing a lethal toxicity potentially due to DPD deficiency is around 2%(1). In France, with about 80 000 patients exposed to capecitabine or 5-FU yearly, the number of toxic deaths (whatever the origin of the death) is thus estimated to be about 1600, and the number of serious toxicity between 12.000 and 24.000. It is acknowledged that as the detection of DPD deficiency is not done routinely, it is not possible to calculate the exact number of cases exclusively related to DPD deficiency.

DPD deficiency is an identified risk for toxicity with capecitabine and 5-FU and its prodrugs

The risk of toxicity in patients with DPD deficiency is a known risk that is detailed in capecitabine's risk management plan as an important identified risk.

This risk is also reflected in the product information of 5-FU, capecitabine and tegafur-containing products. Although there might be differences in the information across the products as some are subject to national marketing authorisations (especially 5-FU), it includes:

- In section 4.3 of the SmPC:
  - a contraindication in patients with 'known complete absence of dihydropyrimidine dehydrogenase (DPD) activity' or in patients with 'Known dihydropyrimidine dehydrogenase (DPD) deficiency';

- in section 4.4 of the SmPC (only for capecitabine and 5-FU):
  - a warning on severe toxicities attributed to a deficiency of DPD activity,
  - details on genetic mutations associated with this risk,
  - the absence of safe dose in case of complete absence of DPD activity and dose recommendation in case of partial DPD deficiency,
  - epidemiological data about the frequency of these genotypes and
  - a recommendation that 'Genotyping for these alleles is recommended to identify patients at increased risk for severe toxicity' although 'other rare variants may also be associated with an increased risk of severe toxicity'. It is also stated for patients with partial DPD deficiency that 'the patients who are tested negative for the above-mentioned alleles may still have a risk of severe adverse events'.

Discussions held at the European level and recommendations for genotyping (for 5-FU- and capecitabine-containing products only)

DPD deficiency was especially discussed in the context of several EU procedures:

In 2001, the marketing authorization of XELODA (capecitabine) was varied to introduce the first contraindication in section 4.3 in patients with known DPD deficiency.

In July 2017, following a discussion at European level taking into account the experience within Member States with genotype-guided dose adjustments, possible impact of upcoming data from on-going studies and information from organisations regarding the latest developments in dosing guidelines, PRAC agreed that an amendment to the product information of capecitabine and i.v. 5-FU was advisable. The need for a mandatory upfront genotyping or phenotyping strategy was also discussed but PRAC considered, at that stage, that it would not be feasible because of different availability of tests, health facilities and clinical practices across EEA. However, a recommendation to perform a genotyping of certain alleles was introduced in the product information, while none was stated for phenotyping.

In 2018, in the context of the capecitabine PSUSA, PRAC reviewed available data on detection methods between 2015 and 2018. Following this review, no recommendation regarding SmPC/PL update was then considered necessary by the Committee.

The importance of considering technological advances to identify patients with DPD deficiency

As DPD deficiency is a key aspect of the benefit-risk ratio of capecitabine and 5-FU, taking into account technological advances related to methods of detection of a DPD deficiency is essential. Currently, two methods are available: genotyping, which is based on the detection of the DPYD (gene coding for the DPD) variants known to be involved in a decreased DPD activity (*2A, *13, p.D949V et HapB3), and phenotyping, based on the direct measurement of the DPD activity via 2 markers: uracilaemia (U) and the dihydrouracilaemia/uracilaemia ratio (UH2/U). Compared to genotyping, phenotyping directly measures the expression of the DPD enzyme, and is the gold standard method to detect a DPD deficiency.

Although it is currently easier to use it in practice, the relevance of genotyping methods is limited by uncertainties on the genetic variants involved in a decreased DPD activity, and by a high variability of DPD activity for a same variant (2).

Issues to be considered

In 2014, the INCA (French Institute of Cancer) founded and launched a 3-year hospital clinical research program (PHRC) FUSAFE (2015-2017), coordinated by the French Group for Clinical Onco-Pharmacology (GPCO-Unicancer) and the French Network for pharmacogenetics (RNPGx). The objective of FUSAFE was to elaborate collegial recommendations to allow a secured prescription of fluoropyrimidines, based on upfront detection of DPD deficiency.
The research program objectives were to:

- Review the literature data and to produce 3 international meta-analyses performed on individual data (genotyping, phenotyping or combined approach) to compare sensitivity, specificity and predictive values of these approaches. These meta-analysis included individual data from 2886 patients treated at the Mayo clinic Cancer Center.
- Collect real life data to (i) assess the need in terms of public health (yearly number of patients concerned), (ii) assess the expectations of the oncologists, as well as the compliance with DPD deficiency detection, and (iii) establish a state of the practices of detection in French hospitals.

In April 2016, interim results of the meta-analysis were published on the website of the GPCO-Unicancer (3). These recommendations concluded on the need to perform an upfront DPD deficiency detection, especially in at-risk patients (e.g. high doses of fluoropyrimidines, previous toxicity in a family member exposed to fluoropyrimidines, comorbidities). Genotyping and phenotyping methods were both recommended because of sensitivity and specificity issues, as well as feasibility in practice.

In February 2018, final recommendations of FUSAFE were published in the review "Bulletin du cancer"(4). These latter recommend (i) a detection of a DPD deficiency should be performed before each first administration of fluoropyrimidines, (ii) with a phenotyping method (uracilaemia) in first intention and to associate a genotyping method (*2A, *13, p.D949V et HapB3), and to (iii) reduce the posology of fluoropyrimidines according to DPD presumed activity, followed by an ascending dose design in next cycles.

This led the French medicines agency (ANSM) to recommend (via a communication on its website) on 28/02/2018 an upfront DPD deficiency detection considering that:

- The current product information recommending genotyping to detect DPD deficiency did not reflect anymore the current evidence and might put patients at risk of some severe toxicities associated with 5-FU or capecitabine;
- Upfront DPD deficiency detection before treatment initiation of capecitabine and i.v. 5-FU–containing products and its prodrugs should be mandatory. Indeed, as DPD deficiency is not symptomatic, it can only become 'known' through a test or through the occurrence of a toxicity after the administration of the concerned products.

In 2018, the French National Cancer Institute (INCA) initiated an in depth review of all available data related to upfront testing to detect a DPD deficiency. In December 2018, the INCA published a very detailed recommendations on the most appropriate methods to screen DPD deficiency in view of the current clinical practices in oncology.

The feasibility of phenotyping and/or genotyping was also discussed with biologists. They highlighted that DPD deficiency screening by phenotyping is doable and, at the national level, would not be more problematic to implement than other screening requirements in oncology.

Based on this data, the INCA and the HAS concluded that:

- Phenotyping of the DPD is as expected the gold standard method to avoid early and serious toxicities;
- Due to recent technological advances, this method is now considered feasible in clinical practice;
- Genotyping method is easier to do in practice, but is not fully reliable to detect DPD deficiency;
- Phenotyping method is probably more suitable for tailoring the dose and minimizing the risks of severe toxicity.

The recommendations mentioned above were based on an extensive review of the literature (see below references (5–19), some of which were not previously assessed at EU level. These recommendations focused on a comparison of the performances of genotyping and phenotyping.

This review especially included one article of interest that was published after the data lock point of the last PSUSA for capecitabine: Henricks et al., 2018 (2).

In the new study conducted by Henricks et al. and published in October 2018, it was reported that (i) genetic variants presumed to be predictive of toxicity, and by extension to an increased risk of toxicity, the real DPD activity (by direct measure of the DPD activity) was highly heterogeneous from one patient to another (see figure 3 and below).

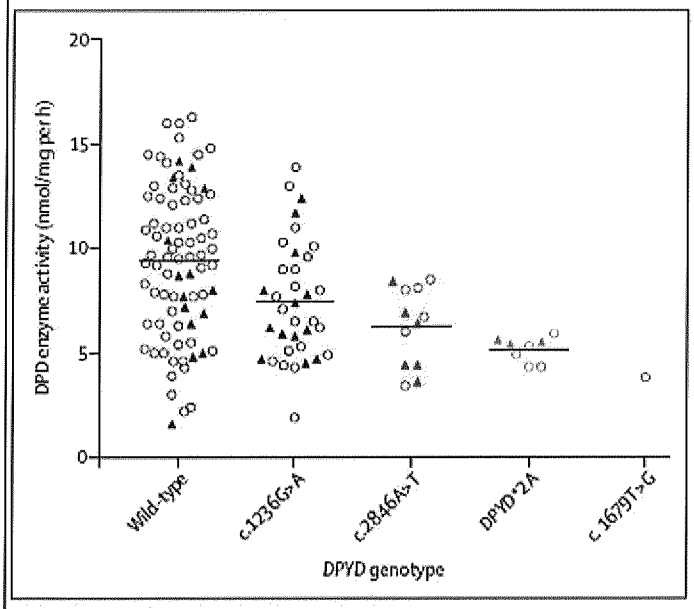

Figure 3: **DPD enzyme activity in peripheral blood mononuclear cells for *DPYD* variant allele carriers and wild-type patients**
Patients with grade 3 or worse fluoropyrimidine-related toxicity are depicted by triangles and patients with grade 0–2 toxicity by circles. DPD=dihydropyrimidine dehydrogenase. *DPYD*=the gene encoding DPD.

For patients with wild-type DPYD genotype, the DPD activity is variable, and that some patients had less apparent DPD activity than patients with all other problematic genetic variants (c.1236G>A, c.2846A>T, DPYD*2A, c.1679T>G). Considering pooled data, the mean DPD activity was significantly reduced in patients with a problematic genetic variant of DPYD (except for c.1679T>G, with only one patient in this group). However, the relevance of this population-based observation to clinical recommendations at the individual level is not acceptable. This new study strongly suggests that the current SmPC recommendation might not be the most appropriate method to efficiently reduce the risk of early and serious toxicity in patients with DPD deficiency.

In view of the above and the necessity to take an action at EU level regarding the detection of the DPD deficient patients (especially genotyping and/or phenotyping), France considers that it is in the interest of the Union to refer the matter to the PRAC and requests that it gives its recommendation under Article 31 of Directive 2001/83/EC as to whether marketing authorisations of these products should be maintained, varied, suspended, or revoked.

As the request results from the evaluation of data resulting from pharmacovigilance activities, the opinion should be adopted by the CHMP on the basis of a recommendation of the PRAC.

[redacted]

Date 13 MARS 2019

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