

Annex II
Scientific conclusions

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5-fluorouracil (5-FU) is a pyrimidine analogue which competitively inhibits the enzyme thymidylate synthase (TS), thereby creating a thymine deficiency and resulting in inhibition of deoxyribonucleic acid (DNA) synthesis and cytotoxicity. It also inhibits, to a lesser extent, the formation of ribonucleic acid (RNA). These effects are most marked in rapidly growing cells and may lead to cell death.

Dihydropyrimidine dehydrogenase (DPD) is the rate limiting step of the catabolism of 5-fluorouracil and has a pivotal role in 5-fluorouracil (and related substances) elimination patterns. Treatment of patients with DPD deficiency with fluorouracil or related substances can therefore result in severe and fatal toxicity.

Although DPD deficiency is a known 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 currently mandated before treatment initiation.

In 2014, the French Institute of Cancer (INCA) 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.

In 2018, INCA initiated an in-depth review of all available data related to upfront testing to detect a DPD deficiency and in December 2018, published a detailed recommendation on the most appropriate methods to screen DPD deficiency in view of the current clinical practices in oncology.

Based on these recommendations, the French medicines agency (ANSM) considered that the product information of systemic fluorouracil and its prodrugs (capecitabine and tegafur) does not reflect the current evidence on the different screening tests to detect DPD deficiency and on 13 March 2019, France triggered a referral under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data, requesting the PRAC to assess the need to take action at EU level regarding the detection of DPD deficient patients (especially through genotyping and/or phenotyping) in patients treated with systemic fluorouracil and fluorouracil related substances (capecitabine and tegafur) and issue a recommendation on whether the relevant marketing authorisations should be maintained, varied, suspended or revoked.

As the risk of systemic exposure of 5-fluorouracil after administration of topical formulation or after metabolism of flucytosine could not be completely excluded, the PRAC further agreed during its March 2019 plenary meeting to extend the scope of the referral procedure to include these products in the review.

The PRAC adopted a recommendation on 12 March 2020 which was then considered by the CHMP, in accordance with Article 107k of Directive 2001/83/EC.

Overall summary of the scientific evaluation by the PRAC

Parenteral 5-fluorouracil and related substances such as capecitabine and tegafur are systemic fluoropyrimidines widely used in oncology as the backbone of a large percentage of current chemotherapy regimens across a broad spectrum of cancers.

5-fluorouracil is also available as topical formulations for the treatment of slightly palpable and/or moderately thick hyperkeratotic actinic keratosis (grade I/II) in immunocompetent adult patients, as well as to treat warts (5-fluorouracil, 0.5% solution) or the treatment of superficial pre-malignant and malignant skin lesions; keratoses including senile, actinic and arsenical forms, keratoacanthoma, Bowen's disease and superficial basal-cell carcinoma (5-FU, 5% cream).

Flucytosine (5-FC), another prodrug of 5-fluorouracil, is specifically indicated for severe systemic fungal infections with susceptible pathogens.

DPD is the main metabolising enzyme of 5-fluorouracil (80-85% of catabolic clearance). Its activity is subject to a wide variability, resulting in a possible range of enzymatic deficiencies that span from partial to complete loss of enzyme activity. DPD deficiency is partly linked to genetic polymorphisms in its gene DPYD but may also have other causes. Prevalence of partial and complete DPD deficiency in the entire population varies between different sources and has been estimated with approximately 3%–9% and 0.01%–0.3%, respectively.

Treatment of patients with DPD deficiency with 5-fluorouracil or related substances can result in severe and life-threatening side effects such as severe diarrhea, stomatitis, neutropenia and neurotoxicity. Fluoropyrimidine-associated toxicity in DPD deficient patient seem to correlate with DPD activity with the strongest, often life-threatening or even fatal toxicities observed in patients with complete DPD deficiency. PRAC therefore is of the view that the benefit-risk balance of parenteral 5-fluorouracil and related substances capecitabine, tegafur and flucytosine is not favourable in patients with complete DPD deficiency and therefore these medicinal products should be contra-indicated in patients with known complete DPD deficiency.

The clinical situation in case of partial loss of DPD activity is less clear. Partial DPD deficiency is also associated with an increased risk for severe toxicity, but in the absence of suitable alternative treatment, patients may be treated with caution. A dose reduction may be considered.

To evaluate methods to identify patients with partial or complete DPD deficiency prior to treatment and mitigate the risk of severe or life-threatening toxicities, the PRAC has considered data submitted during the referral by the marketing authorisation holders of the products concerned in relation to the risk of toxicity associated with dihydropyrimidine dehydrogenase (DPD) deficiency and to the different screening methods currently available to identify patients with DPD deficiency, as well as an analysis of EudraVigilance data by EMA and third parties' interventions. The PRAC also took into account the outcome of a consultation with the Oncology scientific advisory group and the EMA pharmacogenomic working party.

Identification of completely and partially DPD deficient patients can guide the decision as to who should not be treated with fluoropyrimidines and who should be treated with a reduced dose, due to their increased risk for severe or life-threatening toxicities. Genotyping and phenotyping are to date considered to be the best available methods for identification of DPD deficient patients but both methods have some limitations.

Genotyping can only identify DPD deficiencies associated with the tested DPYD variants, although it appears that other rare or unknown DPYD variants, or non-genetic factors, may be also involved in decreased DPD activity. Moreover, DPYD genotype and DPD activity only correlate moderately. A number of patients with heterozygous DPYD genotype have been shown to exhibit normal DPD activity, and thus might be diagnosed false positive. However, among the available DPD screening methods genotyping is the easiest to perform, most robust and best implemented technique.

DPD phenotyping may overcome these challenges by direct measurement of the endogenous DPD substrate uracil (U). However, there are uncertainties on uracil cut-off levels defining complete and partial DPD deficiency, as these have not been validated prospectively. In addition, solid data on both safety and efficacy of adaptive dosing following a test results of DPD phenotyping is missing.

In the absence of data comparing both methods, PRAC proposed that both be included in the SmPC as possible approaches to identify DPD deficient patients.

Pre-treatment testing for rare mutations of the DPYD gene can identify patients with DPD deficiency.

The four DPYD variants c.1905+1G>A [also known as DPYD*2A], c.1679T>G [DPYD*13], c.2846A>T and c.1236G>A/HapB3 can cause complete absence or reduction of DPD enzymatic activity. Other rare variants may also be associated with an increased risk of severe or life-threatening toxicity. Patients with certain heterozygous DPYD variants (including c.1905+1G>A, c.1679T>G, c.2846A>T and c.1236G>A/HapB3 variants) have increased risk of severe toxicity when treated with fluoropyrimidines. Certain homozygous and compound heterozygous mutations in the DPYD gene locus (e.g. combinations of the four variants with at least one allele of c.1905+1G>A or c.1679T>G) are known to cause complete or near complete absence of DPD enzymatic activity.

The frequency of the heterozygous c.1905+1G>A genotype in the DPYD gene in Caucasian patients is around 1%, 1.1% for c.2846A>T, 2.6-6.3% for c.1236G>A/HapB3 variants and 0.07 to 0.1% for c.1679T>G. Data on the frequency of the four DPYD variants in other populations than Caucasian is limited. At the present, the four DPYD variants (c.1905+1G>A, c.1679T>G, c.2846A>T and c.1236G>A/HapB3) are considered virtually absent in populations of African (-American) or Asian origin.

Among the several phenotyping methods investigated so far, measurement of blood uracil levels has been identified as the most clinically useful. For phenotypic characterisation of DPD deficiency, the measurement of pre-therapeutic levels of the endogenous DPD substrate uracil (U) in blood is recommended. Elevated pre-treatment uracil concentrations are associated with an increased risk of toxicity. Despite uncertainties on uracil thresholds defining complete and partial DPD deficiency, a blood uracil level ≥ 16 ng/ml and < 150 ng/ml should be considered indicative of partial DPD deficiency and associated with an increased risk for fluoropyrimidine toxicity. A blood uracil level ≥ 150 ng/ml should be considered indicative of complete DPD deficiency and associated with a risk for life-threatening or fatal fluoropyrimidine toxicity. In order to better characterize the cut-off levels for DPD deficiency and related optimal dose adjustment, more research is still needed.

In addition to pre-emptive DPD testing, therapeutic drug monitoring (TDM) of blood 5-fluorouracil levels is a recommended strategy to optimize the 5-fluorouracil dosing. For patients treated with 5-fluorouracil (i.v.), TDM may therefore constitute a valuable complementary method to the upfront DPD deficiency detection methods such as phenotyping or genotyping and overcome the limited knowledge on safety and efficacy of a reduced dose. Combining upfront phenotyping or genotyping with TDM can improve the benefit-risk balance of 5-fluorouracil-based therapy. Therefore, information about TDM is included in the SmPC of 5-fluorouracil (i.v.) containing products. TDM is not considered useful for patients treated with capecitabine as systemic exposure to capecitabine and capecitabine metabolites in plasma appear to be poorly predictive of safety and efficacy.

The new recommendations for pre-treatment DPD testing qualify as an important change of current practice in relation to the medicinal products and should be communicated to relevant healthcare professionals by DHPC.

The optimal treatment of patients with partial DPD deficiency as well as the best testing methodology to identify patients at increased risk for severe toxicity remains uncertain and should be further explored. MAHs and other relevant stakeholders, including academia, are encouraged to perform further research focussing on current gaps and uncertainties in knowledge, including but not exclusive to, the optimal test method to identify patients at risk of severe DPD-associated toxicity, the optimal dose for patients tested positive for partial DPD deficiency, clinical outcome in terms of efficacy (OS, PFS) and safety (frequency of \geq grade 3 toxicity) in patients with partial DPD deficiency, the robustness of the proposed upper (>150 ng/ml) and lower (≤ 16 ng/ml) cut-off values for uracilemia to discriminate patients with normal DPD activity, partial DPD deficiency and complete DPD deficiency, and the implementation of the recommendation to screen patients for DPD deficiency and to use TDM in the different EU MS.

Unlike fluoropyrimidine exposure in cancer, systemic availability of 5-fluorouracil is usually very low after topical application. In the 5% fluorouracil formulation treated patients, with measurable plasma concentrations of 5-fluorouracil and sufficient data points for calculation of pharmacokinetic parameters, the AUC ranged from 14.507 to 37.518 ng-h/ml, which is 100-1,000 times below recommended AUC for fluoropyrimidine-based therapy in cancer. Hence, benefit-risk balance of topical 5-fluorouracil formulations in all authorised indications remains unchanged and pre-treatment DPD testing is not required for patients treated with topical 5-fluorouracil. However, PRAC considered that information should be provided in the product information of these products to reflect the low risk for patients with DPD deficiency and potential higher risk in case of systemic exposure.

Fluorouracil is a metabolite of flucytosine. DPD is a key enzyme involved in the metabolism and elimination of fluorouracil and although only a small amount of flucytosine is metabolised to fluorouracil the risk of fluorouracil induced severe toxicities due to DPD deficiency cannot be completely ruled out. On this basis, PRAC considered that flucytosine should not be used in patients with known complete DPD deficiency. In addition, determination of DPD activity may be considered where drug toxicity is confirmed or suspected. In the event of suspected drug toxicity, consideration should be given to stopping treatment. PRAC recommended this information to be communicated to relevant healthcare professionals by DHPC. Since fungal infections should be treated rapidly, a delay in initiation of flucytosine is not appropriate and therefore pre-treatment DPD testing is not required.

Grounds for PRAC recommendation

Whereas,

- The PRAC considered the procedure under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data for medicinal products containing 5-fluorouracil and related substances.
- PRAC considered the totality of the data submitted during this review in relation to the risk of toxicity associated with dihydropyrimidine dehydrogenase (DPD) deficiency and to the different screening methods currently available to identify patients with DPD deficiency. These data included the responses submitted by the marketing authorisation holders in writing, an analysis of EudraVigilance data by EMA, third parties' interventions, as well as the outcome of consultation with the Oncology scientific advisory group and the EMA pharmacogenomic working party.
- PRAC confirmed the current knowledge that the use of 5-fluorouracil for systemic use and related substances in patients with DPD deficiency is associated with an increased risk of toxicity.
- The PRAC concluded that the benefit-risk balance of 5-fluorouracil (i.v.) and related substances capecitabine, tegafur and flucytosine is negative in patients with complete DPD deficiency and confirmed that these medicinal products should be contra-indicated in patients with known complete DPD deficiency. PRAC also concluded that patients with partial DPD deficiency should be treated with an adjusted starting dose.
- To minimise the risk of increased toxicity, PRAC recommended that DPD deficiency testing is conducted before initiation of treatment. PRAC considered genotyping and phenotyping by evaluation of blood uracil levels tests as being currently the most suitable methods to identify patients with DPD deficiency. Although both methods have limitations, PRAC agreed that the product information of 5-fluorouracil (i.v.), capecitabine and tegafur containing products should

provide information on these two testing methodologies together with a guidance to consider applicable clinical guidelines.

- For patients requiring treatment with flucytosine, PRAC considered that pre-treatment DPD testing would not be compatible with the need for immediate treatment required for systemic yeast and fungal infections and therefore agreed that pre-treatment testing for DPD deficiency is not required.
- Taking into account the low systemic availability of 5-fluorouracil after topical application, PRAC concluded that the benefit-risk balance of topical 5-fluorouracil formulations remains unchanged in all authorised indications but that information on the risk of toxicity in patients with DPD deficiency in case of systemic exposure should be introduced in the product information.
- PRAC also agreed on direct healthcare professional communications (DHPC), together with the timelines for their distribution.

In view of the above, the Committee considers that the benefit-risk balance of 5-fluorouracil and related substances capecitabine, tegafur and flucytosine containing products remains favourable subject to the agreed amendments to the product information.

The Committee, as a consequence, recommends the variation to the terms of the marketing authorisations for medicinal products containing 5-fluorouracil or related substances capecitabine, flucytosine and tegafur.

CHMP opinion

Having reviewed the PRAC recommendation, the CHMP agrees with the PRAC overall conclusions and grounds for recommendation.