16 November 2020

Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Subject: Citizen Petition Concerning the Use of Fluorouracil and Xeloda Chemotherapy Drugs

The undersigned submits this petition to request the Commissioner of Food and Drugs revise the package inserts for Fluorouracil and Xeloda (Capecitabine).

A. Action Requested

Revise the Drug Label inserts for Fluorouracil and Xeloda (Capecitabine) by:

1) Recommending Pre-Treatment Testing to Identify Patients with Dihydropyrimidine Dehydrogenase (DPD) Deficiency and include the recommendation in the content of the drug labels dealing with:
    a. Patient Counseling
    b. Dosage and Administration
    c. Box Warning.

2) Revising the Patient Counseling Information content to: Shift responsibility for identifying DPD deficiency from the patient to the prescribing physicians who should also discuss with patients the risk associated with DPD deficiency before the start of treatment.

3) Revising the Dosage and Administration content to: Recommend treating physicians pre-screen patients for DPD deficiency and adapt the treatment plan if partial or complete DPD deficiency is identified.

4) Adding a Box Warning that:
    a. Highlights the risk of severe toxicity when treating patients with DPD deficiency, and
    b. Recommends screening for DPD deficiency prior to the start of treatment and prior to resuming treatment after an adverse event that necessitated treatment modification.

B. Statement of Grounds

1) Fluorouracil and capecitabine are fluoropyrimidine products widely used in the chemotherapy treatment of patients with gastrointestinal, head/neck, breast, and other forms of solid tumor cancer. The dihydropyrimidine dehydrogenase (DPD) enzyme is necessary to catabolize the chemotherapy agents to inactive products, thus limiting the circulating levels of fluoropyrimidines (Heggie et al. 1987). When DPD enzyme activity is deficient, patients treated with standard dosing of fluoropyrimidines are at significantly increased risk of severe toxicities (grade 3 or higher) or even death (see Lee et al. (2014) for 5-FU related toxicity symptoms and the increase in risk associated with genetic variants that are deleterious to DPD function; see Brutcher et al. (2018) for a comprehensive summary on how early onset toxicities can be identified in patients receiving 5-FU).
    a. Estimates of severe (grade $\geq$3) 5-FU–related toxicities range from 10-40% in the general population (Amstutz et al. 2018; Lunenburg et al. 2020; Meulendijks et al. 2015). Within the well-controlled Alliance N0147 trial, 33% of patients experienced grade 3 or higher toxicities attributed to 5-FU (Lee et al. 2014).
    b. Compromised DPD enzyme activity is common in patients who have suffered severe 5-FU toxicity (Diasio, Beavers, and Carpenter 1988; Harris et al. 1990; Harris, Carpenter, and Diasio 1991; Lu, Zhang, and Diasio 1993; Johnson and Diasio 2001).
    c. A recent study in France that measured DPD activity in 3680 patients found that as many as 11.5% of patients were DPD deficient (Pallet et al. 2020). The rate of DPD deficiency was shown to be greater among African American women (12.3%) compared to African American men (8%) (Mattison et al. 2006).
    d. Variants in the *DPYD* gene have been shown to contribute to lower DPD enzyme function and have been reproducibly shown to significantly increase risk of 5-FU–related toxicity. For example, Lee et al. (2014), demonstrated that carriers of the minor allele of the *DPYD* variant rs3918290 (a.k.a. *DPYD* c.1905+1G>A or *DPYD* *2A) have 14.9 greater odds of experiencing grade 3 or higher toxicity than non-carriers (adjusted OR=14.9, adjusted for age, sex, and relevant clinical pathological factors as detailed in the referenced manuscript). An adjusted OR of 10.2 was also reported for the DPYD rs67376798 (a.k.a. *DPYD* p.D949V) variant by Lee et al. (2014). Additional studies have demonstrated that carriers of these variants, as well as two additional variants rs55886062 (a.k.a. *DPYD* p.I560S or *DPYD* *13) and rs75017182 (a.k.a. *DPYD* c.1129-5923C>G), are at significantly increased risk for severe 5-FU–related toxicities (Meulendijks et al. 2015; Henricks et al. 2018; Lunenburg et al. 2020; European Medicines Agency 2020).
        i. The four aforementioned *DPYD* variants (rs3918290, rs67376798, rs55886062, and rs75017182) have been repeatedly shown to be deleterious to DPD function in biospecimens obtained from human volunteers (i.e., *ex vivo* measurements) and in direct *in vitro* studies (Meinsma et al. 1995; Albin et al. 1995; Johnson et al. 1999; Van Kuilenburg et al. 1999; Johnson, Wang, and Diasio 2002; van Kuilenburg et al. 2002; Seck et al. 2005; Offer, Lee, et al. 2013; Offer, Wegner, et al. 2013; Offer et al. 2014; Nie et al. 2017; van Kuilenburg et al. 2017; Shrestha et al. 2018).
        ii. The four validated *DPYD* variants described above are primarily found in Caucasian cohorts. Estimates of the number of individuals that are carriers of one or more known risk variants in *DPYD* range from 3-8% (Amstutz et al. 2018; Henricks et al. 2018; Lee et al. 2014; Lee et al. 2016; Shrestha et al. 2018).

iii. Additional variants associated with impaired DPD function have been identified in non-White populations, including the diminished activity variant p.Y186C (rs115232898) carried by approximately 5% of individuals of African ancestry (Elraiyah et al. 2017).

e. Carriers of deleterious *DPYD* variants known to contribute to compromised DPD activity are listed as being at higher adverse reaction risk (severe, life-threatening, or fatal toxicities) according to the FDA Table of Pharmacogenetic Associations (U.S. Food and Drug Administration 2020).

f. Prospective studies show that patients carrying a single copy of a risk variant can and should be treated at reduced dosing levels of 5-fluorouracil or capecitabine (Meulendijks et al. 2016; Henricks et al. 2018; Deenen et al. 2016).

2) The FDA has already taken the following actions relevant to the increased risk of severe and potentially fatal toxicities for patients with DPD deficiency who receive 5-FU or capecitabine:

a. In 2015, the FDA approved uridine triacetate (Vistogard) as an antidote to severe toxicities resulting from treatment with fluorouracil and capecitabine.

b. In 2016, the FDA revised the drug labels for 5-FU and capecitabine to more explicitly state the risks of treatment in patients with DPD deficiency.

c. In February 2020 the FDA published its "Table of Pharmacogenetic Associations" which recognizes that intermediate and poor metabolizers of 5-FU and capecitabine (identified by assessing the *DPYD* gene) have a "higher adverse reaction risk (severe, life-threatening, or fatal toxicities)" (U.S. Food and Drug Administration 2020)

3) The above actions clearly point to the risk associated with the use of these products but they fall short of employing the measures required to manage the risk to patients and to ensure the safe use of these products. To that end, the FDA should approve the Actions Requested in this petition for the reasons given below.

4) <u>Rationale for Recommending Pre-Treatment Testing to Identify DPD Deficient Patients</u> (Add to the content on the Box Warning, Patient Counseling, and Dosage and Administration): The practice of pre-screening for DPD deficiency would enable treating physicians to identify at-risk patients and adjust their treatment plan to reduce the chance of adverse outcomes while ensuring the efficacy of treatment.

a. DPD deficiency is generally only diagnosed ***<u>after</u>*** exposure to fluoropyrimidine chemotherapy. In many patients with DPD deficiency, severe and even life-threatening toxicity can occur with the first cycle of fluoropyrimidine chemotherapy, and pre-treatment diagnosis of DPD deficiency is the only way to pre-emptively identify patients at risk for these severe toxicities.

b. Pre-screening for DPD deficiency is increasingly recommended across the world by health organizations:

i. The European Medicines Agency (EMA) published a communication to healthcare professionals in June of 2020 that recommended pre-treatment testing to identify DPD-deficient patients prior to the start of treatment (European Medicines Agency 2020).

ii. French medical authorities began requiring certification that patients are free of DPD deficiency before the use of fluorouracil or Xeloda (effective in 2019). The standard test uses the uracil and dihydrouracil levels in plasma to assess DPD activity. The application of this in the medical setting has been reported by Launay et al. (2016).

iii. The Canadian province of Quebec has adopted the practice of *DPYD* genotyping prior to treatment (Groupe d'Étude en Oncologie du Québec (GÉOC) 2020).
iv. The United Kingdom recommends testing for DPD deficiency prior to initiation of 5-FU therapy to identify patients at increased risk of severe and fatal toxicity (The Government of the United Kingdom 2020).

c. Key findings of the EMA's 2020 communication (European Medicines Agency 2020) include the following:
   i. Patients with partial or complete DPD deficiency are at increased risk of severe toxicity when treated with fluoropyrimidines;
   ii. Phenotype and/or genotype testing before treatment is recommended;
   iii. Four *DPYD* genotype variants (c.1905+1G>A, c. 1679T>G, c.2846A>T, and c.1236G>A/HapB3) are associated with increased risk of severe toxicity;
   iv. Phenotype test results of a blood uracil level ≥16 ng/ml indicates partial deficiency while a level of ≥150 ng/ml indicates complete DPD deficiency;
   v. Treatment with fluoropyrimidines is contraindicated for patients with known complete deficiency (emphasis added);
   vi. Consider starting treatment at reduced dosage for patients with partial DPD deficiency (emphasis added);
   vii. Therapeutic drug monitoring may improve clinical outcomes of patients receiving continuous infusions.

d. While U.S. medical organizations have not presently adopted recommendations to screen for DPD deficiency prior to fluoropyrimidine chemotherapy, the Colon Cancer Panel of the National Comprehensive Cancer Network (NCCN) does note:
Pretreatment DPYD testing of all patients has the potential to identify the estimated 1% to 2% of the population with truncating alleles and an increased risk of severe toxicity. These patients could be offered alternative regimens or receive dose reductions. Two prospective studies have shown DPYD genotyping and fluoropyrimidine dose individualization to be feasible in clinical practice, improve patient safety, and be cost effective. (emphasis added, NCCN 2020).

e. The absence of universal agreement on a laboratory test method for diagnosis of DPD deficiency should not serve as an impediment to improving the standard of care. Arguments commonly offered in the past against pre-screening for DPD deficiency cited concerns with added costs, poor test sensitivity and specificity, possible treatment delays, the unnecessary withholding of treatment, and the risk associated with false negative results. The following represents a summary of how those concerns have been addressed:
   i. Costs: Up-front genotyping of all patients scheduled to receive 5-FU–based chemotherapy has been demonstrated to be either cost neutral or cost-saving (Deenen et al. 2016; Henricks et al. 2019; Murphy et al. 2018).
   ii. Also relevant to cost, several major insurance carriers now cover pre-emptive *DPYD* genotyping of patients for whom fluoropyrimidine chemotherapy is deemed medically necessary. This includes a local coverage determination by the Centers for Medicare & Medicaid Services (Effective 7/26/2020, see LCD at https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?lcdid=38435&ver=6&bc=CAAAAAAAAAAA) and a determination of medically necessary by Cigna (see policy at https://cignaforhcp.cigna.com/public/content/pdf/coveragePolicies/medical/mm_0500_co

veragepositioncriteria_pharmacogenetic_testing.pdf). Although this determination has not yet been made by other insurance companies, such as Aetna (see policy at http://www.aetna.com/cpb/medical/data/700_799/0715.html), we anticipate that an FDA recommendation for pre-emptive testing would lead to the vast majority of insurance companies covering this test under appropriate circumstances.

iii. Test sensitivity/specificity and treatment delays: Current genotype pre-screening methods based on the four aforementioned variants can significantly reduce the rate of severe toxic outcomes (Henricks et al. 2018). Genotypic assays with high specificity and positive predictive value are readily available in the United States from CLIA-certified laboratories, including Mayo Clinic Laboratories, ARUP Laboratories, and others (See NCBI Genetic Testing Registry: https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=1806[geneid]). As support for screening grows, a combination of expanded genotype and phenotype guided dosing may best serve to identify a greater number of at-risk patients (Meulendijks et al. 2015; Henricks et al. 2018).

iv. Treatment delays or the unnecessary withholding of treatment: The widening availability of test capabilities helps to speed the turnaround time for test results. Early and prompt test scheduling by treating oncologists can also serve to provide results quickly before the start of treatment. Withholding treatment is advised only in cases of complete DPD deficiency, which is consistent with the current FDA approved labeling. Finally, there should be minimal concern that dose reduction in *DPYD* carriers will compromise treatment efficacy, even in the 20-40% who would not have experienced severe toxicity (i.e., false positives). Matched analyses have not detected any reduction in response or survival (Launay et al. 2016, Henricks et al. 2019), likely due to two factors. First, dose reduction in *DPYD* carriers normalizes their systemic drug concentrations with non-carriers receiving standard dosing (Deenen et al. 2016), suggesting they should receive full treatment benefit. Second, dosing guidelines recommend initial dose reduction followed by dose escalation as tolerated (Amstutz et al. 2018, Henricks et al. 2018), ensuring these patients receive maximal treatment benefit.

v. The risk of false negative test results:
    1. Although a positive test strongly indicates unacceptable risk of severe toxicity (positive predictive value=82%-88% (Lee et al. 2014), a negative test does not provide certainty that the patient is not DPD deficient or will not experience severe toxicity (false negative risk=23% (Henricks et al. 2018)). False negative results will be even more common in non-Caucasian patients if the genotype panels used fail to test for the common variants in those racial/ethnic groups, such as p.Y186C (rs115232898) in patients of African descent (Offer, Lee, et al. 2013; Offer and Diasio 2014; Saif et al. 2014; Elraiyah et al. 2017; Zaanan et al. 2014).
    2. However, a false negative result is no different than today's practice of not screening patients: a patient with a false negative test will receive standard dosing and experience toxicity, just as they would have in the absence of testing. Nevertheless, continued improvements in test capabilities should serve to minimize false negatives which represent an otherwise unnecessary expenditure

and have an indirect harm from the missed opportunity to predict and prevent severe toxicity.

f. We propose the FDA update drug labels for these products to recommend treating physicians screen for DPD deficiency prior to treatment.
    i. Appropriate tests for determining DPD status, whether genotypic and/or phenotypic, should be based on current knowledge in the field and be compatible with continued refinement of test performance (which will naturally follow from an FDA recommendation to adopt testing);
    ii. Recommendations should clearly indicate that a negative test result does not mean that a patient is not at risk for adverse events;
    iii. Recommendations should be based on peer-reviewed data and incorporate tests that include risk factors determined using racially and ethnically diverse subjects, as well as factors that have been identified in specific racial, ethnic, and/or geographic groups.

5) Rationale for Revising the Patient Counseling Information: Today, the FDA makes the patient responsible for identifying DPD deficiency to the physician (see drug label inserts section 17). This measure fails to ensure safe use of the drugs because in most cases patients with DPD deficiency are asymptomatic prior to receiving 5-FU or capecitabine, meaning no overt predictive measure of toxicity would be present if not for genetic or phenotypic testing. As such, the current drug Warnings and Contraindications are "meaningless without knowing, thus testing for DPD deficiency" (Lunenburg et al. 2016). Too frequently patients' deficiencies are not identified until after suffering a severe, life-threatening toxic reaction, or death, from treatment with these drugs. It is therefore necessary to shift responsibility to identify DPD deficiency from the patient to the physician. In addition, before the start of treatment, physicians should discuss the risk of treatment with patients and make tests available to them to identify DPD deficiency.

6) Rationale for Revising the Dosage and Management Content to Encourage the Use of DPD Test Results to Guide Treatment. Patients with DPD deficiency may have either partial or complete deficiency of DPD enzymatic function. For example, the *DPYD* *2A allele results in complete allelic loss of function of the DPD enzyme. Therefore, heterozygous carriers of the *DPYD**2A allele should have 50% of normal enzymatic function of DPD, while homozygous carriers of *DPYD* *2A would be expected to have a complete loss of function of DPD. While avoidance of fluoropyrimidine chemotherapies may be necessary for rare patients with complete loss of DPD activity, there is growing evidence from prospective clinical studies that patients with partial DPD deficiency can be safely managed with fluoropyrimidine chemotherapy dose reductions.
    a. Genotype guided dosing served to reduce severe toxicities from 73% to 23% and fatalities from 10% to 0 for patients with the *DPYD*2A* variant (Deenen et al. 2016).
    b. Phenotype guided dosing used in treating patients in Marseille France reported only 3% of the patients suffered early on-set severe toxicity compared to a historical rate of 15-30% (Launay et al. 2016).
    c. The Clinical Pharmacogenetics Implementation Consortium (Amstutz et al. 2018), publishes freely accessible and regularly updated guidelines for fluoropyrimidine chemotherapy dose adjustment based on DPD activity scores.
    d. The EMA has recommended Therapeutic Drug Monitoring as a complement to pre-screening to reduce the risk of severe toxicity to patients with DPD deficiency (European Medicines Agency 2020).

7) Rationale for Adding a Box Warning: DPD deficiency, whether partial or complete, puts patients at risk of severe toxicity or even death when treated with FDA approved doses of fluorouracil or capecitabine.
    a. The FDA has already acknowledged that carriers of deleterious *DPYD* variants are at higher risk of adverse reaction (severe, life-threatening, or fatal toxicities) when treated with standard fluoropyrimidine dosing (U.S. Food and Drug Administration 2020).
    b. The risk is not trivial: 33% of patients studied in the Alliance N0147 trial experienced grade ≥3 toxicities attributed to 5-FU (Lee et al. 2014).
    c. The risk of severe toxicity is significant among patients that are carriers of *DPYD* variants associated with DPD deficiency. When treated with standard dosing of fluoropyrimidines, they carry a 50-88% risk of severe toxicity (Lee et al. 2014; Deenen et al. 2016; Lunenburg et al. 2016) and a 2.5-10% risk of acute treatment-related death (Rai, Batukbhai, and Brooks 2019; Deenen et al. 2016).
    d. Even when not directly life-threatening, drug-induced toxicities related to DPD deficiency often necessitate treatment delay or discontinuation, thus negatively impacting outcomes of cancer treatment.
    e. The FDA has established a logical precedent for using Box Warnings to include genetic screening recommendations prior to treatment to prevent severe adverse reactions in patients who are known to have unacceptable risk of treatment-related fatality. See the FDA approved Box Warning for ZIAGEN (abacavir sulfate).

8) Finally, considering the merits of the recommendations given above, the FDA should update the remaining sections of the drug labels as appropriate to bring about a clear statement on the safe use of these products.

C. Environmental Impact

None

D. Economic Impact

The intent of this proposal is to ensure the safe use of these drugs in the treatment of cancer patients and to improve treatment outcomes by putting measures in place to reduce treatment related severe toxicities and fatalities. This can be achieved without an overall increase in patient costs. The cost to pre-screen patients is off-set by the reduction in costly hospitalizations of patients who suffer severe toxicity or death. The cost of testing has been shown to be less than or not to exceed the cost of treating patients suffering severe toxicities (Deenen et al. 2016; Henricks et al. 2019; Murphy et al. 2018) and it is noteworthy that these analyses were conducted prior to the approval of Vistogard (MSRP: $80,000.00/dose), the antidote for early onset toxicities.

-- Certification is Provided on the Following Page --

E. Certification

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

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