PharmaTech CJSC
RA, Yerevan 0064, Raffii street 111

15 November 2018

IMPORTANT SAFETY UPDATE OF PRESCRIBING INFORMATION FOR XELODA® (CAPECITABINE)

Dear Healthcare Provider,

On behalf of F. Hoffmann-La Roche Ltd (hereafter referred to as Roche), we, PharmaTech CJSC would like to inform you about new recommendations concerning the treatment of patients with dihydropyrimidine dehydrogenase (DPD) deficiency with Xeloda (capecitabine).

Summary

1. Contraindications
   This section has been updated to add the contraindication in patients with known complete absence of dihydropyrimidine dehydrogenase (DPD) activity.

   - The rationale for the update is as following:
     - Patients with complete DPD deficiency suffer life-threatening or fatal 5-FU toxicity resulting in an unfavorable benefit-risk for the patient treated with 5-FU or capecitabine.
     - Patients with complete DPD deficiency may have been identified either during childhood or based on previously recognized 5-FU toxicity or may have been tested.
     - Current guidelines (2017 Clinical Pharmacogenetics Implementation Consortium (CPIC), 2016 European Society for Medical Oncology (ESMO)) strongly recommend avoiding the use of 5-FU containing regimens in patients with complete DPD-deficiency, alternative treatments should be offered to those patients.

   Due to this unfavorable benefit-risk in Xeloda treated patients with known complete DPD deficiency, a Contraindication is proposed in this specific sub-population.
2. *Warnings and Precautions*
   This section has been updated to add general wording about the possibility of testing for DPD deficiency based on the local test availability and current guidelines.

   - *The rationale for the update is as following:*
     In recent years, DPD test approaches are rapidly developing and changing. Multiple techniques are available. Guidelines recommend pre-emptive testing for DPYD variants as an option to identify patients with DPD deficiency at increased risk for severe toxicity.
     Despite the current limitations of DPD-deficiency testing, in some cases testing might be

an option as part of minimizing this risk. Therefore, the MAH is proposing to add a statement in the W&P section for the testing of DPD-deficiency, depending on the local test availability and current guidelines; and due to the unreliability of testing there continues to be a risk of life-threatening toxicity even when a negative test result is received.

Roche is working closely with health authorities to update the product information. Once approved by the health authorities, the revised Xeloda product information will be available on website of «SCIENTIFIC CENTRE OF DRUG AND MEDICAL TECHNOLOGY EXPERTISE AFTER ACADEMICIAN E. GABRIELYAN» CJSC.

Further information on the background of the new recommendations

To include 'patients with known complete absence of DPD activity' in the Contraindication section:

Dihydropyrimidine dehydrogenase (DPD) is the initial rate-limiting enzyme involved in degradation of fluorouracil for fluoropyrimidine drugs such as 5-FU and capecitabine.

Complete DPD deficiency is an autosomal, recessive trait caused by mutations in the DPD gene (*DPYD)* and is found in approx. 0.2% of the population. The complete absence of DPD enzyme activity apparent in infancy is possibly associated with signs and/or symptoms of neurological abnormalities with convulsive disorders, motor retardation, and mental retardation.

Based on evidence from available published literature and post marketing reports, complete deficiency of DPD enzyme activity is an important identified risk for the treatment with Xeloda as it leads to accumulation of cytotoxic drug, and is associated with severe life-threatening and fatal toxicity (e.g. mucosal inflammation/diarrhea, neutropenia).

Current guidelines (2017 Clinical Pharmacogenetics Implementation Consortium (CPIC), 2016 European Society for Medical Oncology (ESMO)) strongly recommend avoiding the use of 5-fluorouracil containing regimens in patients with complete DPD-deficiency, alternative treatments should be offered to those patients.

Although there is a warning and precaution for patients with complete absence of DPD activity resulting the high risks of life-threatening or fatal reactions in the W&P section, due to this unfavorable benefit-risk in Xeloda treated patients with known complete DPD deficiency, a contraindication is proposed in this specific sub-population.

To add general wording about the possibility of testing for DPD deficiency in the Warnings and Precautions section:

Early recognition of patients with complete DPD deficiency at increased risk of developing toxicities in *response to capecitabine* treatment is of utmost importance.

In recent years, research has made substantial progress in the identification and evaluation of *parameters predicting increased* fluoropyrimidin-related toxicity. New *DPYD* variants and testing

methods were discovered and evidence was generated of their association with decreased DPD enzyme activity.

The genotyping technique, based on *DPYD* sequencing, although quite advanced in development, is not able to predict DPD deficiency with related increased 5-FU toxicity in all cases. This is mostly due to the high polymorphism of *DPYD* and presence of other genes (*CDA, TYMS, SLC22A7, UMPS* and *MTHFR*) that are predictable of fluoropyrimidine toxicity. The low allele frequencies and variation of the allelic distribution by ethnicity further lower the prediction power (i.e. sensitivity) of *DPYD* single nucleotide polymorphisms and are important caveats for implementation of genotyping in routine clinical practice. Extended genotyping may improve the predictability of the testing, but is to date not routinely offered in the clinical practice.

The literature suggests that currently the four decreased function *DPYD* variants are considered of primary relevance due to their population frequency and established impact on DPD function and toxicity risk: c.190511G>A (rs3918290, also known as *DPYD**2A, *DPYD*:IVS14+1G>A), c.1679T>G (rs55886062, *DPYD**13, p.I560S), c.2846A>T (rs67376798, p.D949V), and c.1129–5923C>G (rs75017182, HapB3).

Phenotyping methods, based on analysis of DPD enzyme activity or an alternative technique, are more accurate (i.e. have higher sensitivity) in predicting 5-FU toxicity related DPD deficiency, but these methods are far less developed and have their own limitations. However, the available tests do have a high specificity, i.e. have high ability to accurately predict severe toxicity in a given patient.

Although genotypic and phenotypic screening tests for DPD deficiency are available in some centers, there are limitations for worldwide implementation of pre-emptive testing, including low allele frequencies, variability of allele distribution by ethnicity and different prevalence of DPD deficiency in different territories (3-5% in EU vs 0-0.0197% in Asia), low sensitivity, and variable availability of testing methods worldwide. In the absence of reliable methods of DPD-deficiency testing, there continues to remain a risk of life-threatening toxicity even when a result is negative for the *DPYD* gene.

Despite the current limitations of DPD-deficiency testing, in some cases testing might be an option as part of minimizing this risk. Therefore, the MAH is proposing to add a statement in the W&P section for the testing of DPD-deficiency, depending on the local test availability and current guidelines; and due to the unreliability of testing there continues to be a risk of life-threatening toxicity even when a negative test result is received.

Call for reporting

Health care professionals should report any serious adverse events suspected to be associated with the use of Xeloda according to national reporting requirements to «SCIENTIFIC CENTRE OF DRUG AND MEDICAL TECHNOLOGY EXPERTISE AFTER ACADEMICIAN E. GABRIELYAN» CJSC via following contacts:

Address: 49/4 Komitas av., 0051 Yerevan, Armenia.
Phone: +37410231682 (ext: 123)
Hot line for ADR reporting: + 37410237265
Email: vigilance@pharm.am

Company contact point

Should you have any questions or require additional information regarding the use of Xeloda (capecitabine) please feel free to contact Safety Responsible of Hoffmann-La Roche product in Armenia Gayane Ghazaryan via following details:

PharmaTech CJSC
Adress: RA, Yerevan 0064, Raffi street 111
Mob. +374 91 796688
E-mail: gayaneh.ghazaryan@gmail.com or moscow.ds@roche.com

Yours sincerely,

Vahan Arushanyan
General Director, PharmaTech CJSC

15.11.18 / date / signature

Gayane Ghazaryan
Safety Responsible for Roche products in Armenia, PharmaTech CJSC

15.11.18 / date / signature