PHARMACY AND POISONS BOARD
HONG KONG
香港藥劑業及毒藥管理局

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28th June 2021

To: Certificate holders of
registered pharmaceutical products

Dear Sir / Madam,

New Warnings for Fluorouracil, Capecitabine, Tegafur and Flucytosine

On 24th June 2021, the Pharmacy and Poisons (Registration of Pharmaceutical Products and Substances: Certification of Clinical Trial/Medicinal Test) Committee (the Committee) considered the latest new warnings for pharmaceutical products containing fluorouracil, capecitabine, tegafur and flucytosine by the drug regulatory authorities of Canada, European Union and United Kingdom and decided that the sales pack labels and / or package inserts of such products should include the following new safety information (or equivalent) as appropriate:

(I) For pharmaceutical products containing parenteral fluorouracil, as well as capecitabine and tegafur:

Contraindications

Known complete dihydropyrimidine dehydrogenase (DPD) deficiency.

Special warnings and precautions for use

Dihydropyrimidine dehydrogenase (DPD) deficiency:

DPD activity is rate limiting in the catabolism of fluorouracil. Patients with DPD deficiency are therefore at increased risk of fluoropyrimidines-related toxicity, including for example stomatitis, diarrhoea, mucosal inflammation, neutropenia and neurotoxicity.

DPD-deficiency related toxicity usually occurs during the first cycle of treatment or after dose increase.

Complete DPD deficiency

Complete DPD deficiency is rare (0.01-0.5% of Caucasians). Patients with complete DPD deficiency are at high risk of life-threatening or fatal toxicity and must not be treated with [Product Name / Generic Name].

Partial DPD deficiency

Partial DPD deficiency is estimated to affect 3-9% of the Caucasian population. Patients with partial DPD deficiency are at increased risk of severe and potentially life-threatening toxicity. A reduced starting dose should be considered to limit this toxicity. DPD deficiency should be considered as a parameter to be taken into account in conjunction with other routine measures for dose reduction. Initial dose reduction may impact the efficacy of treatment. In the absence of serious toxicity, subsequent doses may be increased with careful monitoring.

Testing for DPD deficiency

Phenotype and/or genotype testing prior to the initiation of treatment with [Product Name / Generic Name] is recommended despite uncertainties regarding optimal pre-treatment testing methodologies. Consideration should be given to applicable clinical guidelines.

Genotypic characterisation of DPD deficiency

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.*

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.

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.

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.

Phenotypic characterisation of DPD deficiency

For phenotypic characterisation of DPD deficiency, the measurement of pre-therapeutic blood levels of the endogenous DPD substrate uracil (U) in plasma 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.

[The following wording should also be introduced for fluorouracil containing medicinal products (intravenous use) only]

Fluorouracil therapeutic drug monitoring (TDM)

TDM of fluorouracil may improve clinical outcomes in patients receiving continuous fluorouracil infusions by reducing toxicities and improving efficacy. AUC is supposed to be between 20 and 30mg x h/L."

(II) For pharmaceutical products containing fluorouracil 5% for topical use:

Special warnings and precautions for use

Significant systemic drug toxicity is unlikely via percutaneous absorption of fluorouracil when [Product Name / Generic Name] is administered as per the approved prescribing information. However, the likelihood of this is increased if the product is used on skin areas in which the barrier function is impaired (e.g. cuts), if the product is applied under an occlusive dressing,

and/or in individuals with deficiency in dihydropyrimidine dehydrogenase (DPD). DPD is a key enzyme involved in metabolising and eliminating fluorouracil. Determination of DPD activity may be considered where systemic drug toxicity is confirmed or suspected. There have been reports of increased toxicity in patients who have reduced activity of the enzyme dihydropyrimidine dehydrogenase. In the event of suspected systemic drug toxicity, [Product Name / Generic Name] treatment should be stopped.

(III) <u>For pharmaceutical products containing flucytosine:</u>

Contraindications

Known complete dihydropyrimidine dehydrogenase (DPD) deficiency.

Special warnings and precautions for use

<u>Dihydropyrimidine dehydrogenase (DPD) enzyme deficiency</u>

Fluorouracil is a metabolite of flucytosine. DPD is a key enzyme involved in the metabolism and elimination of fluorouracil. Therefore, the risk of severe drug toxicity is increased when [Product Name / Generic Name] is used in individuals with deficiency in dihydropyrimidine dehydrogenase (DPD).

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 [Product Name / Generic Name] treatment.

You are therefore required to review and revise, if necessary, the sales pack labels and / or package inserts of the concerned products registered by your company to ensure that the products comply with the above new requirements. The revised sales pack labels and / or package inserts should be submitted to the Committee for approval within 2 months from the date of this letter. Failing to comply with the above requirements may result in de-registration of the products or registration not renewed by the Committee.

If you have any enquiries on the above issue, please contact Ms. Queenie CHAN at 3974 4147.

Yours faithfully,

(T.K. YIM)
Secretary,
Pharmacy and Poisons (Registration of Pharmaceutical Products and Substances: Certification of Clinical Trial/Medicinal Test) Committee

c.c. 7-15/3, Product Files

TK/QC