Annex III

Amendments to relevant sections of the product information

Note:

These amendments to the relevant sections of the product information are the outcome of the referral procedure.

The product information may be subsequently updated by the Member State competent authorities, in liaison with the reference Member State, as appropriate, in accordance with the procedures laid down in Chapter 4 of Title III of Directive 2001/83/EC.

Amendments to relevant sections of the product information

[The existing product information shall be amended (insertion, replacement or deletion of the text, as appropriate) to reflect the agreed wording as provided below]

A - 5-fluorouracil (intravenous use), capecitabine and tegafur containing medicinal products:

Summary of product characteristics

[The existing information concerning DPD deficiency in sections 4.3 and 4.4 should be replaced by the following]

4.3 Contraindications

[This section should include the following wording]

Known complete dihydropyrimidine dehydrogenase (DPD) deficiency (see section 4.4).

4.4 Special warnings and precautions for use

[A warning should be <added> <revised> as follows]

Dihydropyrimidine dehydrogenase (DPD) deficiency:

DPD activity is rate limiting in the catabolism of 5-fluorouracil (see Section 5.2). 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> (see section 4.3).

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] 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 5-fluorouracil containing medicinal products (intravenous use) only]

5-Fluorouracil Therapeutic drug monitoring (TDM)

TDM of 5-fluorouracil may improve clinical outcomes in patients receiving continuous 5-fluorouracil infusions by reducing toxicities and improving efficacy. AUC is supposed to be between 20 and 30mg x h/L.

Package Leaflet

[The existing information concerning DPD deficiency should be replaced by the following:]

Section 2. What you need to know before you take [PRODUCT NAME]

Do not take [PRODUCT NAME]:

- if you know that you do not have any activity of the enzyme dihydropyrimidine dehydrogenase (DPD) (complete DPD deficiency).

Warnings and precautions

[this section should include the following wording:]

Talk to your doctor or pharmacist before taking [PRODUCT NAME]

- if you know that you have a partial deficiency in the activity of the enzyme dihydropyrimidine dehydrogenase (DPD)
- if you have a family member who has partial or complete deficiency of the enzyme dihydropyrimidine dehydrogenase (DPD)

DPD deficiency: DPD deficiency is a genetic condition that is not usually associated with health problems unless you receive certain medicines. If you have DPD deficiency and take [PRODUCT NAME], you are at an increased risk of severe side effects (listed under section 4 Possible side effects). It is recommended to test you for DPD deficiency before start of treatment. If you have no activity of the enzyme you should not take [PRODUCT NAME]. If you have a reduced enzyme activity (partial deficiency) your doctor might prescribe a reduced dose. If you have negative test results for DPD deficiency, severe and life-threatening side effects may still occur.

Section 4. Possible side effects

[For capecitabine containing products to be added below the following paragraph:

If caught early, these side effects usually improve within 2 to 3 days after treatment discontinuation. If these side effects continue, however, contact your doctor immediately. Your doctor may instruct you to restart treatment at a lower dose.

For products not aligned with Xeloda, the statement should be added to the list after "stop taking <product name> immediately…]

If severe stomatitis (sores in your mouth and/or throat), mucosal inflammation, diarrhoea, neutropenia (increased risk for infections), or neurotoxicity occurs during the first cycle of treatment a DPD deficiency may be involved (please see Section 2: Warning and precautions).

B –5-fluorouracil (5%) containing medicinal products (cutaneous use)

Summary of product characteristics

4.4 Special warnings and precautions for use

[The existing information concerning DPD deficiency in section 4.4 should be replaced by the following]

Significant systemic drug toxicity is unlikely via percutaneous absorption of fluorouracil when [PRODUCT 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] treatment should be stopped.

Package Leaflet

Section 2. **What you need to know before you take [PRODUCT NAME]**

Warnings and precautions

[The existing information in relation to DPD deficiency should be replaced by the following]

Talk to your doctor or pharmacist before taking [PRODUCT NAME]

- if you know that you have reduced or no activity of the enzyme dihydropyrimidine dehydrogenase (DPD) (partial or complete DPD deficiency).

C - 5-fluorouracil (0.5%) containing medicinal products (cutaneous use)

Summary of product characteristics

4.4 Special warnings and precautions for use

[The existing information concerning DPD deficiency in section 4.4 should be replaced by the following]

The enzyme dihydropyrimidine dehydrogenase (DPD) plays an important role in the breakdown of fluorouracil. Inhibition, deficiency or decreased activity of this enzyme can result in accumulation of fluorouracil. However, as percutaneous absorption of fluorouracil is negligible when [PRODUCT NAME] is administered as per the approved prescribing information, no differences in the safety profile of [PRODUCT NAME] are expected in this sub-population and no dose adjustments are considered necessary.

Package Leaflet

Section 2. **What you need to know before you take [PRODUCT NAME]**

Warnings and precautions

[The existing information in relation to DPD deficiency should be replaced by the following]

Talk to your doctor or pharmacist before you use [PRODUCT NAME]

- if you know that you do not have any activity of the enzyme dihydropyrimidine dehydrogenase (DPD) (complete DPD deficiency)

D – Flucytosine containing medicinal products

Summary of product characteristics

[The existing information in relation to DPD deficiency in sections 4.3 and 4.4 should be replaced by the following]

Section 4.3 Contraindications

Known complete dihydropyrimidine dehydrogenase (DPD) deficiency.

Section 4.4 Special warnings and precautions for use

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

5-Fluorouracil is a metabolite of flucytosine. DPD is a key enzyme involved in the metabolism and elimination of 5-fluorouracil. Therefore, the risk of severe drug toxicity is increased when [PRODUCT 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] treatment.

Package leaflet

Section 2. What you need to know before you take [PRODUCT NAME]

[The existing information in relation to DPD deficiency should be replaced by the following]

Do not take [PRODUCT NAME] if you know that you do not have any activity of the enzyme dihydropyrimidine dehydrogenase (DPD) (complete DPD deficiency).