EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Fluorouracil and fluorouracil related substances (capecitabine, tegafur and flucytosine) containing medicinal products

Procedure started

Under evaluation

PRAC recommendation

CHMP opinion

European Commission final decision

Table of contents

CURRENT STATUS:
European Commission final decision

Overview

EMA recommendations on DPD testing prior to treatment with fluorouracil, capecitabine, tegafur and flucytosine

On 30 April 2020, EMA recommended that patients should be tested for the lack of the enzyme dihydropyrimidine dehydrogenase (DPD) before starting cancer treatment with fluorouracil given by injection or infusion (drip) or with the related medicines, capecitabine and tegafur.

As treatment for severe fungal infections with flucytosine (another medicine related to fluorouracil) should not be delayed, testing patients for DPD deficiency before they start treatment is not required.

Patients who completely lack DPD must not be given any fluorouracil medicines. For patients with partial deficiency, the doctor may consider starting cancer treatment at lower doses than normal or stoppingflucytosine treatment if severe side effects occur.

These recommendations do not apply to fluorouracil medicines used on the skin for conditions such as actinic keratosis and warts, as only very low levels of the medicine are absorbed through the skin.

A significant proportion of the general population ha s a deficiency of DPD,1 which is needed to break down fluorouracil and the related medicines capecitabine, tegafur and flucytosine. As a result, following treatment with these medicines, fluorouracil can build up in their blood, leading to severe and life-threatening side effects such as neutropenia (low levels of neutrophils, a type of white blood cells needed to fight infection), neurotoxicity (damage to the nervous system), severe diarrhoea and stomatitis (inflammation of the lining of the mouth).

Patients can be tested for DPD deficiency by measuring the level of uracil (a substance broken down by DPD) in the blood, or by checking for the presence of certain mutations (changes) in the gene for DPD. Relevant clinical guidelines should be taken into consideration.

---

[1]Up to 9% of the Caucasian population have low levels of a working DPD enzyme, and up to 0.5% completely lack the enzyme.

Information for patients

Treatment with fluorouracil, capecitabine or tegafur

- Before starting cancer treatment with fluorouracil given by injection or infusion (drip), capecitabine or tegafur, your doctor should do a test to check whether you have a working DPD enzyme.
- If you have a known complete lack of DPD, you will not be given these treatments as they will increase the risk of severe and life-threatening side effects.
- If you have a partial DPD deficiency, your doctor may start treatment at low doses, which can be increased if there are no serious side effects.
- If you know that you have a partial DPD deficiency or if you have a family member who has partial or complete DPD deficiency, talk to your doctor or pharmacist before taking these medicines.
- If you are using fluorouracil applied to the skin for conditions such as actinic keratosis and warts you do not need a DPD test, as the level of fluorouracil absorbed through the skin into the body is very low.
- If you have any questions about your treatment or about DPD testing, talk to your doctor or pharmacist.

Treatment with flucytosine

- Flucytosine is a medicine related to fluorouracil that is used to treat severe yeast and fungal infections, including some forms of meningitis (inflammation of the membranes that surround the brain and spinal cord).
- As flucytosine may have to be given urgently, pre-treatment DPD testing (which may take up to one week) is not required in order to avoid any delay in starting therapy.
- If you have a known complete DPD deficiency you must not be given flucytosine, due to the risk of life-threatening side effects.

In case of side effects, your doctor may consider stopping treatment with flucytosine. Your doctor may also consider testing DPD activity, since the risk of severe side effects is higher in patients with a low DPD activity.
- If you have any questions about your treatment or about DPD testing, speak to your doctor.

Information for healthcare professionals

Fluorouracil, capecitabine and tegafur

- Patients with partial or complete DPD deficiency are at increased risk of severe toxicity during treatment with fluoropyrimidines (fluorouracil, capecitabine, tegafur). Phenotype and/or genotype testing is therefore recommended before starting treatment with fluoropyrimidines.
- Treatment with fluorouracil, capecitabine or tegafur-containing medicines is contraindicated in patients with known complete DPD deficiency.
- A reduced starting dose should be considered in patients with identified partial DPD deficiency.
- Therapeutic drug monitoring of fluorouracil may improve clinical outcomes in patients receiving continuous fluorouracil infusions.

Flucytosine

- Pre-treatment testing for DPD deficiency is not required, in order to avoid delay in starting treatment with flucytosine.
- Treatment with flucytosine is contraindicated in patients with known complete DPD deficiency due to the risk of life-threatening toxicity.
- In case of drug toxicity, consideration should be given to stopping treatment with flucytosine. Determination of DPD activity may be considered where drug toxicity is confirmed or suspected.

Two direct healthcare professional communications (one DHPC for fluorouracil, capecitabine and tegafur, and a separate one for flucytosine) will be sent in due course to healthcare professionals prescribing, dispensing or administering the medicines. The DHPCs will also be published on a dedicated page on the EMA website.

More about the medicine

The review concerns fluorouracil medicines given by injection or applied to the skin as well as medicines containing capecitabine and tegafur taken by mouth (so-called fluorouracil prodrugs), which are converted to fluorouracil in the body. It also includes the antifungal medicine flucytosine which is given by injection or by mouth and some of which is converted into fluorouracil in the body.

Fluorouracil given by injection or infusion and its prodrug medicines are used to treat various cancers. They work by interfering with enzymes involved in making new DNA, thereby blocking the growth of cancer cells.

Fluorouracil applied to the skin is used for various skin conditions such as actinic keratosis and dermal warts.

Capecitabine has been authorised through EMA with the brand name Xeloda as well as various generic medicines. A medicine containing tegafur has been authorised through EMA with the brand name Teysuno.

Some tegafur- and capecitabine-containing medicines have also been authorised at national level, as have all fluorouracil and flucytosine medicines.

More about the procedure

Article 31 of Directive 2001/83/EC.

The review was first carried out by the Pharmacovigilance Risk Assessment Committee (PRAC), the Committee responsible for the evaluation of safety issues for human medicines, which made a set of recommendations.

The PRAC recommendations were sent to the Committee for Medicinal Products for Human Use (CHMP), responsible for questions concerning medicines for human use, which adopted the Agency's opinion. The CHMP opinion was forwarded to the European Commission, which issued final legally binding decisions for the medicines concerned between 3 July and 7 July 2020 that are applicable in all EU Member States.

Fluorouracil and fluorouracil related substances Article 31 referral - EMA recommendations on DPD testing prior to treatment with fluorouracil, capecitabine, tegafur and flucytosine (PDF/170.01 KB) (updated)

First published: 30/04/2020
Last updated: 15/07/2020
EMA/367286/2020

Key facts

Approved name

Fluorouracil and fluorouracil related substances (capecitabine, tegafur and flucytosine) containing medicinal products

International non-proprietary name (INN) or common name

capecitabine, fluorouracil, tegafur, flucytosine

Associated names

- Xeloda
- Teysuno
- Capecitabine Accord
- Capecitabine Medac
- Capecitabine Teva
- Ecansya (previously Capecitabine Krka)

Current status

European Commission final decision

Reference number

EMEA/H/A-31/1481

Type

Article 31 referrals

This type of referral is triggered when the interest of the Union is involved, following concerns relating to the quality, safety or efficacy of a medicine or a class of medicines.

Decision making model

PRAC-CHMP-EC

Authorisation model

Centrally and nationally authorised products (mixed)

Procedure start date

15/03/2019

PRAC recommendation date

12/03/2020

CHMP opinion/CMDh position date

30/04/2020

EC decision date

07/07/2020

Outcome

Variation

All documents

Procedure started

Fluorouracil and fluorouracil related substances Article 31 referral - Notification (PDF/461.39 KB)

First published: 15/03/2019

Fluorouracil and fluorouracil related substances Article 31 referral - Annex I (PDF/394.2 KB) (updated)

First published: 15/03/2019
Last updated: 21/07/2020
EMA/176877/2019 Rev. 1

Available languages (24)

Fluorouracil and fluorouracil related substances Article 31 referral - Timetable for the procedure (PDF/123.95 KB)

First published: 15/03/2019
Last updated: 11/12/2019
EMA/PRAC/165647/2019 Rev.4

Fluorouracil and fluorouracil related substances Article 31 referral - PRAC List of questions (PDF/84 KB)

First published: 15/03/2019
EMA/PRAC/165648/2019

Opinion provided by Committee for Medicinal Products for Human Use

Fluorouracil and fluorouracil related substances Article 31 referral - Annex III (PDF/198.08 KB)

First published: 30/04/2020
EMA/CHMP/171789/2020

European Commission final decision

Fluorouracil and fluorouracil related substances Article 31 referral - EMA recommendations on DPD testing prior to treatment with fluorouracil, capecitabine, tegafur and flucytosine (PDF/170.01 KB) (updated)

First published: 30/04/2020
Last updated: 15/07/2020
EMA/367286/2020

Fluorouracil and fluorouracil related substances Article 31 referral - Annex I (PDF/394.2 KB) (new)

First published: 23/07/2020

Available languages (24)

Fluorouracil and fluorouracil related substances Article 31 referral - Annex III (PDF/194.87 KB) (new)

First published: 23/07/2020

Available languages (24)

Fluorouracil and fluorouracil related substances Article 31 referral - Annex II (PDF/202.1 KB) (new)

First published: 23/07/2020

Available languages (24)

Fluorouracil and fluorouracil related substances Article 31 referral - Assessment report (PDF/989.63 KB) (new)

Adopted

First published: 15/07/2020
EMA/274404/2020

Document description

- Annex I - List of the medicines affected by the referral
- Annex II - Scientific conclusions of the CHMP or CMDh
- Annex III - Changes to the summary of product characteristics, labelling or package leaflet - available when the CHMP or CMDh recommends changes to the product information. Also includes conditions for lifting of suspensions, if applicable
- Annex IV - Conditions of the marketing authorisation - available when the CHMP or CMDh recommends other measures to be taken for the marketing authorisation such as safety measures or additional studies
- Notification - A letter from a Member State, the European Commission or a marketing-authorisation holder requesting the initiation of a referral procedure
- Rationale for triggering - Background provided by the party triggering the referral explaining the issues leading to the initiation of the procedure
- PRAC list of questions - Questions agreed by the PRAC requesting further information to evaluate the issues identified
- PRAC timetable - Timeframe agreed by the PRAC to receive information, assess the issues and adopt a recommendation
- PRAC / CHMP or CMDh assessment report - The assessment and conclusions of the PRAC and CHMP or CMDh on the issues investigated

News

- Meeting highlights from the Committee for Medicinal Products for Human Use (CHMP) 28-30 April 2020
  30/04/2020
- Meeting highlights from the Pharmacovigilance Risk Assessment Committee (PRAC) 9-12 March 2020
  13/03/2020
- Meeting highlights from the Pharmacovigilance Risk Assessment Committee (PRAC) 10-13 February 2020
  14/02/2020
- Meeting highlights from the Pharmacovigilance Risk Assessment Committee (PRAC) 13-16 January 2020
  17/01/2020
- Meeting highlights from the Pharmacovigilance Risk Assessment Committee (PRAC) 28-31 October 2019
  31/10/2019
- Meeting highlights from the Pharmacovigilance Risk Assessment Committee (PRAC) 8-11 July 2019
  11/07/2019
- Meeting highlights from the Pharmacovigilance Risk Assessment Committee (PRAC) 13-16 May 2019
  17/05/2019
- Meeting highlights from the Pharmacovigilance Risk Assessment Committee (PRAC) 12-15 March 2019
  15/03/2019

- Capecitabine Accord: EPAR
- Capecitabine Medac: EPAR
- Capecitabine Teva: EPAR
- Ecansya (previously Capecitabine Krka): EPAR
- Teysuno: EPAR
- Xeloda: EPAR
- Teysuno: Withdrawn application

CONTACT

European Medicines Agency
Domenico Scarlattilaan 6
1083 HS Amsterdam
The Netherlands

Tel: +31 (0)88 781 6000

For delivery address, see:
How to find us

European Union agencies network

An agency of the European Union

附件三

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

30 April 2020
EMA/229267/2020

EMA recommendations on DPD testing prior to treatment with fluorouracil, capecitabine, tegafur and flucytosine

EMA has recommended that patients should be tested for the lack of the enzyme dihydropyrimidine dehydrogenase (DPD) before starting cancer treatment with fluorouracil given by injection or infusion (drip) or with the related medicines, capecitabine and tegafur.

As treatment for severe fungal infections with flucytosine (another medicine related to fluorouracil) should not be delayed, testing patients for DPD deficiency before they start treatment is not required

Patient who completely lack DPD must not be given any fluorouracil medicines. For patients with partial deficiency, the doctor may consider starting cancer treatment at lower doses than normal or stopping flucytosine treatment if severe side effects occur.

These recommendations do not apply to fluorouracil medicines used on the skin for conditions such as actinic keratosis and warts, as only very low levels of the medicine are absorbed through the skin.

A significant proportion of the general population has a deficiency of DPD,[1] which is needed to break down fluorouracil and the related medicines capecitabine, tegafur and flucytosine. As a result, following treatment with these medicines, fluorouracil can build up in their blood, leading to severe and life-threatening side effects such as neutropenia (low levels of neutrophils, a type of white blood cells needed to fight infection), neurotoxicity (damage to the nervous system), severe diarrhoea and stomatitis (inflammation of the lining of the mouth).

Patients can be tested for DPD deficiency by measuring the level of uracil (a substance broken down by DPD) in the blood, or by checking for the presence of certain mutations (changes) in the gene for DPD. Relevant clinical guidelines should be taken into consideration.

Information for patients

Treatment with fluorouracil, capecitabine or tegafur

- Before starting cancer treatment with fluorouracil given by injection or infusion (drip), capecitabine or tegafur, your doctor should do a test to check whether you have a working DPD enzyme.
- If you have a known complete lack of DPD, you will not be given these treatments as they will increase the risk of severe and life-threatening side effects.

[1] Up to 9% of the Caucasian population have low levels of a working DPD enzyme, and up to 0.5% completely lack the enzyme.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

- If you have a partial DPD deficiency, your doctor may start treatment at low doses, which can be increased if there are no serious side effects.
- If you know that you have a partial DPD deficiency or if you have a family member who has partial or complete DPD deficiency, talk to your doctor or pharmacist before taking these medicines.
- If you are using fluorouracil applied to the skin for conditions such as actinic keratosis and warts you do not need a DPD test, as the level of fluorouracil absorbed through the skin into the body is very low.
- If you have any questions about your treatment or about DPD testing, talk to your doctor or pharmacist.

Treatment with flucytosine

- Flucytosine is a medicine related to fluorouracil that is used to treat severe yeast and fungal infections, including some forms of meningitis (inflammation of the membranes that surround the brain and spinal cord).
- As flucytosine may have to be given urgently, pre-treatment DPD testing (which may take up to one week) is not required in order to avoid any delay in starting therapy.
- If you have a known complete DPD deficiency you must not be given flucytosine, due to the risk of life-threatening side effects.
- In case of side effects, your doctor may consider stopping treatment with flucytosine. Your doctor may also consider testing DPD activity, since the risk of severe side effects is higher in patients with a low DPD activity.
- If you have any questions about your treatment or about DPD testing, speak to your doctor.

Information for healthcare professionals

Fluorouracil, capecitabine and tegafur

- Patients with partial or complete DPD deficiency are at increased risk of severe toxicity during treatment with fluoropyrimidines (fluorouracil, capecitabine, tegafur). Phenotype and/or genotype testing is therefore recommended before starting treatment with fluoropyrimidines.
- Treatment with fluorouracil, capecitabine or tegafur-containing medicines is contraindicated in patients with known complete DPD deficiency.
- A reduced starting dose should be considered in patients with identified partial DPD deficiency.
- Therapeutic drug monitoring of fluorouracil may improve clinical outcomes in patients receiving continuous fluorouracil infusions.

Flucytosine

- Pre-treatment testing for DPD deficiency is not required, in order to avoid delay in starting treatment with flucytosine.
- Treatment with flucytosine is contraindicated in patients with known complete DPD deficiency due to the risk of life-threatening toxicity.
- In case of drug toxicity, consideration should be given to stopping treatment with flucytosine. Determination of DPD activity may be considered where drug toxicity is confirmed or suspected.

Two direct healthcare professional communications (one DHPC for fluorouracil, capecitabine and tegafur, and a separate one for flucytosine) will be sent in due course to healthcare professionals prescribing, dispensing or administering the medicines. The DHPCs will also be published on a dedicated page on the EMA website.

More about the medicine

The review concerns fluorouracil medicines given by injection or applied to the skin as well as medicines containing capecitabine and tegafur taken by mouth (so-called fluorouracil prodrugs), which are converted to fluorouracil in the body. It also includes the antifungal medicine flucytosine which is given by injection or by mouth and some of which is converted into fluorouracil in the body.

Fluorouracil given by injection or infusion and its prodrug medicines are used to treat various cancers. They work by interfering with enzymes involved in making new DNA, thereby blocking the growth of cancer cells.

Fluorouracil applied to the skin is used for various skin conditions such as actinic keratosis and dermal warts.

Capecitabine has been authorised through EMA with the brand name Xeloda as well as various generic medicines. A medicine containing tegafur has been authorised through EMA with the brand name Teysuno.

Some tegafur- and capecitabine-containing medicines have also been authorised at national level, as have all fluorouracil and flucytosine medicines.

More about the procedure

The review was initiated March 2019 at the request of the French Medicines Agency (ANSM), under Article 31 of Directive 2001/83/EC.

The review was first carried out by the Pharmacovigilance Risk Assessment Committee (PRAC), the Committee responsible for the evaluation of safety issues for human medicines, which made a set of recommendations.

The PRAC recommendations were sent to the Committee for Medicinal Products for Human Use (CHMP), responsible for questions concerning medicines for human use, which adopted the Agency's opinion. The CHMP opinion will now be forwarded to the European Commission, which will issue a final legally binding decision applicable in all EU Member States in due course.

附件四

Product Information as approved by the CHMP on 30 April 2020, pending endorsement by the European Commission

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

Dihydropyrimidine dehydrogenase (DPD) enzyme deficiency

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).