Annex I

Scientific conclusions and grounds for the variation to the terms of the Marketing Authorisation(s)

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR(s) for 5 fluorouracil (i.v. application), the scientific conclusions are as follows:

The data available on DPD deficiency as well as the benefits and limitations of an upfront genotyping in patients treated with 5-fluorouracil and its prodrug capecitabine were discussed at EU level in 2017 (PRAC minutes July 2017; EMEA/H/C/000316/II/0074). The PRAC considered that the product information of 5-fluorouracil (i.v. application)-containing medicinal products should be updated to include information on DPD deficiency and DPYD genotyping in line with the conclusions of this review.

Any information that no specific antidote exists should be removed from section 4.9 of the Summary of product characteristics (SmPC), as it would not be in line with the reviewed literature data.

Furthermore, data from the reporting interval, cumulative data, literature reports and a plausible mechanism of action indicate that there is a possible association between 5-Fluorouracil (i.v. application) treatment and hyperammonaemic encephalopathy. The clinical prognosis of hyperammonaemic encephalopathy as well as the known risk of leukoencephalopathy is highly dependent on an early diagnosis of the condition and an immediate treatment; therefore a general warning should be added to ensure early recognition and treatment. The possible mechanism and the proportion of patients with renal or hepatic impairment among cases of hyperammonaemic encephalopathy support that these might be risk factors for this adverse event. This should also be reflected in section 4.4. Hyperammonaemic encephalopathy should also be listed in section 4.8 of the SmPC. Leukoencephalopathy is a known risk in patients receiving high doses of 5-FU and in patients with DPD deficiency. Whilst the data is limited, information from the literature does not allow to exclude that it may also be a risk at lower doses or in patients without DPD deficiency. Existing wording in section 4.8 should be updated accordingly.

Cardiac disorders are an important identified risk of 5-fluorouracil. Considering all information available on cardiotoxicity in patients treated with 5-fluorouracil, including recently European society position paper and updated oncology guideline, the PRAC considered that a warning should be reflected in section 4.4 to describe the type of cardiotoxicity observed and warn that these are more common in patients receiving continuous infusion. To prompt the monitoring of cardiac function during treatment and discontinue treatment in case of severe cardiotoxicity. The warning should also inform that prior history of coronary artery disease may be a risk factor for cardiac adverse reactions. Care should therefore be exercised in treating patients who experienced chest pain during courses of treatment, or patients with a history of heart disease. Also demonstrate a causal relationship between treatment with 5-fluorouracil and cases of cardiac arrest and pericarditis. These should be included as adverse drug reactions in the product information. Based on data from the literature and spontaneous reporting, the PRAC considered that there is a causal association between 5-Fluorouracil treatment and pericarditis. These adverse drug reactions should be included in the product information with the frequency unknown.

Case reports of cardiac arrest, febrile neutropenia and infections following 5-fluorouracil treatment have been identified. These adverse drug reactions should be included in the product information of 5-fluorouracil (i.v. application)-containing medicinal products.

The CMDh agrees with the scientific conclusions made by the PRAC.

Grounds for the variation to the terms of the Marketing Authorisation(s)

On the basis of the scientific conclusions for 5 fluorouracil (i.v. application) the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing 5 fluorouracil (i.v. application) is unchanged subject to the proposed changes to the product information.

The CMDh reaches the position that the marketing authorisation(s) of products in the scope of this single PSUR assessment should be varied. To the extent that additional medicinal products containing 5 fluorouracil (i.v. application) are currently authorised in the EU or are subject to future authorisation procedures in the EU, the CMDh recommends that the concerned Member States and applicant/marketing authorisation holders take due consideration of this CMDh position.

Annex II

Amendments to the product information of the nationally authorised medicinal product(s)

Amendments to be included in the relevant sections of the Product Information (new text **underlined and in bold**, deleted text ~~strike through~~)

Summary of Product Characteristics

- Section 4.3

A contraindication should be added as follows:

- **In patients with known complete absence of dihydropyrimidine dehydrogenase (DPD) activity (see section 4.4)**

- Section 4.4

Warnings should be added as follows:

Cardiotoxicity

Cardiotoxicity has been associated with fluoropyrimidine therapy, including myocardial infarction, angina, arrhythmias, myocarditis, cardiogenic shock, sudden death and electrocardiographic changes (including very rare cases of QT prolongation). These adverse events are more common in patients receiving continuous infusion of 5-fluorouracil rather than bolus injection. Prior history of coronary artery disease may be a risk factor for cardiac adverse reactions. Care should therefore be exercised in treating patients who experienced chest pain during courses of treatment, or patients with a history of heart disease. Cardiac function should be regularly monitored during treatment with fluorouracil. In case of severe cardiotoxicity the treatment should be discontinued.

[...]

Encephalopathy

Cases of encephalopathies (including hyperammonaemic encephalopathy, leukoencephalopathy) associated with 5-fluorouracil treatment have been reported from post-marketing sources. Signs or symptoms of encephalopathy are altered mental status, confusion, disorientation, coma or ataxia. If a patient develops any of these symptoms withhold treatment and test serum ammonia levels immediately. In case of elevated serum ammonia levels initiate ammonia-lowering therapy.

Caution is necessary when administering fluorouracil to patients with renal and/or hepatic impairment. Patients with impaired renal and/or hepatic function may have an increased risk for hyperammonaemia and hyperammonaemic encephalopathy.

[...]

Dihydropyrimidine dehydrogenase (DPD) deficiency

Rarely, unexpected, severe toxicity (e.g. stomatitis, diarrhoea, mucosal inflammation, neutropenia and neurotoxicity) associated with 5-fluorouracil has been attributed to a deficiency of DPD activity.

Patients with low or absent DPD activity, an enzyme involved in fluorouracil degradation, are at increased risk for severe, life-threatening, or fatal adverse reactions caused by

fluorouracil. Although DPD deficiency cannot be precisely defined, it is known that patients with certain homozygous or certain compound heterozygous mutations in the DPYD gene locus (e.g. DPYD*2A, c.1679T>G, c.2846A>T and c.1236G>A/HapB3 variants), which can cause complete or near complete absence of DPD enzymatic activity (as determined from laboratory assays), have the highest risk of life-threatening or fatal toxicity and should not be treated with 5-fluorouracil (see section 4.3). No dose has been proven safe for patients with complete absence of DPD activity.

Patients with certain heterozygous DPYD variants (including DPYD*2A, c.1679T>G, c.2846A>T and c.1236G>A/HapB3 variants) have been shown to have increased risk of severe toxicity when treated with fluoropyrimidines.

The frequency of the heterozygous DPYD*2A 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. Genotyping for these alleles is recommended to identify patients at increased risk for severe toxicity. Data on the frequency of these DPYD variants in other populations than Caucasian is limited. It cannot be excluded that other rare variants may also be associated with an increased risk of severe toxicity.

Patients with partial DPD deficiency (such as those with heterozygous mutations in the DPYD gene) and where the benefits of 5-fluorouracil are considered to outweigh the risks (taking into account the suitability of an alternative non-fluoropyrimidine chemotherapeutic regimen), must be treated with extreme caution and frequent monitoring with dose adjustment according to toxicity should be conducted. A reduction of the starting dose in these patients may be considered to avoid serious toxicity. There is insufficient data to recommend a specific dose in patients with partial DPD activity as measured by specific test. It has been reported that the DPYD*2A, c.1679T>G variants lead to a greater reduction in enzymatic activity compared to other variants with a higher risk of side effects. The consequences of a reduced dose on the efficacy are currently uncertain. Therefore, in the absence of serious toxicity the dose could be increased while carefully monitoring the patient.

The patients who are tested negative for the above-mentioned alleles may still have a risk of severe adverse events.

In patients with unrecognised DPD deficiency treated with 5-fluoruracil as well as in those patients who test negative for specific DPYD variations, life-threatening toxicities manifesting as acute overdose may occur (see section 4.9). In the event of grade 2-4 acute toxicity, treatment must be discontinued immediately. Permanent discontinuation should be considered based on clinical assessment of the onset, duration and severity of the observed toxicities.

- Section 4.8

The following adverse reaction(s) should be added under the SOC Blood and lymphatic system disorders with a frequency common:

- **febrile neutropenia**

The following adverse reaction(s) should be added under the SOC Infections and infestations with the frequency very common:

- **infections**

The following adverse reaction(s) should be added under the SOC Cardiac disorders with a frequency very rare:

- **cardiac arrest**

The following adverse reaction(s) should be added under the SOC Cardiac disorders with a frequency unknown:

- **pericarditis**

The following adverse reaction(s) should be added under the SOC nervous system disorders with a frequency unknown:

- **hyperammonaemic encephalopathy**

If applicable, the description of the following adverse reaction(s) should be changed under the SOC nervous system disorders:

- leukoencephalopathy including ataxia, acute cerebellar syndrome, dysarthria, confusion, disorientation, myasthenia, aphasia, convulsion or coma ~~in patients receiving high doses of 5-FU and in patients with DPD deficiency~~

• Section 4.9

Any reference to the fact that no antidote exists should be deleted.

• Section 5.2

The following should be added:

5-fluorouracil is catabolised by the enzyme dihydropyrimidine dehydrogenase (DPD) to the much less toxic dihydro-5-fluorouracil (FUH2). Dihydropyrimidinase cleaves the pyrimidine ring to yield 5-fluoro-ureidopropionic acid (FUPA). Finally, β-ureido-propionase cleaves FUPA to α-fluoro-β- alanine (FBAL) which is cleared in the urine. Dihydropyrimidine dehydrogenase (DPD) activity is the rate limiting step. Deficiency of DPD may lead to increased toxicity of 5-fluorouracil (see section 4.3 and 4.4).

Package Leaflet

2. What you need to know before you use [product name]

Do not use [product name]:

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

Warnings and precautions

Talk to your doctor or pharmacist before using [product name]

- **if you know that you have a partial deficiency in the activity of the enzyme dihydropyrimidine dehydrogenase (DPD)**
- **if you have problems with your heart. Tell your doctor if you experience any chest pain during treatment.**

DPD deficiency: DPD deficiency is a rare condition present at birth that is not usually associated with health problems unless you receive certain medicines. If you have an unrecognised DPD deficiency and take 5-fluorouracil, you are at an increased risk of acute

early-onset of severe forms of the side effects listed under section 4 Possible side effects. Contact your doctor immediately if you are concerned about any of the side effects or if you notice any additional side effects not listed in the leaflet (see section 4 Possible side effects).

Contact your healthcare provider immediately, if you experience the following signs or symptoms: new onset of confusion, disorientation, or otherwise altered mental status, difficulty with balance or coordination, visual disturbances. These could be signs of encephalopathy which can lead to coma and death, if left untreated.

4. Possible side effects

If any of the following happen, tell your doctor immediately:

[...]

- chest pains

- shortness of breath

[...]

Very common: may affect more than 1 in 10 people

- infections

Common: may affect up to 1 in 10 people

[...]

- low white blood cells accompanied by fever

[...]

Uncommon: may affect up to 1 in 100 people

Rare: may affect up to 1 in 1,000 people

Very rare: may affect up to 1 in 10,000 people

[...]

- cardiac arrest

[...]

Not known: frequency cannot be estimated from the available data

[...]

- hyperammonaemic encephalopathy (brain dysfunction caused by elevated ammonia)

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	September 2018 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	3 November 2018
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	2 January 2019