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 (IV use), the scientific conclusions are as follows:

In view of available data on hypertriglyceridaemia, extravasation, colitis, enterocolitis, vitamin B1 deficiency, Wernicke's encephalopathy and misdiagnosis of dihydropyrimidine dehydrogenase (DPD) deficiency from the literature, spontaneous reports including in some cases a close temporal relationship, a positive de-challenge and/or re-challenge and in view of a plausible mechanism of action, the PRAC considers a causal relationship between 5 fluorouracil (IV use) and hypertriglyceridaemia, extravasation, enterocolitis, vitamin B1 deficiency, Wernicke's encephalopathy and misdiagnosis of DPD is at least a reasonable possibility. The PRAC concluded that the product information of products containing 5-fluorouracil (for intravenous use) should be amended accordingly.

Having reviewed the PRAC recommendation, the CMDh agrees with the PRAC overall conclusions and grounds for recommendation.

Grounds for the variation to the terms of the marketing authorisation(s)

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

The CMDh recommends that the terms of the marketing authorisation(s) should be varied.

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 4.4

A warning should be amended as follows:

Testing for DPD deficiency

Phenotype and/or genotype testing prior to the initiation of treatment with 5-fluorouracil is recommended despite uncertainties regarding optimal pre-treatment testing methodologies. Consideration should be given to applicable clinical guidelines.

Impaired kidney function can lead to increased blood uracil levels resulting in an increased risk for misdiagnosis in patients with DPD deficiency with moderate or severe renal impairment.

[…]

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 $\geqslant$ 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 $\geqslant$ 150 ng/ml should be considered indicative of complete DPD deficiency and associated with a risk for life-threatening or fatal fluoropyrimidine toxicity. **Blood uracil levels should be interpreted with caution in patients with impaired kidney function (see 'Testing for DPD deficiency' above).**

Encephalopathy

Cases of encephalopathies (including hyperammonaemic encephalopathy, leukoencephalopathy, posterior reversible encephalopathy syndrome [PRES], **Wernicke's encephalopathy**) 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 **and vitamin B1** levels immediately. In case of elevated serum ammonia levels **or vitamin B1 deficiency** initiate ~~**ammonia-lowering**~~ **appropriate** therapy. Hyperammonaemic encephalopathy often occurs together with lactic acidosis.

- Section 4.8

The following adverse reaction(s) should be added under the SOC Metabolism and nutrition disorders with a frequency not known:

- **Hypertriglyceridaemia**
- **Vitamin B1 deficiency**

The following adverse reaction(s) should be added under the SOC Nervous system disorders with a frequency not known:

- **Wernicke's encephalopathy**

The following adverse reaction(s) should be added under the SOC Gastrointestinal disorders with a frequency not known:

- **Enterocolitis**
- **Colitis (including necrotising colitis)**

The following adverse reaction(s) should be added under the SOC General disorders and administration site conditions with a frequency not known:

- **Local reaction caused by extravasation (pain, swelling, erythema)**

Package Leaflet

An update of section 2 corresponding to the updates in section 4.4 of the SmPC is not proposed. Current information concerning encephalopathy and DPD deficiency is sufficient.

- ***Section 4. Possible Side Effects***

Not known: frequency cannot be estimated from the available data

- **High blood levels of triglycerides, a type of fat**
- **Pain, redness or swelling at the infusion site during or shortly after the injection/infusion (may be due to the injection not going into the vein properly)**
- **Vitamin B1 deficiency and Wernicke's encephalopathy (brain damage caused by vitamin B1 deficiency)**
- **Inflammation in the small and large bowel causing pain and diarrhoea, which can lead to death of bowel tissue (colitis, enterocolitis)**

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	September CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	03 November 2024
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	04 January 2025