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:

In view of available data on risk(s) from the literature and spontaneous reports including in some cases a close temporal relationship, a positive de-challenge and/or re-challenge, the PRAC considers a causal relationship between 5-fluorouracil (i.v.) and cutaneous lupus erythematosus is at least a reasonable possibility. The PRAC concluded that the product information of products containing 5-fluorouracil (i.v.) should be amended accordingly.

In view of available data on risk(s) from the literature and spontaneous reports including a close temporal relationship, a positive de-challenge and/or re-challenge, the PRAC considers a causal relationship between 5-fluorouracil (i.v.) and stress cardiomyopathy (takotsubo syndrome) is at least a reasonable possibility. The PRAC concluded that the product information of products containing 5-fluorouracil (i.v.) should be amended accordingly.

In view of available data on risk(s) from the literature and spontaneous reports including a close temporal relationship, a positive de-challenge and/or re-challenge, the PRAC considers a causal relationship between 5-fluorouracil (i.v.) and pneumatosis intestinalis is at least a reasonable possibility. The PRAC concluded that the product information of products containing 5-fluorouracil (i.v.) should be amended accordingly.

In view of available data on risk(s) from the literature and spontaneous reports including a close temporal relationship, a positive de-challenge, the PRAC considers a causal relationship between 5-fluorouracil (i.v.) and posterior reversible encephalopathy syndrome (PRES) is at least a reasonable possibility. The PRAC concluded that the product information of products containing 5-fluorouracil (i.v.) should be amended accordingly.

In view of available data on risk(s) from the literature and spontaneous reports including a close temporal relationship, a positive de-challenge, the PRAC considers a causal relationship between 5-fluorouracil (i.v.) and lactic acidosis is at least a reasonable possibility. The PRAC concluded that the product information of products containing 5-fluorouracil (i.v.) should be amended accordingly.

In view of available data on risk(s) from the literature and spontaneous reports including a close temporal relationship and in view of a plausible mechanism of action, the PRAC considers a causal relationship between 5-fluorouracil (i.v.) and tumour lysis syndrome is at least a reasonable possibility. The PRAC concluded that the product information of products containing 5-fluorouracil (i.v.) should be amended accordingly.

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 4.4

Warnings should be included and amended as follows:

Cardiotoxicity

Cardiotoxicity has been associated with fluoropyrimidine therapy, including myocardial infarction, angina, arrhythmias, myocarditis, cardiogenic shock, sudden death**, stress cardiomyopathy (takotsubo syndrome)** and electrocardiographic changes (including very rare cases of QT prolongation). These adverse events are more common in patients receiving continuous infusion of 5-FU rather than bolus injection. Prior history of coronary artery disease may be a risk factor for **some** 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 5-FU. In case of severe cardiotoxicity the treatment should be discontinued.

Encephalopathy

Cases of encephalopathies (including hyperammonaemic encephalopathy, leukoencephalopathy, **posterior reversible encephalopathy syndrome [PRES]**) 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. **Hyperammonaemic encephalopathy often occurs together with lactic acidosis.**

Tumour Lysis Syndrome

Cases of tumour lysis syndrome associated with fluorouracil treatment have been reported from post-marketing sources. Patients at increased risk of tumour lysis syndrome (e.g. with renal impairment, hyperuricemia, high tumour burden, rapid progression) should be closely monitored. Preventive measures (e.g. hydration, correction of high uric acid levels) should be considered.

- Section 4.8

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

cutaneous lupus erythematosus

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

stress cardiomyopathy (takotsubo syndrome)

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

pneumatosis intestinalis

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

posterior reversible encephalopathy syndrome (PRES)

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

lactic acidosis

tumour lysis syndrome

Package Leaflet

Section 4

Not Known: frequency cannot be estimated from the available data

Inflammation of the skin causing red scaly patches and possibly occurring together with pain in the joints and fever (cutaneous lupus erythematosus [CLE])

Heart disease that presents with chest pain, shortness of breath, dizziness, fainting, irregular heartbeat (stress cardiomyopathy)

Air in the intestinal wall

Serious condition that presents with difficulty breathing, vomiting and abdominal pain with muscle cramps (lactic acidosis)

Condition characterised by headache, confusion, seizures and changes in vision (posterior reversible encephalopathy syndrome [PRES])

Serious complication with rapid break down of cancer cells causing high levels of uric acid, potassium and phosphate (tumour lysis syndrome)

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	September 2021 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	31 October 2021
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	30 December 2021