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 (topical application), the scientific conclusions are as follows:

Cumulatively, 62 case reports on application site/skin haemorrhage were received, including three serious cases. Seven cases were received during the current PSUR period. In the majority of cases there was an at least reasonable time relation with the administration of topical 5-FU and causality with 5-FU has to be assessed as least as possible. Moreover, causality was assessed by the MAH as probably related in about 10 cases. Given the expected inflammatory response after application of the drug as outlined in the SmPC (including erythema, vesiculation, erosion, ulceration, necrosis and epithelisation), bleeding at the application site is pharmacologically plausible. Patients and prescribers should be adequately informed on the risk of bleeding. Therefore, application site haemorrhage should be added to section 4.8 of the SmPC and corresponding to the PIL with unknown frequency.

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 (topical application) the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing 5 fluorouracil (topical 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 (topical 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 4.8

The following adverse reaction should be added under the SOC "General disorders and administration site conditions" with a frequency unknown:

Application site haemorrhage

Package Leaflet

Section 4

Not known side effect (frequency cannot be estimated from the available data)

Bleeding at the application site

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	September 2019 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	03/11/2019
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	02/01/2020