

**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 hydroxycarbamide (except for centrally authorised product), the scientific conclusions are as follows:

High number of hydroxycarbamide cases with reported Interstitial lung disease were identified, including cases describing positive rechallenge, positive dechallenge and fatal outcome. Time to onset varied from days to several years and is considered unpredictable. In most cases withdrawal of hydroxyurea together with administration of corticosteroids led to rapid improvement. In conclusion, based on high number of cases in which a contributing role of hydroxycarbamide could not be excluded and based on the seriousness of the ADR, a change of SmPC in section 4.4 and 4.8 is warranted.

Development of non-melanoma skin cancer is a well described risk of hydroxycarbamide. It most often occurs on sun-exposed areas of the skin, in patients with Fitzpatrick skin types I and II and in older patients with higher cumulative exposures to UV radiation. Recurrence and skin cancers have been observed to develop several years after discontinuation of hydroxycarbamide therapy, necessitating long term surveillance. In conclusion, section 4.4 of the SmPC should be varied to include relevant information to minimise the risk of skin cancer.

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 hydroxycarbamide (except for centrally authorised product) the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing hydroxycarbamide (except for centrally authorised product) 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 hydroxycarbamide (except for centrally authorised product) are currently authorised in the EU or are subject to future authorisation procedures in the EU, the CMDh recommends that 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 added as follows:

**Skin cancer has been reported in patients receiving long-term hydroxycarbamide. Patients should be advised to protect skin from sun exposure. In addition, patients should conduct self-inspection of the skin during the treatment and after discontinuation of the therapy with hydroxycarbamide and be screened for secondary malignancies during routine follow-up visits.**

(...)

Respiratory disorders:

**Interstitial lung disease including pulmonary fibrosis, lung infiltration, pneumonitis, and alveolitis/allergic alveolitis have been reported in patients treated for myeloproliferative neoplasm and may be associated with fatal outcome. Patient developing pyrexia, cough, dyspnoea or other respiratory symptoms should be closely monitored, investigated and treated. Promptly discontinue of hydroxyurea and treatment with corticosteroids appears to be associated with resolution of the pulmonary events (see section 4.8)**

- Section 4.8

The following adverse reaction(s) should be added under the SOC Respiratory, Thoracic and Mediastinal Disorders with a frequency unknown:

Respiratory, Thoracic and Mediastinal Disorders

Unknown: **Interstitial lung disease**

### Package Leaflet

Section 2

Warnings and precautions

**Skin cancer has been reported in patients receiving long term hydroxycarbamide. You should protect your skin from the sun and regularly inspect your skin yourself during the treatment and after discontinuation of the therapy with hydroxycarbamide. Your doctor will also inspect your skin during routine follow-up visits.**

Section 4

Contact your doctor immediately if you experience symptoms such as:

**-fever, cough or breathing problems, this could be a sign of serious lung disease (frequency not known)**

**Annex III**

**Timetable for the implementation of this position**

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Adoption of CMDh position:	July 2018 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position :	8 September 2018
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	7 November 2018