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 busulfan, the scientific conclusions are as follows:

During the current review, the MAH identified several literature articles investigating the pharmacokinetics of busulfan. The different literature articles concluded that an interaction between busulfan and deferasirox could not be ruled out. In addition, three case reports were identified in the literature with two reporting a positive dechallenge. The literature also provided two possible mechanisms for the interaction and the decreased clearance of busulfan when given with deferasirox, however, the exact mechanism is still to be elucidated.

The review of the available information warrants an update in the product information.

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 busulfan the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing busulfan 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 busulfan 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 4.5

(…)

Increases in busulfan exposure have been observed at concomitant administration of busulfan and deferasirox. The mechanism behind the interaction is not fully elucidated. It is recommended to regularly monitor busulfan plasma concentrations and, if necessary, adjust the busulfan dose in patients who are or have recently been treated with deferasirox.

(…)

Package Leaflet

2. What you need to know before you take busulfan

Other medicines and busulfan

(…)

In particular, tell your doctor or pharmacist if you are taking any of the following:

(…)

- **Deferasirox (a medicine used to remove excess iron from your body).**

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	03/2020 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	10 May 2020
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	09 July 2020