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 lomustine, the scientific conclusions are as follows:

In view of available data on **overdose** from the literature and spontaneous reports, the PRAC considers a causal relationship between lomustine and overdose is at least a reasonable possibility. The PRAC concluded that the product information of products containing lomustine should be amended accordingly.

In view of available data on **thrombocytopenia** from the literature and in view of a plausible mechanism of action the PRAC considers a causal relationship between lomustine and thrombocytopenia is at least a reasonable possibility. The PRAC concluded that the product information of products containing lomustine 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 lomustine the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing lomustine 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

[…]

Patients must be strictly instructed not to use higher doses of <product> than recommended by a physician and should be told that <product> is taken as a single oral dose <(or as a divided dose over three days)> and will not be repeated for at least 6 weeks (see section 4.2).[1]

[…]

- Section 4.8

The frequency of the adverse reaction thrombocytopenia should be changed to very common.

Package Leaflet

- Section 2

Warnings and precautions

[…]

You should take <product> exactly as prescribed by your physician and not repeat the prescribed dose at least for 6 weeks.[1]

[…]

- Section 3

If you take more <Product> than you should

Seek medical advice immediately. Accidental overdose with <product> has been reported, including fatal cases. An overdose might express in abdominal pain, diarrhoea, regurgitation, lack of appetite, lethargy, a feeling of dizziness, cough or shortness of breath, unexplained bruising or bleeding or susceptibility to infections.

- Section 4

The following adverse reaction should be moved from frequency 'not known' to 'very common':

Low levels of blood platelets which can lead to bleeding and bruising.

[1] An existing warning on section 4.4. of the SmPC and section 2 of the PL should be **boldened and underlined** or added if missing (new added text should be **boldened and underlined**; the possibility of dividing doses remains as an option only for products where such posology is possible as per existing dosing recommendations in SmPC Section 4.2)

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	October 2023 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	27 November 2023
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	25 January 2024