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 bendamustine hydrochloride the scientific conclusions are as follows:

In view of available data on progressive multifocal encephalopathy (PML) in patients treated with bendamustine in combination with other substances from clinical trials, including in some cases a close temporal relationship and in view of a plausible mechanism of action, the PRAC considers a causal relationship between bendamustine and PML is at least a reasonable possibility. The PRAC concluded that the product information of products containing bendamustine should be amended accordingly

In view of the temporal relationship, the plausible mechanism of action and the severity of PML the PRAC concluded that a warning should be included in section 4.4 of the SmPC. The product information of products containing bendamustine hydrochloride should be amended accordingly.

In view of the available data on non-melanoma skin cancer in patients treated with bendamustine containing regimens from two clinical studies, including in some cases a close temporal relationship, and in view of a plausible mechanism of action, the PRAC considers a causal relationship between bendamustine hydrochloride and non-melanoma skin cancers is at least a reasonable possibility. The PRAC concluded that the product information of products containing bendamustine hydrochloride should be amended accordingly.

Update of section 4.4 of the SmPC to add a warning on PML and non-melanoma skin cancer. The Package leaflet is updated 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 bendamustine hydrochloride the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing bendamustine hydrochloride 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 bendamustine hydrochloride 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)

The following changes to the product information of medicinal products containing the active substance bendamustine hydrochloride are recommended (new text **underlined and in bold**, deleted text ~~strike through~~):

Summary of Product Characteristics

- Section 4.4

A warning should be amended as follows:

Infections

Serious and fatal infections have occurred with bendamustine hydrochloride, including bacterial (sepsis, pneumonia) and opportunistic infections such as Pneumocystis jirovecii pneumonia (PJP), varicella zoster virus (VZV) and cytomegalovirus (CMV). **Cases of progressive multifocal leukoencephalopathy (PML) including fatal ones have been reported following the use of bendamustine mainly in combination with rituximab or obinutuzumab.** Treatment with bendamustine hydrochloride may cause prolonged lymphocytopenia (< 600/µl) and low CD4-positive T-cell (T-helper cell) counts (< 200/µl) for at least 7–9 months after the completion of treatment. Lymphocytopenia and CD4-positive T-cell depletion are more pronounced when bendamustine is combined with rituximab**.** Patients with lymphopenia and low CD4-positive T-cell count following treatment with bendamustine hydrochloride are more susceptible to (opportunistic) infections. In case of low CD4-positive T-cell counts (< 200/µl) Pneumocystis jirovecii pneumonia (PJP) prophylaxis should be considered. All patients should be monitored for respiratory signs and symptoms throughout treatment. Patients should be advised to report new signs of infection, including fever or respiratory symptoms promptly. Discontinuation of bendamustine hydrochloride should be considered if there are signs of (opportunistic) infections.

Consider PML in the differential diagnosis in patients with new or worsening neurological, cognitive or behavioural signs or symptoms. If PML is suspected then appropriate diagnostic evaluations should be undertaken and treatment suspended until PML is excluded.

A warning should be added as follows:

Non-melanoma skin cancer

In clinical studies, an increased risk for non-melanoma skin cancers (basal cell carcinoma and squamous cell carcinoma) has been observed in patients treated with bendamustine containing therapies. Periodic skin examination is recommended for all patients, particularly those with risk factors for skin cancer.

Package Leaflet

2. What you need to know before you take [Product Name]

Warnings and precautions

At any time during or after your treatment, tell your doctor immediately if you notice or someone notices in you: memory loss, trouble thinking, difficulty walking or sight loss – these may be due to a very rare but serious brain infection which can be fatal (progressive multifocal leukoencephalopathy or PML).

Contact your doctor if you notice any suspicious skin changes because there may be an increased risk of certain types of skin cancer (non-melanoma skin cancer) with the use of this medicine.

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	September 2020 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	1 November 2020
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	31 December 2020