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:

Based on review of data from post-marketing surveillance, clinical trials and literature, the PRAC considered that a causal relationship between the use of bendamustine and the occurrence of drug reaction with eosinophilia and systemic symptoms (DRESS), urticaria, as well as pneumonitis and pulmonary alveolar haemorrhage could not be excluded and therefore requests that the product information is updated to reflect these adverse drug reactions with the frequencies not known, common and not known, respectively. Additionally, section 4.4 was updated to reflect the information on DRESS, with additional instructions for patients.

In addition, based on reports of pneumocystis infection, the PRAC considered an update to section 4.4 of the SmPC necessary with the recommendation to consider antimicrobial pneumocystis prophylaxis (e.g. trimethoprim-sulfamethoxazole) in patients with low CD4 T-cell count.

The Package Leaflet was 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)

<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

Special warnings and precautions for use should be revised 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). 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.** ~~Therefore,~~ **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.

Skin reactions

A number of skin reactions have been reported. These events have included rash, ~~toxic skin reactions~~ **severe cutaneous reactions** and bullous exanthema. Cases of Stevens – Johnson syndrome (SJS)**,** ~~and~~ Toxic Epidermal Necrolysis (TEN) **and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS),** some fatal, have been reported with the use of bendamustine hydrochloride. **Patients should be advised of the signs and symptoms of these reactions by their prescribers and should be told to seek medical attention immediately if they develop these symptoms.** Some events occurred when bendamustine hydrochloride was given in combination with other anticancer agents, so the precise relationship is uncertain. (…)

- Section 4.8

The following adverse reaction should be added under the System Organ Class (SOC) Skin and subcutaneous tissue disorders with a frequency not known:

- **Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)**

The following adverse reaction should be added under the SOC Skin and subcutaneous tissue disorders with a frequency common:

- **Urticaria**

The following adverse reaction should be added under the SOC Respiratory, thoracic and mediastinal disorders with a frequency not known:

- **Pneumonitis**
- **pulmonary alveolar haemorrhage**

Package Leaflet

- Section 4. Possible side effects

Frequency common:

- **itchy rash (urticaria)**

Frequency not known:

- **pneumonitis**
- **bleeding from the lungs**

Contact your doctor or seek medical attention immediately if you notice any of the following side effects (frequency not known):

Serious skin rashes including Stevens-Johnson syndrome and toxic epidermal necrolysis. These can appear as reddish target-like macules or circular patches often with central blisters on the trunk, skin peeling, ulcers of mouth, throat, nose, genitals and eyes and can be preceded by fever and flu-like symptoms.

Widespread rash, high body temperature, enlarged lymph nodes and other body organs involvement (Drug Reaction with Eosinophilia and Systemic Symptoms which is also known as DRESS or drug hypersensitivity syndrome).

~~A small number of cases of severe skin reactions (Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis) have been reported. The relationship of these reactions with Levact is unclear.~~

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	September 2017 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	28 October 2017
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	27 December 2017