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:

PRAC reviewed the available post marketing safety data, published literature and data from clinical trials. PRAC concluded that a causal association could be established for the below listed ADR , based on the number of cases over time, the temporal association in the majority of cases, the known mode of action of bendamustine, and the absence of plausible alternative etiologies in some of the cases reviewed: Opportunistic infection (including Herpes zoster, cytomegalovirus, hepatitis B); Pneumocystis jirovecii pneumonia; Pancytopenia; Bone marrow failure; Headache; Dizziness; Atrial fibrillation; Stevens – Johnson syndrome, Toxic Epidermal Necrolysis (TEN); Renal failure; Myelodysplastic syndrome, acute myeloid leukemia.

Based on this review PRAC also concluded that there was a need to revise the existing warnings in section 4.4 of the SmPC concerning Tumour lysis syndrome, opportunistic infections and skin reactions. In addition a warning has been included in section 4.4 regarding the risk of reactivation of hepatitis B.

Therefore, in view of the data presented in the reviewed PSUR(s), the PRAC considered that changes to the product information of medicinal products bendamustine hydrochloride, were warranted.

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 such marketing authorisations are varied accordingly.

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

A warning should be revised as follows:

Infections

~~Infection, including pneumonia and sepsis, has been reported.~~ **Serious and fatal infections have occurred with bendamustine hydrochloride, including opportunistic infections such as Pneumocystis jirovecii pneumonia (PJP), varicella zoster virus (VZV) and cytomegalovirus (CMV).** ~~In rare cases, infection has been associated with hospitalization, septic shock and death.~~ Patients with neutropenia and/or lymphopenia following treatment with bendamustine hydrochloride are more susceptible to infections. ~~Patients with myelosuppression following bendamustine hydrochloride treatment should be advised to contact a physician if they have symptoms or signs of infection, including fever or respiratory symptoms~~. **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.**

A warning should be added as follows:

Hepatitis B reactivation

Reactivation of hepatitis B in patients who are chronic carriers of this virus has occurred after these patients received bendamustine hydrochloride. Some cases resulted in acute hepatic failure or a fatal outcome. Patients should be tested for HBV infection before initiating treatment with bendamustine hydrochloride. Experts in liver disease and in the treatment of hepatitis B should be consulted before treatment is initiated in patients with positive hepatitis B tests (including those with active disease) and for patients who test positive for HBV infection during treatment. Carriers of HBV who require treatment with bendamustine hydrochloride should be closely monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy (see section 4.8).

A warning should be revised as follows:

Skin reactions

A number of skin reactions have been reported. These events have included rash, toxic skin reactions and bullous exanthema. **Cases of Stevens – Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN), some fatal, have been reported with the use of bendamustine hydrochloride.** Some events occurred when bendamustine hydrochloride was given in combination with other anticancer agents, so the precise relationship is uncertain. Where skin reactions occur, they may be progressive and increase in severity with further treatment. If skin reactions are progressive, [product name] should be withheld or discontinued. For severe skin reactions where a relationship to bendamustine hydrochloride is suspected, treatment should be discontinued.

A warning should be revised as follows:

Tumour lysis syndrome

Tumour lysis syndrome **(TLS)** associated with [product name] treatment has been reported in patients in clinical trials. The onset tends to be within 48 hours of the first dose of [product name] and, without intervention, may lead to acute renal failure and death. Preventive measures ~~include~~**such as** adequate **hydration**~~volume status~~, close monitoring of blood chemistry, particularly potassium and uric acid levels**, and the use of hypouricemic agents (allopurinol and rasburicase) should be considered prior to therapy**. ~~The use of allopurinol during the first one to two weeks of [product name] therapy can be considered but not necessarily as standard. However,~~ ~~t~~**T**here have been a few cases of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis reported when bendamustine and allopurinol are administered concomitantly.

- Section 4.8

The following wording should be revised:

The table below reflects the data obtained with bendamustine hydrochloride ~~in clinical trials~~.

The following adverse reactions should be added under the SOC Infections and infestations with a frequency:

very common: **Opportunistic infection (including Herpes zoster, cytomegalovirus, hepatitis B)**

uncommon: **Pneumocystis jirovecii pneumonia**

The following adverse reactions should be added under the SOC Blood and lymphatic system disorders with a frequency:

uncommon: **Pancytopenia**

rare: **Bone marrow failure**

The following adverse reactions should be added under the SOC Nervous system disorders with a frequency:

Very common: **Headache**

common: **Dizziness**

The following adverse reaction should be added under the SOC Cardiac disorders with a frequency:

not known: **Atrial fibrillation**

The following adverse reactions should be added under the SOC Skin and subcutaneous tissue *disorders* with a frequency

not known: **Stevens – Johnson syndrome, Toxic Epidermal Necrolysis (TEN)**

The following adverse reaction should be added under the SOC Renal and urinary disorders with a frequency

not known: **Renal failure**

The following adverse reactions should be added under the SOC Neoplasms benign, malignant with a frequency

uncommon: **Myelodysplastic syndrome, acute myeloid leukemia**

The following description of selected adverse reactions should be amended below Tab.1 Adverse reactions in patients treated with bendamustine hydrochloride:

(new text **underlined and in bold**, deleted text ~~strike through~~)

Description of selected adverse reactions

~~A small number of cases of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis have been reported in patients using bendamustine in combination with allopurinol or in combination with allopurinol and rituximab.~~

The CD4/CD8 ratio may be reduced. A reduction of the lymphocyte count was seen. In immuno-suppressed patients, the risk of infection (e.g. with herpes zoster**, CMV, PJP**) may be increased.

There have been isolated reports of necrosis after accidental extra-vascular administration and ~~toxic epidermal necrolysis,~~ tumour lysis syndrome and anaphylaxis.

~~There are reports of secondary tumours, including myelodysplastic syndrome, myeloproliferative disorders, acute myeloid leukaemia and bronchial carcinoma. The association with bendamustine hydrochloride therapy has not been determined.~~

The risk of myelodysplastic syndrome and acute myeloid leukaemias is increased in patients treated with alkylating agents (including bendamustine). The secondary malignancy may develop several years after chemotherapy has been discontinued.

Package Leaflet

A warning should be revised as follows:

2. BEFORE YOU USE [PRODUCT NAME]

Take special care with [product name]

…

- in case of reactions on your skin during treatment with [product name]. The reactions may increase in severity.
- **in case of painful red or purplish rash that spreads and blisters and/or other lesions begin to appear in the mucous membrane (e.g. mouth and lips), in particular if you had before light sensitivity, infections of the respiratory system (e.g. bronchitis) and/or fever.**
- in cases of existing heart disease (e.g. heart attack, chest pain, severely disturbed heart rhythms).
- in case you notice any pain in your side, blood in your urine or reduced amount of urine. When your disease is very severe, your body may not be able to clear all the waste products from the dying cancer cells. This is called tumour lysis syndrome and can cause kidney failure and heart problems within 48 hours of the first dose of [product name]. Your doctor ~~will be aware of this and~~ may **ensure you are adequately hydrated and** give you other medicines to help prevent it.

4. POSSIBLE SIDE FFECTS

The following adverse reactions should be added with a frequency of very common:

- **Headache**

The following adverse reactions should be added with a frequency of common:

- **Dizziness**

The following adverse reactions should be added with a frequency of uncommon:

- **Ineffective production of all blood cells (myelodysplastic syndrome)**
- **Acute leukemia**

The following adverse reactions should be added with a frequency of rare:

- **Reduction in your bone marrow function, which may make you feel unwell or show up in your blood tests**

The following adverse reactions should be added with a frequency of not known:

- **Renal failure**
- **Irregular and often rapid heart rate (atrial fibrillation)**
- **Painful red or purplish rash that spreads and blisters and/or other lesions begin to appear in the mucous membrane (e.g. mouth and lips), in particular if you had before light sensitivity, infections of the respiratory system (e.g. bronchitis) and/or fever.**

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	September 2016 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	29 October 2016
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	28 December 2016