Direct Healthcare Professional Communication

Bendamustine: increased mortality observed when used in non-approved combination treatments or outside the approved indications

Dear healthcare professional,

In agreement with the MHRA, Seacross Pharmaceuticals Limited would like to inform you of important new safety information regarding Bendamustine.

Summary

- **Increased mortality** was observed in recent clinical studies when Bendamustine was used **in non-approved combination treatments (obinutuzumab and rituximab) or outside the approved indications (follicular lymphoma [FL])**
- Fatal toxicities were mainly due to (opportunistic) infections, but some fatal cardiac, neurological, and respiratory toxicities were also reported

Prescribers are reminded of important aspects of the safety profile arising from post-marketing data:

- **Serious and fatal infections** have occurred with Bendamustine, including bacterial (sepsis, pneumonia) and (opportunistic) infections such as *Pneumocystis jirovecii* pneumonia (PJP), varicella zoster virus (VZV), and cytomegalovirus (CMV) infection.
- **Reactivation of hepatitis B** in patients who are chronic carriers of this virus has also occurred. Some cases resulted in acute hepatic failure or a fatal outcome
- **Treatment with Bendamustine may cause prolonged lymphocytopenia (< 600 cells/µl) and low CD4-positive T-cell (T-helper cell) counts (< 200 cells/µl)**, **which may persist for at least 7-9 months after the completion of treatment**, in particular when Bendamustine is combined with rituximab.
- Patients with lymphopenia and low CD4-positive T-cell counts following treatment with Bendamustine are more susceptible to (opportunistic) infections
- The summary of product characteristics is being revised and warnings regarding (opportunistic) infections are being updated.

Background on the safety concern (also see Appendix A)

Bendamustine is indicated for:

• First-line of chronic lymphocytic leukaemia (Binet stage B or C) in patients for whom fludarabine combination chemotherapy is not appropriate.

• Indolent non-Hodgkin's lymphomas as monotherapy in patients, who have progressed during or within 6 months following treatment with rituximab or a rituximab containing regimen.

• Front line treatrnent of multiple myeloma (Durie-Salmon stage Il with progress or stage Ill) in combination with prednisone for patients older than 65 years who are not eligible for autologous stem cell transplantation and who have clinical neuropathy at time of diagnosis precluding the use of thalidomide or bortezomib-containing treatment.

Call for reporting

Please continue to report suspected adverse drug reactions (ADRs) to the MHRA through the Yellow Card Scheme. Please report:

- All suspected ADRs that are serious or result in harm. Serious reactions are those that are fatal, life-threatening, disabling or incapacitating, those that cause a congenital abnormality or result in hospitalisation, and those that are considered medically significant for any other reason.
- All suspected ADRs associated with new drugs and vaccines identified by the black triangle ▼.

It is easiest and quickest to report ADRs online via the Yellow Cards website：.

Suspected adverse reactions to Bendamustine may also be reported to Seacross Pharmaceuticals Limited via email or by telephone to Seacross Pharmaceuticals Limited: drugsafety@seacrosspharma.com, Tel: +44(0)2087315273, Fax: +44(0)2037270712.

Sincerely,

UK QPPV name: Dr. Kausar Aamir

2020.10.26

UK QPPV signature

Appendix A

Background on the safety concern

In detail, Bendamustine was associated with increased mortality and unfavorable safety profile when used in combination with rituximab - compared to standard rituximab - chemotherapy regimen (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone [R-CHOP] or rituximab plus cyclophosphamide, vincristine, and prednisone [R-CVP]) - for first-line treatment of indolent non-Hodgkin lymphoma (NHL) or mantle cell lymphoma (MCL) in the BRIGHT study. Similarly, in a recent clinical trial investigating efficacy and safety in previously untreated follicular lymphoma, the combination of Bendamustine with obinutuzumab or rituximab was associated with a high rate of deaths: 5.6% (19 patients) for obinutummab -Bendamustine and 4.4% (15 patients) for rituximab - Bendamustine versus 1.6-2% for cyclophosphamide-doxorubicin-vincristine-prednisone (CHOP)-rituximab, CHOP-obinutuzumab, cyclophosphamide-vincristine-prednisone (CVP)-rituximab and CVP-obinutuzumab (GALLIUM study). Moreover, increased mortality in clinical studies investigating the treatment of chronic lymphatic leukaemia (CLL) and indolent NHL was reported for the off-label combination of Bendamustine-rituximab-idelalisib last year.

In addition, a recent safety analysis of post-marketing data showed a signal of **increased frequency of (opportunistic) infections** after treatment with Bendamustine. The review also highlighted the potential of lymphocytopenia (< 600 cells/µl) and low CD4-positive T-cell (T-helper cell) counts (< 200 cells/µl), in particular when Bendamustine was combined with rituximab.

Overall, 245 cases of cytomegalovirus (**CMV**) infection (5% fatal), 206 cases of varicella zoster virus (**VZV**) infection (1 % fatal), 79 cases of *Pneumocystis jirovecii* pneumonia (**PJP**) (42% fatal), and 42 cases of hepatitis B virus (**HBV**) reactivation (18% fatal) were identified in the safety review. The majority of the cases were assessed as causally related with Bendamustine treatment and a substantial number recovered after Bendamustine was withdrawn and/or corrective medication were given. In addition, recent data suggest higher frequencies of (opportunistic) infections compared to previous data, and significantly higher rates compared to the background incidence in this population. In a pooled analysis of historical Bendamustine monotherapy trials (n=564), the frequency of VZV, PJP and CMV events was 4.1 % (range 2-15%), 0.4%(range 0-2%); and 0.9%(range 0-5%) respectively, with one reported death caused by CMV reactivation.

Both frequency and outcome of infections seem to be highly variable and dependent on the clinical setting. High frequencies of (opportunistic) infections may be linked to lymphocytopenia and low CD4-positive T-cell (T-helper cell) counts. Lymphocytopenia (< 600 cells/µl)) and low CD4-positive T-cell (T-helper cell) counts (< 200 cells/µl) for at least 7-9 months after end of treatment with Bendamustine have been reported in a significant portion of patients, in particular when Bendamustine is combined with rituximab.

In recent clinical studies, increased mortality was observed when Bendamustine was used in non-approved combination treatment or outside the approved

indications. Fatal toxicities were mainly infections, but some fatal cardiac, neurological, and respiratory toxicities were also reported.

Consequently, the summary of product characteristics is being revised and warnings regarding (opportunistic) infections are being updated