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Direct Healthcare Professional Communication

Ribomustin (bendamustine): Increased mortality observed in recent clinical studies with bendamustine

Dear healthcare professional,

In agreement with Saudi Food and Drug Authority, Astellas would like to inform you of important new safety information regarding Ribomustin (bendamustine).

Summary

• **Increased mortality** was observed in recent clinical studies when bendamustine was used **in non-approved combination treatments or outside the approved indications**. Fatal toxicities were mainly due to (opportunistic) infections, but also some fatal cardiac, neurological, and respiratory toxicities were 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

Bendamustine is indicated for:

• First-line treatment 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 treatment of multiple myeloma (Durie-Salmon stage II with progress or stage III) 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.

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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 also some fatal cardiac, neurological, and respiratory toxicities were reported.

In detail, bendamustine was associated with increased mortality and unfavourable 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 obinutuzumab-bendamustine and 4.4% (15 patients) for rituximab-bendamustine vs 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 leukemia (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.

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

Call for reporting

Healthcare professionals are reminded to continue to report suspected adverse reactions associated with this product in accordance with the national spontaneous reporting system.

All suspected adverse reactions associated with Ribomustin should be reported in accordance with your national reporting system:

The National Pharmacovigilance and Drug Safety Centre (NPC)
o Fax: +966-11-205-7662
o Toll free phone: 8002490000
o E-mail: npc.drug@sfda.gov.sa
o Website: https://ade.sfda.gov.sa/

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Suspected adverse reactions to Ribomustin may also be reported to Astellas via Salehiya:

Email: qupv@salehiya.com
Phone number: +966 555653588

Sincerely,

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