Bendamustine Hydrochloride for Injection

**Description**
Bendamustine, (1H-benzimidazole-2-butanoic acid, 5-[bis(2-chloroethyl) amino]-1-methyl)-monochloroacetate, is a para-aminobenzyl alcylating agent. Its empirical molecular formula is C_{22}H_{18}Cl_{2}N_{3}O_3.HCl, and the molecular weight is 394.7. Structurally, Bendamustine comprises three elements: a 2-chloroethylphosphoryl alkylating group, a bendamustine ring, and a butyric acid side chain. The 2-chloroethylphosphoryl alkylating group is shared with other members of the nitrogen mustard family of alkylators, which includes cyclophosphamide, chlorambucil, and melphalan, and the butyric acid side chain is shared with chlorambucil. This bendamustine conformation is unique to Bendamustine, the intent of adding this structure to the nitrogen mustard was to include the antitumoral properties shown for bendamustine. This heterocyclic ring structure may contribute to the unique antitumoral activity of Bendamustine and distinguishes it from conventional 2-chloroethylphosphoryl alkylates.

Bendamustine has the following structural formula:

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\text{Bendamustine (2-chloroethylphosphoryl alkylating group, a bendamustine ring, and a butyric acid side chain)}
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**Mechanism of Action**
Even though the exact mechanism of action of Bendamustine is unknown, the following mechanisms have been reported in an in vitro study:

- **Alkylating Agent:** Bendamustine is a DNA cross-linking agent that causes DNA breaks. However, DNA single- and double-strand breaks caused by Bendamustine are more extensive and significantly more durable than those caused by cyclophosphamide, cyclophosphamide, or carboplatin (platinum(II) dichloride).

- **Cytoxicity:** In vitro study shows clear differences between Bendamustine and the other alkylating agents, in the forms of different trends in gene regulation within distinct functional pathways. Bendamustine results in the initiation of the 'canonical' p53-dependent stress pathway that results in a strong activation of intrinsic apoptosis. Bendamustine shows higher levels of p53 activation (upregulation at Sor11) and induction of p53-dependent genes, compared with other alkylating agents. Although other nitrogen mustards have been previously reported to induce a p53-mediated stress response, Bendamustine may provide a stronger and more rapidly induced signal compared with such drugs as chlorambucil or cyclophosphamide.

- **Pharmacokinetics**
  - **Absorption:** Oral administration of Bendamustine hydrochloride is not recommended.
  - **Distribution:** Bendamustine is highly (>90%) protein bound, primarily to albumin, at clinically relevant concentrations. Protein binding is not affected by advanced age (>70 years), low serum albumin levels (31 g/L) or presence of advanced tumors.2
  - **Elimination:** Metabolism of Bendamustine occurs primarily through hydrolysis, which gives rise to metabolites with low cytotoxic effect. Two active minor metabolites, M3 (gamma-hydroxy Bendamustine) and M4 (N-desmethyl-Bendamustine) are formed via CYP1A2, but the concentration of these metabolites are very low in comparison to the parent compound. Consequently, suggesting that Bendamustine is primarily responsible for the cytotoxic activity.

- **Half-life:** t1/2 of M3 and M4 are approximately 3 hours and 30 minutes respectively. Biliary excretion of these metabolites are not available.

**Pharmacodynamics**
- **Absorption:** Oral absorption is not significant at the end of infusion. Studies analyzing the dose proportionality of Bendamustine are not available.
- **Distribution:** Bendamustine is highly (>95%) protein bound, primarily to albumin, at clinically relevant concentrations. Protein binding is not affected by advanced age (>70 years), low serum albumin levels (31 g/L) or presence of advanced tumors.2
- **Metabolism:** Metabolism of Bendamustine occurs primarily through hydrolysis, which gives rise to metabolites with low cytotoxic effect. Two active minor metabolites, M3 (gamma-hydroxy Bendamustine) and M4 (N-desmethyl-Bendamustine) are formed via CYP1A2, but the concentration of these metabolites are very low in comparison to the parent compound. Consequently, suggesting that Bendamustine is primarily responsible for the cytotoxic activity.

**Dosing**
- **Dosage:** Bendamustine is administered intravenously as a bolus injection over 60 minutes on Days 1 and 2 of a 21-day cycle, up to 8 cycles. Bendamustine is administered as an intravenous injection over 30 minutes.
  - **Dosage and Administration for CLL:** The recommended dose is 120 mg/m2 administered intravenously on Days 1 and 2 of a 28-day cycle, up to 6 cycles.
  - **Dosage and Administration for HL:** The recommended dose is 120 mg/m2 administered intravenously over 60 minutes on Days 1 and 2 or 21-day cycle, up to 8 cycles. Bendamustine is administered as an intravenous injection over 30 minutes.
  - **Dosage and Administration for LM:** The recommended dose is 120 mg/m2 administered intravenously on Days 1 and 2, once every 3 weeks.
  - **Dosage and Administration for MM:** The recommended dose is 120 mg/m2 administered intravenously over 60 minutes on Days 1 and 2 of a 28-day cycle, up to 6 cycles. Bendamustine is administered as an intravenous injection over 30 minutes.
  - **Dosage and Administration for MMM:** The recommended dose is 120 mg/m2 administered intravenously on Days 1 and 2, once every 3 weeks.
  - **Dosage and Administration for NSCLC:** The recommended dose is 120 mg/m2 administered intravenously on Days 1 and 2, once every 3 weeks.
  - **Dosage and Administration for NHL:** The recommended dose is 120 mg/m2 administered intravenously on Days 1 and 2, once every 3 weeks.

**Formulation**
- **MyMust:** MyMust (Bendamustine hydrochloride) is also indicated for the treatment of patients with Chronic Lymphocytic Leukemia (CLL). Efficiency reduce to find the optimum phosphoramide other than chlorambucil has not been established.
MyMust - Bendamustine 100 mg/ml

Dosage adjustment for CLL patients
Dosage adjustment for hematologic toxicity: For Grade 3 or greater toxicity, reduce the dose to 50 mg/m² on Days 1 and 2 of each cycle. If Grade 3 or greater toxicity recurs, reduce the dose to 25 mg/m² on Days 1 and 2 of each cycle.

Dosage adjustment for non-hematologic toxicity: For clinically significant Grade 3 or greater toxicity, reduce the dose to 50 mg/m² on Days 1 and 2 of each cycle. Use escalation in subsequent cycles may be considered at the discretion of the treating physician.

Preparation and administration
MyMust 100 mg/ml should be aseptically reconstituted with 20 mL of sterile water for injection. Reconstitution should only be done with sterile water for injection. The lyophilized powder should completely dissolve in 5 minutes.

The reconstituted solution is clear and colorless to pale yellow. If particulate matter is observed, the reconstituted product should not be used. The concentration of Bendamustine HCl is 5 mg/mL in the reconstituted solution.

Aseptically withdraw the volume needed for the required dose (based on 5 mg/mL concentration and immediately dilute it with 500 mL of 0.9% Sodium Chloride Injection (the dilution process should be completed within 30 minutes of reconstituting). The resulting final concentration of Bendamustine HCl should be within 2 to 5.6 mg/mL. The diluted solution should be clear and colorless to slightly yellow in color.

As it is done with any other parenteral drug, prior to the administration of the drug, the diluted solution should be visually inspected for particulate matter and discoloration.

Overdose
The intravenous LD₅₀ of Bendamustine HCl is 240 mg/m² in the mouse and rat. Clinical deaths have reported ECG changes with a single dose of 280 mg/m². There is no specific antidote for Bendamustine overdose, this management should include general supportive measures and monitoring of cardiac and hemato logical parameters.

Drug Interactions
Drug interactions with Bendamustine have not been formally studied. However, Bendamustine concentrations may be decreased by drugs that induce CYP1A2 (metabolism, protecting), although the concentrations of MDA (guanine-5-oxo-guanine) Bendamustine and 8-Methoxypsoralen are increased. CYP1A2 inhibitors (flunitrazepam, theophylline) may increase the concentration of Bendamustine and decrease the concentrations of MDA, 8-Methoxypsoralen. Use with caution or consider alternative administrations, if concurrent treatment with CYP1A2 inhibitors or inducers are needed.

Stability
The diluted solution of Bendamustine is stable at controlled room temperature (15–25°C) for 3 hours and for 24 hours when it is stored at 2–8°C.

Safe Handling and Disposal
As with any other cytotoxic agent, appropriate care should be taken during preparation, administration and disposal of Bendamustine.

Adverse Events
Adverse events associated with the use of Bendamustine in CLL may include, but are not limited to, the following:

- Neutropenia
- Thrombocytopenia
- Anemia
- Leukopenia
- Lymphopenia
- Infections
- Nausea
- Fatigue
- Rash
- Incontinence
- Flavor

Details of some of the adverse events reported with the use of Bendamustine in treatment naïve patients with CLL are as follows:

Grade 3/4 Hematologic adverse events:
- Neutropenia — 42%
- Leukopenia — 20%
- Thrombocytopenia — 12%
- Anemia — 12%

Grade 3/4 Non-hematologic adverse events:
- Gastrointestinal toxicity (all grades) — 32%
- Infection (grade 3/4) — 6%
- Skin toxicity (grade 3/4) — 5%

Precautions
MyMust is common with Bendamustine and may be dose limiting, including neutropenia, thrombocytopenia, anemia, leukopenia, and febrile neutropenia. Monitor neutropenia, leukocytosis, and platelet counts.

Prior to the initiation of the next cycle of therapy, the ANC should be ≥1 x 10⁹/L and the platelet count should be ≥75 x 10⁹/L.

Infection reactions are common with the first dose including fever, chills, rigors, or rash. Infusion reactions and severe anaphylactic reactions occur rarely with subsequent doses. Discontinue Bendamustine in patients with severe infection reactions. In patients with mild reactions to the first infusion, premedicate with antihistamines, antiproteases and corticosteroids prior to subsequent doses. Skin reactions have been reported, including rash, basic skin reactions, and bullous eruptions; interrupt or discontinue Bendamustine in patients with severe or progressive reactions.

Tumor lysis syndrome may occur during the first cycle, without intervention it may lead to acute renal failure and death. Prophylaxis measures include maintaining adequate volume status, close monitoring of blood chemistry, particularly potassium and lipase levels, and the use of allopurinol during the first few weeks of Bendamustine therapy in patients at high risk.

Regulatory
MyMust is contraindicated in patients with known hypersensitivity to Bendamustine or Mannitol.

PATIENT INFORMATION
Allergic Reactions
Mild or serious allergic reactions may occur with Bendamustine therapy, as patients should immediately bring the attention of the clinician if they develop any skin rash, facial swelling, or difficulty in breathing during or soon after infusion.

Myelosuppression
Bendamustine therapy may reduce the blood cell count (white blood cells, red blood cells, and platelets). So frequent monitoring of these parameters are required. If the patients experience any shortness of breath, significant fatigue, bleeding, fever or signs of infection, they are advised to bring it to the notice of the clinician immediately.

Fatigue
Bendamustine therapy may cause lassitude, so patients are advised to avoid driving or operating dangerous tasks or machinery if they experience this side effect.

Nausea and Vomiting
Bendamustine therapy has the potential to cause nausea and/or vomiting. Patients are advised to report such events to the clinician so that symptomatic treatment may be provided.

Diarrhea
Bendamustine therapy has the potential to cause diarrhea. Patients are advised to report such events to the clinician so that symptomatic treatment may be provided.

MyMust is contraindicated in patients with known hypersensitivity to Bendamustine or Mannitol.

CONTRAINDICATIONS
MyMust should be stored below 25°C, with excipients permitted up to 30°C. Refer the product in the original carton until the time of use to protect it from light.

REFERENCES

MyMust - Bendamustine 100 mg/ml

Size: 250 x 210 mm