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Formulation and Evaluation of Anticancer Dosage Forms

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ABSTRACT

Form the overall characterization of aqueous-based formulations of Bendamustine Hydrochloride, it can be concluded that no physical description complication was observed with aqueous-based formulations. Also, the assay test parameter result was observed satisfactory. But Concerning the results of related substances, the impurity A monohydroxy Bendamustine was observed in the significant levels which are about 3.3% indicating the hydrolytic degradation nature of impurity A. though the Hydroxypropylbetacyclodextrin quantity was increased from AF1 to AF4 the higher quantities are not able to reduce the % content of Impurity A. However, other two known impurities are well within the control. % content of unknown impurities is not satisfactory. From the above experiment, it can be concluded that Bendamustine hydrochloride can't be formulated in the aqueous-based formulations as the impurity A which is a hydrolytic impurity is observed in the significant levels which are also not in line with the requirements of ICH Q3 B R(2).

INTRODUCTION

Cancer can be detected in several ways, including the presence of certain signs and symptoms, screening tests, or medical imaging. Once a possible cancer is detected it is diagnosed by microscopic examination of a tissue sample. Cancer is usually treated with chemotherapy, radiation therapy, and surgery. The chances of surviving the disease vary greatly by the type and location of cancer and the extent of disease at the start of treatment. While cancer can affect people of all ages, and a few types of cancer are more common in children, the risk of developing cancer generally increases with age. In 2007, cancer caused about 13% of all human deaths worldwide (7.9 million). Rates are rising as more people live to old age and as mass lifestyle changes occur in the developing world.[4]

B-cell chronic lymphocytic leukemia (B-CLL), also known as chronic lymphoid leukemia (CLL), is the most common type of leukemia. Leukemias are cancers of the white blood cells (leukocytes). CLL affects B cell lymphocytes. B cells originate in the bone marrow, develop in the lymph nodes, and normally fight infection by producing antibodies. B cells grow out of control and accumulate in the bone marrow and blood, where they crowd out healthy blood cells. CLL is a stage of small lymphocytic lymphoma (SLL), a type of B-cell lymphoma, which presents primarily in the lymph nodes.[6] CLL and SLL are considered the same underlying disease, just with different appearances.CLL is a disease of adults, but, in rare cases, it can occur in teenagers and occasionally in children (inherited). Most (>75%) people newly diagnosed with CLL are over the age of 50, and the majority are men.DNA analysis has distinguished two major types of CLL, with different survival times. CLL that is positive for the marker ZAP-70 has an average survival of 8 years. CLL that is negative for ZAP-70 has an average survival of more than 25 years. Many patients, especially older ones, with slowly progressing disease can be reassured and may not need any treatment in their lifetimes.[7]

Bendamustine is nitrogen mustard [an alkylating agent] contains a mechlorethamine group and a benzimidazole heterocyclic ring with a butyric acid substituent and used in the treatment of chronic lymphocytic leukemia (CLL) and lymphomas. It belongs to the family of drugs called alkylating agents. It is also being studied for the treatment of sarcoma.

Bendamustine was first synthesized in 1963 by Ozegowski and Krebs in East Germany (the former German Democratic Republic). Until 1990 it was available only in East Germany.

East German investigators found that it was useful for treating chronic lymphocytic leukemia, Hodgkin's disease, non-Hodgkin's lymphoma, multiple myeloma, and lung cancer.

Bendamustine received its first marketing approval in Germany, which is marketed under the trade name Ribomustin, by AstellasPharma GmbH's licensee, Mundipharma International Corporation Limited, which it is indicated as a single-agent or in combination with other anti-cancer agents for indolent NHL, multiple myeloma, and CLL. SymBio Pharmaceuticals Ltd holds exclusive rights to develop and market BendamustineHCl in Japan and selected Asia Pacific Rim countries.

In March 2008, Cephalon received approval from the United StatesFDA to market Bendamustine in the US, where it is sold under the trade name Treanda, for treatment of CLL.

As per the literature available, the lengthy exposure of Bendamustine to water during the reconstitution process increases the potential loss of potency and impurity formation due to the hydrolysis of the product by water. To control the degradation due to water, an organic solvent called tertiary butyl alcohol is preferred in the formulation.

Keeping all these facts in view the present study is aimed at giving a scientific basis for the native claims and traditional knowledge.

ROUTE OF ADMINISTRATION: Intravenous

INDICATIONS AND USAGE:

Chronic Lymphocytic Leukemia (CLL)

TREANDA® is indicated for the treatment of patients with chronic lymphocytic leukemia. Efficacy relative to first-line therapies other than chlorambucil has not been established.

Non-Hodgkin's Lymphoma (NHL)

TREANDA for Injection is indicated for the treatment of patients with indolent B-cell non-Hodgkin's lymphoma that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen. The recommended dose is 100 mg/m^2 administered intravenously over 30 minutes on Days 1 and 2 of a 28-day cycle, up to 6 cycles.

Dose Delays, Dose Modifications and Reinitiation of Therapy for CLL:

TREANDA administration should be delayed in the event of Grade 4 hematologic toxicity or clinically significant ≥ Grade 2 non-hematologic toxicity. Once non-hematologic toxicity has recovered to ≤ Grade 1 and/or the blood counts have improved [Absolute Neutrophil Count (ANC) ≥ 1 x 10^9/L, platelets ≥ 75 x 10^9/L], TREANDA can be reinitiated at the discretion of the treating physician. Also, dose reduction may be warranted.

Dose modifications for hematologic toxicity:

For Grade 3 or greater toxicity, reduce the dose to 50 mg/m^2 on Days 1 and 2 of each cycle; if Grade 3 or greater toxicity recurs, reduce the dose to 25 mg/m^2 on Days 1 and 2 of each cycle.

Dose modifications for non-hematologic toxicity:

For clinically significant Grade 3 or greater toxicity, reduce the dose to 50 mg/m^2 on Days 1 and 2 of each cycle. Dose re-escalation in subsequent cycles may be considered at the discretion of the treating physician. Recommended Dosage: The recommended dose is 120 mg/m^2 administered intravenously over 60 minutes on Days 1 and 2 of a 21-day cycle, up to 8 cycles.

Dose Delays, Dose Modifications and Reinitiation of Therapy for NHL:

TREANDA administration should be delayed in the event of a Grade 4 hematologic toxicity or clinically significant ≥ Grade 2 non-hematologic toxicity. Once non-hematologic toxicity has recovered to ≤ Grade 1 and/or the blood counts have improved [Absolute Neutrophil Count (ANC) ≥ 1 x 10^9/L, platelets ≥ 75 x 10^9/L], TREANDA can be reinitiated at the discretion of the treating physician. Also, dose reduction may be warranted.

Dose modifications for hematologic toxicity:

For Grade 4 toxicity, reduce the dose to 90 mg/m^2 on Days 1 and 2 of each cycle; if Grade 4 toxicity recurs, reduce the dose to 60 mg/m^2 on Days 1 and 2 of each cycle.

Dose modifications for non-hematologic toxicity:

For Grade 3 or greater toxicity, reduce the dose to 90 mg/m^2 on Days 1 and 2 of each cycle; if Grade 3 or greater toxicity recurs, reduce the dose to 60 mg/m^2 on Days 1 and 2 of each cycle.

MATERIALS AND METHODS:

MATERIALS:

List of chemicals:

Bendamustine Hydrochloride: Manufacturer-Shilpa Medicare Limited, Karnataka, India

Mannitol: Manufacturer - Roquette, Lestrem, France

Add Hydroxypropylbetacyclodextrin

Manufacturer - Finar Chemicals Limited, Mumbai

Chemicals:

Trifluoroacetic acid, Ammonium acetate, Triethylamine, Dilute acetic acid, Methanol (HPLC Grade), Acetonitrile (HPLC Grade) and Water For Injection

Trifluoroacetic acid and Ammonium acetate were procured from SISCOResearchLaboratory Pvt.Ltd.Mumbai, Triethylamine, Dilute acetic acid, Methanol (HPLC Grade) and Acetonitrile (HPLC Grade) were procured from Qualigens of AR grade Mumbai.

METHODS:

PREPARATION OF AQUEOUS BASED FORMULATIONS:

The possibility of Bendamustine hydrochloride in water for injection without any solvent was evaluated to check the feasibility and degradation profile of Bendamustine hydrochloride Injection. The bulk solution was prepared as per the formula mentioned in Table 1A total of four aqueous-based formulations were prepared. The concentration chosen of Bendamustine Hydrochloride was 5 mg/mL based on the solubility. Aqueous formulations containing Hydroxypropylbetacyclodextrin were prepared apart from containing Mannitol as an

osmolality contributing agent. There is no pH adjusting agent used in the formulation as the injection formulation pH was observed in the range of 2.5 to 3.0 without adjustment.

Table No. 1: Composition details of aqueous-based formulation trial using different concentration of HPBCD [solvent free formulation]

Sr. No.	Ingredients	AF1	AF2	AF3	AF4
1	Benndamustine Hydrochloride	5 mg/mL	5 mg/mL	5 mg/mL	5 mg/mL
2	Mannitol	20 mg/mL	20 mg/mL	20 mg/mL	20 mg/mL
3	Hydroxypropyl betacyclodextrin	10 mg/mL	15 mg/mL	20 mg/mL	25 mg/mL
4	Water For Injection	Qs to 1mL	Qs to 1 mL	Qs to 1 mL	Qs to 1 mL

Note: AF is an aqueous formulation

Brief Manufacturing Procedure:

1. Dispensed the required quantity of ingredients as per the above composition table.

2. Required quantity (about 80%) of Water for injection was collected into the mixing vessel and maintain the temperature of the WFI at 2°C to 8°C and also purge with filtered nitrogen and remaining water for injection (about 20%) was kept aside for final volume makeup. (Observations: Temperature: 6.3°C).

3. The weighed quantity of Mannitol was added to the mixing vessel under stirring. Stirred for about 5 mins.

4. The weighed quantity of Hydroxypropylbetacyclodextrin was added to the mixing vessel under stirring. Stirred for about 5 mins.

5. The weighed quantity of Bendamustine Hydrochloride was added to step 3 under stirring. Stirred for about 10 mins. (Observations: Temperature: 6.3°C).

6. The solution was made to 100% using remaining WFI having a temperature of 2°C – 8°C from step 2. (Observations: Temperature: 5.2°C) pH of the solution was recorded 2.74 (after 100% final volume make up).

Note: The temperature of the solution was maintained at 2°C-8°C and continuous nitrogen was sparged throughout the process for the above all different batches [AF1 to AF4].

RESULT AND DISCUSSION

Evaluation aqueous formulations of Bendamustine Hydrochloride:

Table No. 2: Physical and Chemical Evaluation of Aqueous Bendamustine Hydrochloride Formulations

Sr. No.	Formulation codes	Description	pH	Light transmission	Assay	Related substances
1	AF1	#	2.62	98.98%	97.95%	Imp A:3.28% Imp B:0.12% Imp C:0.08% Highest UNK Imp: 0.25% Total Imp: 3.92%
2	AF2	#	2.68	99.12%	98.12%	Imp A:3.12% Imp B:0.16% Imp C:0.04% Highest UNK Imp: 0.29% Total Imp: 4.02%
3	AF3	#	2.79	99.98%	97.31%	Imp A: 3.28% Imp B:0.18% Imp C:0.11% Highest UNK Imp: 0.19% Total Imp: 3.89%
4	AF4	#	2.92	99.14%	98.45%	Imp A: 3.28% Imp B:0.11% Imp C:0.09% Highest UNK Imp:0.20% Total Imp:3.82%

#: A clear colorless solution, LT: Light Transmission, Imp: Impurity, UNK: Unknown, AF is an aqueous formulation.

CONCLUSION

Form the overall characterization of aqueous-based formulations of Bendamustine Hydrochloride, it can be concluded that no physical description complication was observed with aqueous-based formulations. Also, the assay test parameter result was observed satisfactory. But Concerning the results of related substances, the impurity A monohydroxyBendamustine was observed in the significant levels which are about 3.3% indicating the hydrolytic degradation nature of impurity A. though the Hydroxypropylbetacyclodextrin quantity was increased from AF1 to AF4 the higher quantities are not able to reduce the % content of Impurity A. However, other two known impurities are well within the control. % content of unknown impurities is not satisfactory. From the above experiment, it can be concluded that Bendamustine hydrochloride can't be formulated in the aqueous-based formulations as the impurity A which is a hydrolytic impurity is observed in the significant levels which are also not in line with the requirements of ICH Q3 B R(2).

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