SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Bendastine 25 mg/vial or 100 mg/vial Lyophilized Powder for Injection, for intravenous use

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial contains 25 mg bendamustine hydrochloride (as bendamustine hydrochloride).
One vial contains 100 mg bendamustine hydrochloride (as bendamustine hydrochloride).
1 mL of the concentrate contains 5 mg bendamustine hydrochloride when reconstituted according to section 6.6

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Bendastin Lyophilized Powder for Injection: white to off-white lyophilized powder in a single-dose vial for reconstitution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Bendastine is indicated

- The treatment of patients with chronic lymphocytic leukemia (CLL). Efficacy relative to first line therapies other than chlorambucil has not been established.
- The treatment of patients with indolent B-cell non-Hodgkin lymphoma (NHL) that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen.

4.2 Posology and method of administration

Posology

Dosing Instructions for CLL
Recommended Dosage:
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:
Delay Bendastin Lyophilized Powder for Injection administration 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], reinitiate Bendastin Lyophilized Powder for Injection at the discretion of the treating physician. In addition, consider dose reduction. [see section 4.4]
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.
Consider dose re-escalation in subsequent cycles at the discretion of the treating physician.

Dosing Instructions for NHL
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:
Delay Bendastin Lyophilized Powder for Injection administration in the event of a Grade 4 hematologic toxicity or clinically significant greater than or equal to 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], reinitiate Bendastin Lyophilized Powder for Injection at the discretion of the treating physician. In addition, consider dose reduction. [see section 4.4]
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.

Renal Impairment
Do not use Bendastin Lyophilized Powder for Injection in patients with creatinine clearance (CLcr) < 30 mL/min. [see section 5.2]

Hepatic Impairment
Do not use Bendastin Lyophilized Powder for Injection in patients with AST or ALT 2.5-10 × upper limit of normal (ULN) and total bilirubin 1.5-3 × ULN, or total bilirubin > 3 × ULN [see section 5.2]

Pediatric Use
Safety and effectiveness in pediatric patients have not been established.
Safety, pharmacokinetics and efficacy were assessed in a single open-label trial (NCT01088984) in patients aged 1-19 years with relapsed or refractory acute leukemia, including 27 patients with acute lymphocytic leukemia (ALL) and 16 patients with acute myeloid leukemia (AML). Bendastin Lyophilized Powder for Injection was administered as an intravenous infusion over 60 minutes on Days 1 and 2 of each 21-day cycle. There was no treatment response (CR+ CRp) in any patient in the Phase 2 portion of the trial at a dose of 120 mg/m^2. However, 2 patients with ALL achieved CR at a dose of 90 mg/m^2 in the Phase 1 portion of the study. The safety profile in these patients was consistent with that seen in adults, and no new safety signals were identified.
The pharmacokinetics of bendamustine in 43 patients, aged 1 to 19 years (median age of 10 years) were within range of values previously observed in adults given the same dose based on body surface area.

Geriatric Use
No overall differences in safety were observed between patients ≥65 years of age and younger patients. Efficacy was lower in patients 65 and over with CLL receiving Bendastin Lyophilized Powder for Injection based upon an overall response rate of 47% for patients 65 and over and 70% for younger patients. Progression free survival was also longer in younger patients with CLL receiving Bendastin Lyophilized Powder for Injection (19 months vs. 12 months). No overall differences in efficacy in patients with non-Hodgkin Lymphoma were observed between geriatric patients and younger patients.

Method of administration
Bendastin Lyophilized Powder for Injection is a cytotoxic drug. Follow applicable special handling and disposal procedures
If a closed system transfer device (CSTD) or adapter that contains polycarbonate or acrylonitrile-butadienestyrene-styrene (ABS) is used as supplemental protection prior to dilution, only use Bendastin Lyophilized Powder for Injection, the lyophilized powder formulation
For instructions on reconstitution and dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Bendastin Lyophilized Powder for Injection is contraindicated in patients with a known hypersensitivity (e.g., anaphylactic and anaphylactoid reactions) to bendamustine. [see section 4.4]

4.4 Special warnings and precautions for use

Myelosuppression

Bendastin Lyophilized Powder for Injection caused severe myelosuppression (Grade 3-4) in 98% of patients in the two NHL studies (see Table 4). Three patients (2%) died from myelosuppression-related adverse reactions; one each from neutropenic sepsis, diffuse alveolar hemorrhage with Grade 3 thrombocytopenia, and pneumonia from an opportunistic infection (CMV).

Monitor complete blood counts, including leukocytes, platelets, hemoglobin (Hgb), and neutrophils frequently. In the clinical trials, blood counts were monitored every week initially. Hematologic nadirs were observed predominantly in the third week of therapy. Myelosuppression may require dose delays and/or subsequent dose reductions if recovery to the recommended values has not occurred by the first day of the next scheduled cycle. Prior to the initiation of the next cycle of therapy, the ANC should be $\geq 1 \times 10^9$ /L and the platelet count should be $\geq 75 \times 10^9$ /L. [see section 4.4]

Infections

Infection, including pneumonia, sepsis, septic shock, heptatitis and death has occurred in adult and pediatric patients in clinical trials and in postmarketing reports. Patients with myelosuppression following treatment with Bendastin Lyophilized Powder for Injection are more susceptible to infections. Advise patients with myelosuppression following Bendastin Lyophilized Powder for Injection treatment to contact a physician if they have symptoms or signs of infection.

Patients treated with Bendastin Lyophilized Powder for Injection are at risk for reactivation of infections including (but not limited to) hepatitis B, cytomegalovirus, Mycobacterium tuberculosis, and herpes zoster. Patients should undergo appropriate measures (including clinical and laboratory monitoring, prophylaxis, and treatment) for infection and infection reactivation prior to administration.

Progressive Multifocal Leukoencephalopathy (PML)

Progressive multifocal leukoencephalopathy (PML), including fatal cases, have occurred following treatment with bendamustine, primarily in combination with rituximab or obinutuzumab [see Adverse Reactions (6.2)]. Consider PML in the differential diagnosis in patients with new or worsening neurological, cognitive or behavioral signs or symptoms. If PML is suspected, withhold TREANDA treatment and perform appropriate diagnostic evaluations. Consider discontinuation or reduction of any concomitant chemotherapy or immunosuppressive therapy in patients who develop PML.

Anaphylaxis and Infusion Reactions

Infusion reactions to Bendastin Lyophilized Powder for Injection have occurred commonly in clinical trials. Symptoms include fever, chills, pruritus and rash. In rare instances severe anaphylactic and anaphylactoid reactions have occurred, particularly in the second and subsequent cycles of therapy. Monitor clinically and discontinue drug for severe reactions. Ask patients about symptoms suggestive of infusion reactions after their first cycle of therapy. Patients who experience Grade 3 or worse allergic-type reactions should not be rechallenged. Consider measures to prevent severe reactions,including antihistamines, antipyretics and corticosteroids in subsequent cycles in patients who have experienced Grade 1 or 2 infusion reactions. Discontinue Bendastin Lyophilized Powder for Injection for patients with Grade 4 infusion reactions. Consider discontinuation for Grade 3 infusions reactions as clinically appropriate considering individual benefits, risks, and supportive care.

Tumor Lysis Syndrome

Tumor lysis syndrome associated with Bendastin Lyophilized Powder for Injection treatment has occurred in patients in clinical trials and in postmarketing reports. The onset tends to be within the first treatment cycle of Bendastin Lyophilized Powder for Injection and, without intervention, may lead to acute renal failure and death. Preventive measures include vigorous hydration and close monitoring of blood chemistry, particularly potassium and uric acid levels. Allopurinol has also been used during the beginning of Bendastin Lyophilized Powder for Injection therapy. However, there may be an increased risk of severe skin toxicity when Bendastin Lyophilized Powder for Injection and allopurinol are administered concomitantly [see section 4.4].

Skin Reactions

Fatal and serious skin reactions have been reported with Bendastin Lyophilized Powder for Injection treatment in clinical trials and postmarketing safety reports, including toxic skin reactions [Stevens - Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS)], bullous exanthema, and rash. Events occurred when Bendastin Lyophilized Powder for Injection was given as a single agent and in combination with other anticancer agents or allopurinol.

Where skin reactions occur, they may be progressive and increase in severity with further treatment. Monitor patients with skin reactions closely. If skin reactions are severe or progressive, withhold or discontinue Bendastin Lyophilized Powder for Injection.

Hepatotoxicity
Fatal and serious cases of liver injury have been reported with Bendastin Lyophilized Powder for Injection. Combination therapy, progressive disease or reactivation of hepatitis B were confounding factors in some patients [see section 4.4]. Most cases were reported within the first three months of starting therapy. Monitor liver chemistry tests prior to and during bendamustine therapy.

Other Malignancies
There are reports of pre-malignant and malignant diseases that have developed in patients who have been treated with Bendastin Lyophilized Powder for Injection, including myelodysplastic syndrome, myeloproliferative disorders, acute myeloid leukemia and bronchial carcinoma, and non-melanoma skin cancer, including basal cell carcinoma and squamous cell carcinoma [see Warnings and Precautions (6.2)]. Monitor patients for the development of secondary malignancies. Perform dermatologic evaluations during and after treatment with Bendastin Lyophilized Powder for Injection.

Extravasation Injury
Bendastin Lyophilized Powder for Injection extravasations have been reported in post marketing resulting in hospitalizations from erythema, marked swelling, and pain [see Warnings and Precautions (6.2)]. Assure good venous access prior to starting Bendastin Lyophilized Powder for Injection infusion and monitor the intravenous infusion site for redness, swelling, pain, infection, and necrosis during and after administration of Bendastin Lyophilized Powder for Injection.

Embryo-Fetal Toxicity
Based on findings from animal reproduction studies and the drug's mechanism of action, Bendastin Lyophilized Powder for Injection can cause fetal harm when administered to a pregnant woman. Single intraperitoneal doses of bendamustine (that approximated the maximum recommended human dose based on body surface area) to pregnant mice and rats during organogenesis caused adverse developmental outcomes, including an increase in resorptions, skeletal and visceral malformations, and decreased fetal body weights. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use an effective method of contraception during treatment with Bendastin Lyophilized Powder for Injection and for at least 6 months after the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with Bendastin Lyophilized Powder for Injection and for at least 3 months after the final dose [see section 4.2 and 5.1].

4.5 Interaction with other medicinal products and other forms of interaction

CYP1A2 Inhibitors
The coadministration of Bendamustine Hydrochloride with CYP1A2 inhibitors may increase bendamustine plasma concentrations and may result in increased incidence of adverse reactions with Bendamustine Hydrochloride [see section 5.2]. Consider alternative therapies that are not CYP1A2 inhibitors during treatment with Bendamustine Hydrochloride.
CYP1A2 Inducers
The coadministration of Bendamustine Hydrochloride with CYP1A2 inducers may decrease bendamustine plasma concentrations and may result in decreased efficacy of Bendamustine Hydrochloride [see section 5.3]. Consider alternative therapies that are not CYP1A2 inducers during treatment with Bendamustine Hydrochloride.

4.6 Fertility, pregnancy and lactation

Bendastin Lyophilized Powder for Injection can cause fetal harm when administered to a pregnant woman [see section 4.4 and pregnancy]
Pregnancy Testing
Pregnancy testing is recommended for females of reproductive potential prior to initiation of treatment with Bendastin Lyophilized Powder for Injection.
Contraception
Females
Bendastin Lyophilized Powder for Injection can cause embryo-fetal harm when administered to pregnant women [see pregnancy]. Advise female patients of reproductive potential to use effective contraception during treatment with Bendastin Lyophilized Powder for Injection and for at least 6 months after the final dose.

Males
Based on genotoxicity findings, advise males with female partners of reproductive potential to use effective contraception during treatment with Bendastin Lyophilized Powder for Injection and for at least 3 months after the final dose *[see Nonclinical Toxicology (13.1)]*.
Infertility
Males
Based on findings from clinical studies, Bendastin Lyophilized Powder for Injection may impair male fertility. Impaired spermatogenesis, azoospermia, and total germinal aplasia have been reported in male patients treated with alkylating agents, especially in combination with other drugs. In some instances spermatogenesis may return in patients in remission, but this may occur only several years after intensive chemotherapy has been discontinued. Patients should be warned of the potential risk to their reproductive capacities.
Based on findings from animal studies, Bendastin Lyophilized Powder for Injection may impair male fertility due to an increase in morphologically abnormal spermatozoa. The long-term effects of Bendastin Lyophilized Powder for Injection on male fertility, including the reversibility of adverse effects, have not been studied *[see Nonclinical Toxicology (13.1)]*.

Pregnancy
Risk Summary
In animal reproduction studies, intraperitoneal administration of bendamustine to pregnant mice and rats during organogenesis at doses 0.6 to 1.8 times the maximum recommended human dose (MRHD) resulted in embryo-fetal and/or infant mortality, structural abnormalities, and alterations to growth (*see Animal Data*). There are no available data on bendamustine hydrochloride use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Advise pregnant women of the potential risk to a fetus. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15•20%, respectively.
Animal data
Bendamustine hydrochloride was intraperitoneally administered once to mice from 210 mg/m^2 (approximately 1.8 times the MRHD) during organogenesis and caused an increase in resorptions, skeletal and visceral malformations (exencephaly, cleft palates, accessory rib, and spinal deformities), and decreased fetal body weights. This dose did not appear to be maternally toxic and lower doses were not evaluated. Repeat intraperitoneal administration of bendamustine hydrochloride to mice on gestation days 7-11 resulted in an increase in resorptions from 75 mg/m^2 (approximately 0.6 times the MRHD) and an increase in abnormalities from 112.5 mg/m^2 (approximately 0.9 times the MRHD), similar to those seen after a single intraperitoneal administration.
Bendamustine hydrochloride was intraperitoneally administered once to rats from 120 mg/m^2 (approximately the MRHD) on gestation days 4, 7, 9, 11, or 13 and caused embryo and fetal lethality as indicated by increased resorptions and a decrease in live fetuses. A significant increase in external (effect on tail, head, and herniation of external organs [exomphalos]) and internal (hydronephrosis and hydrocephalus) malformations were seen in dosed rats.

Lactation
There are no data on the presence of bendamustine hydrochloride or its metabolites in either human or animal milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in the breastfed child, advise patients that breastfeeding is not recommended during treatment with Bendastin Lyophilized Powder for Injection, and for at least 1 week after the last dose.

4.7 Effects on ability to drive and use machines

Bendamustine has major influence on the ability to drive and use machines. Ataxia, peripheral neuropathy and somnolence have been reported during treatment with bendamustine hydrochloride (see section 4.8). Patients should be instructed that if they experience these symptoms they should avoid potentially hazardous tasks such as driving and using machines.

4.8 Undesirable effects

- Adverse reactions (frequency >5%) during infusion and within 24 hours post-infusion are nausea and fatigue.
- Most common adverse reactions (≥15%) for CLL are anemia, thrombocytopenia, neutropenia, lymphopenia, leukopenia, pyrexia, nausea, vomiting.

- Most common adverse reactions (≥15%) for NHL are lymphopenia, leukopenia, anemia, neutropenia, thrombocytopenia, nausea, fatigue, vomiting, diarrhea, pyrexia, constipation, anorexia, cough, headache, weight decreased, dyspnea, rash, and stomatitis.

4.9 Overdose

The intravenous LD_{50} of bendamustine HCl is 240 mg/m^2 in the mouse and rat. Toxicities included sedation, tremor, ataxia, convulsions and respiratory distress.

Across all clinical experience, the reported maximum single dose received was 280 mg/m^2. Three of four patients treated at this dose showed ECG changes considered dose-limiting at 7 and 21 days post-dosing. These changes included QT prolongation (one patient), sinus tachycardia (one patient), ST and T wave deviations (two patients) and left anterior fascicular block (one patient). Cardiac enzymes and ejection fractions remained normal in all patients.
No specific antidote for Bendastin Lyophilized Powder for Injection overdose is known. Management of overdosage should include general supportive measures, including monitoring of hematologic parameters and ECGs.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agent, alkylating agent and nitrogen mustard analogues ATC code: L01AA09

Mechanism of action
Bendamustine is a bifunctional mechlorethamine derivative containing a purine-like benzimidazole ring. Mechlorethamine and its derivatives form electrophilic alkyl groups. These groups form covalent bonds with electron-rich nucleophilic moieties, resulting in interstrand DNA crosslinks. The bifunctional covalent linkage can lead to cell death via several pathways. Bendamustine is active against both quiescent and dividing cells. The exact mechanism of action of bendamustine remains unknown.

Pharmacodynamic effects
Based on the pharmacokinetics/pharmacodynamics analyses of data from adult NHL patients, nausea increased with increasing bendamustine C_{max}.

Cardiac Electrophysiology
The effect of bendamustine on the QTc interval was evaluated in 53 patients with indolent NHL and mantle cell lymphoma on Day 1 of Cycle 1 after administration of rituximab at 375 mg/m^2 intravenous infusion followed by a 30-minute intravenous infusion of bendamustine at 90 mg/m^2/day. No mean changes greater than 20 milliseconds were detected up to one hour post-infusion. The potential for delayed effects on the QT interval after one hour was not evaluated.

5.2 Pharmacokinetic properties

Absorption
Following a single IV dose of bendamustine hydrochloride C_{max} typically occurred at the end of infusion. The dose proportionality of bendamustine has not been studied.

Distribution
The protein binding of bendamustine ranged from 94-96% and was concentration independent from 1-50 μg/mL. The blood to plasma concentration ratios in human blood ranged from 0.84 to 0.86 over a concentration range of 10 to 100 μg/mL. The mean steady-state volume of distribution (V_{ss}) of bendamustine was approximately 20-25 L.

Elimination
After a single intravenous dose of 120 mg/m^2 of bendamustine over 1 hour, the intermediate half-life ($t_{1/2}$) of the parent compound is approximately 40 minutes. The mean terminal elimination $t_{1/2}$ of two active metabolites, γ-hydroxybendamustine (M3) and N desmethylbendamustine (M4) are approximately 3 hours and 30 minutes, respectively. Bendamustine clearance in humans is approximately 700 mL/min.

Metabolism

Bendamustine is extensively metabolized via hydrolytic, oxidative, and conjugative pathways. Bendamustine is primarily metabolized via hydrolysis to monohydroxy (HP1) and dihydroxy-bendamustine (HP2) metabolites with low cytotoxic activity in vitro. Two active minor metabolites, M3 and M4, are primarily formed via CYP1A2 in vitro. M3 and M4 concentrations in plasma are $1/10^{th}$ and $1/100^{th}$ that of the parent compound, respectively.

Excretion

Following IV infusion of radiolabeled bendamustine hydrochloride in cancer patients, approximately 76% of the dose was recovered. Approximately 50% of the dose was recovered in the urine (3.3% unchanged) and approximately 25% of the dose was recovered in the feces. Less than 1% of the dose was recovered in the urine as M3 and M4, and less than 5% of the dose was recovered in the urine as HP2.

Specific Populations

No clinically meaningful effects on the pharmacokinetics of bendamustine were observed based on age (31 to 84 years), sex, mild to moderate renal impairment (CLcr ≥ 30 mL/min), or hepatic impairment with total bilirubin 1.5 < ULN and AST or ALT < 2.5 × ULN. The effects of severe renal impairment (CLcr < 30 mL/min), or hepatic impairment with total bilirubin 1.5-3 × ULN and AST or ALT 2.5-10 × ULN or total bilirubin > 3 × ULN on the pharmacokinetics of bendamustine is unknown.

Race/Ethnicity

Exposures in Japanese subjects (n=6) were 40% higher than that in non-Japanese subjects receiving the same dose. The clinical importance of this difference on the safety and efficacy of bendamustine hydrochloride in Japanese subjects has not been established.

Drug Interaction Studies

In Vitro Studies

Effect of Bendamustine on CYP Substrates

Bendamustine did not inhibit CYP1A2, 2C9/10, 2D6, 2E1, or 3A4/5. Bendamustine did not induce metabolism of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2E1, or CYP3A4/5.

Effect of Transporters on Bendamustine Hydrochloride

Bendamustine is a substrate of P-glycoprotein and breast cancer resistance protein (BCRP).

Clinical trials:

Chronic Lymphocytic Leukemia (CLL)

The safety and efficacy of Bendastin Lyophilized Powder for Injection were evaluated in an open-label, randomized, controlled multicenter trial comparing Bendastin Lyophilized Powder for Injection to chlorambucil. The trial was conducted in 301 previously-untreated patients with Binet Stage B or C (Rai Stages I -IV) CLL requiring treatment. Need-to-treat criteria included hematopoietic insufficiency, B-symptoms, rapidly progressive disease or risk of complications from bulky lymphadenopathy. Patients with autoimmune hemolytic anemia or autoimmune thrombocytopenia, Richter's syndrome, or transformation to prolymphocytic leukemia were excluded from the study.

The patient populations in the Bendastin Lyophilized Powder for Injection and chlorambucil treatment groups were balanced with regard to the following baseline characteristics: age (median 63 vs. 66 years), gender (63% vs. 61% male), Binet stage (71% vs. 69% Binet B), lymphadenopathy (79% vs. 82%), enlarged spleen (76% vs. 80%), enlarged liver (48% vs. 46%), hypercellular bone marrow (79% vs. 73%), "B" symptoms (51% vs. 53%), lymphocyte count (mean $65.7x10^9$/L vs. $65.1x10^9$/L), and serum lactate dehydrogenase concentration (mean 370.2 vs. 388.4 U/L). Ninety percent of patients in both treatment groups had immuno-phenotypic confirmation of CLL (CD5, CD23 and either CD19 or CD20 or both).

Patients were randomly assigned to receive either Bendastin Lyophilized Powder for Injection at 100 mg/m^2 , administered intravenously over a period of 30 minutes on Days 1 and 2 or chlorambucil at 0.8 mg/kg (Broca's normal weight) administered orally on Days 1 and 15 of each 28-day cycle. Efficacy endpoints of objective response rate and progression-free survival were calculated using a pre-specified algorithm based on NCI working group criteria for CLL.

The results of this open-label randomized study demonstrated a higher rate of overall response and a longer progression-free survival for Bendastin Lyophilized Powder for Injection compared to chlorambucil (see Table 1). Survival data are not mature.

Table 1: Efficacy Data for CLL

	Bendastin Lyophilized Powder for Injection (N=153)	Chlorambucil (N=148)	p-value
Response Rate n (%)			
Overall response rate	90 (59)	38 (26)	<0.0001
(95% CI)	(51.0, 66.6)	(18.6, 32.7)	
Complete response (CR)*	13 (8)	1 (<1)	
Nodular partial response(nPR)**	4 (3)	0	
Partial response (PR) †	73 (48)	37 (25)	
Progression-Free Survival††			
Median, months (95% CI)	18 (11.7, 23.5)	6 (5.6, 8.6)	
Hazard ratio (95% CI)	0.27 (0.17, 0.43)		<0.0001

CI = confidence interval

* CR was defined as peripheral lymphocyte count ≤ 4.0 x 10^9/L, neutrophils ≥ 1.5 x 10^9/L, platelets >100 x 10^9/L, hemoglobin > 110g/L, without transfusions, absence of palpable hepatosplenomegaly, lymph nodes ≤ 1.5 cm, < 30% lymphocytes without nodularity in at least a normocellular bone marrow and absence of "B" symptoms. The clinical and laboratory criteria were required to be maintained for a period of at least 56 days.

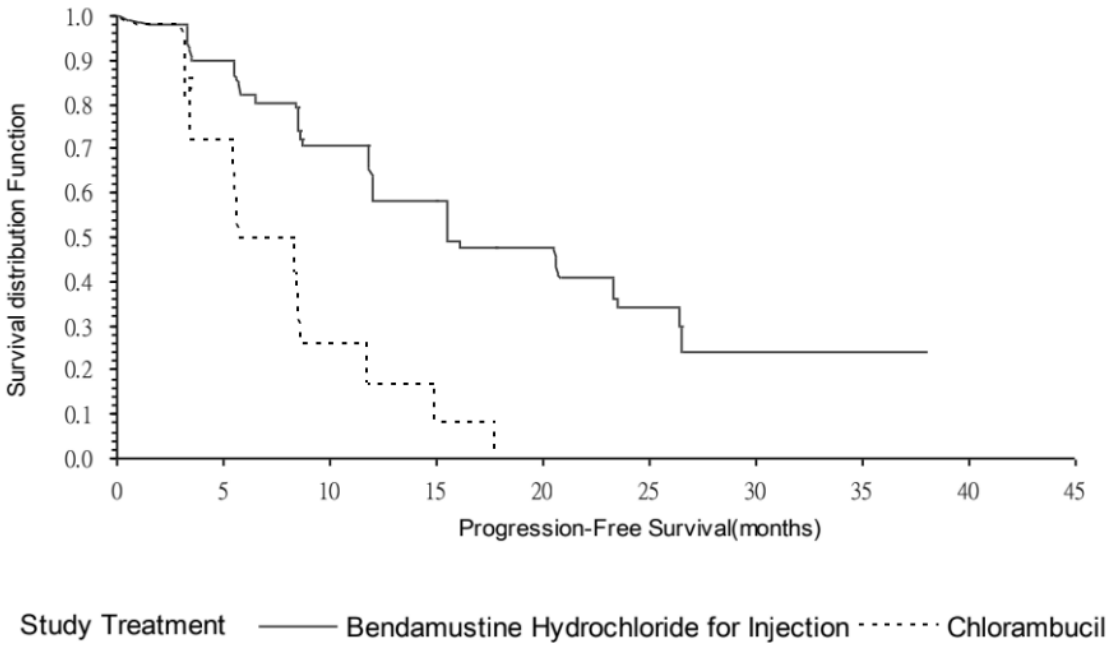
** nPR was defined as described for CR with the exception that the bone marrow biopsy shows persistent nodules.

† PR was defined as ≥ 50% decrease in peripheral lymphocyte count from the pretreatment baseline value, and either ≥50% reduction in lymphadenopathy, or ≥50% reduction in the size of spleen or liver, as well as one of the following hematologic improvements: neutrophils ≥ 1.5 x 10^9/L or 50% improvement over baseline, platelets >100 x 10^9/L or 50% improvement over baseline, hemoglobin >110g/L or 50% improvement over baseline without transfusions, for a period of at least 56 days.

†† PFS was defined as time from randomization to progression or death from any cause.

Kaplan-Meier estimates of progression-free survival comparing Bendastin Lyophilized Powder for Injection with chlorambucil are shown in Figure 1.

Figure 1. Progression-Free Survival



Non-Hodgkin Lymphoma (NHL)

The efficacy of Bendastin Lyophilized Powder for Injection was evaluated in a single arm study of 100 patients with indolent B-cell NHL that had progressed during or within six months of treatment with rituximab or a rituximab-containing regimen. Patients were included if they relapsed within 6 months of either the first dose (monotherapy) or last dose (maintenance regimen or combination therapy) of rituximab. All patients received Bendastin Lyophilized Powder for Injection intravenously at a dose of 120 mg/m^2, on Days 1 and 2 of a 21-day treatment cycle. Patients were treated for up to 8 cycles.

The median age was 60 years, 65% were male, and 95% had a baseline WHO performance status of 0 or 1. Major tumor subtypes were follicular lymphoma (62%), diffuse small lymphocytic lymphoma (21%), and marginal zone lymphoma (16%). Ninety-nine percent of patients had received previous chemotherapy, 91% of patients had received previous alkylator therapy, and 97% of patients had relapsed within 6 months of either the first dose (monotherapy) or last dose (maintenance regimen or combination therapy) of rituximab.
Efficacy was based on the assessments by a blinded independent review committee (IRC) and included overall response rate (complete response + complete response unconfirmed + partial response) and duration of response (DR) as summarized in Table 2.

Table 2: Efficacy Data for NHL*

	Bendastin Lyophilized Powder for Injection (N=100)
Response Rate (%)	
Overall response rate	74
(CR+CRu+PR)	
(95% CI)	(64.3, 82.3)
Complete response (CR)	13
Complete response unconfirmed (CRu)	4
Partial response (PR)	57
Duration of Response (DR)	
Median, months (95% CI)	9.2 months (7.1, 10.8)

CI = confidence interval
*IRC assessment was based on modified International Working Group response criteria (IWG-RC). Modifications to IWG-RC specified that a persistently positive bone marrow in patients who met all other criteria for CR would be scored as PR. Bone marrow sample lengths were not required to be ≥20 mm.

5.3 Preclinical safety data

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6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Each 25-mg vial contains
25 mg of bendamustine hydrochloride
42.5 mg of mannitol, USP

Each 100-mg vial contains
100 mg of bendamustine hydrochloride
170 mg of mannitol, USP

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Storage at below 30°C. Retain in original package until time of use to protect from light.

6.5 Nature and contents of container

No data

6.6 Special precautions for disposal and other handling

Bendastin Lyophilized Powder for Injection is a cytotoxic drug. Follow applicable special handling and disposal procedures. Care should be exercised in the handling and preparation of solutions prepared from Bendastin Lyophilized Powder for Injection. The use of gloves and safety glasses is recommended to avoid exposure in case of breakage of the vial or other accidental spillage. If gloves come in contact with Bendastin Lyophilized Powder for Injection prior to dilution, remove gloves and follow disposal procedures. If a solution of Bendastin Lyophilized Powder for Injection, contacts the skin, wash the skin immediately and thoroughly with soap and water. If Bendastin Lyophilized Powder for Injection, contacts the mucous membranes, flush thoroughly with water.

If a closed system transfer device or adapter that contains polycarbonate or ABS is to be used as supplemental protection during preparation, only use Bendastin Lyophilized Powder for Injection, the lyophilized formulation.

- Each vial of Bendastin Lyophilized Powder for Injection is intended for single-dose only.
- Aseptically reconstitute each Bendastin Lyophilized Powder for Injection vial as follows:
    - 25 mg Bendastin Lyophilized Powder for Injection vial: Add 5 mL of only Sterile Water for Injection, USP.
    - 100 mg Bendastin Lyophilized Powder for Injection vial: Add 20 mL of only Sterile Water for Injection, USP.
- Shake well to yield a clear, colorless to a pale yellow solution with a bendamustine HCl concentration of 5 mg/mL. The lyophilized powder should completely dissolve in 5 minutes. The reconstituted solution must be transferred to the infusion bag within 30 minutes of reconstitution. If particulate matter is observed, the reconstituted product should not be used.
- Aseptically withdraw the volume needed for the required dose (based on 5 mg/mL concentration) and immediately transfer to a 500 mL infusion bag of 0.9% Sodium Chloride Injection, USP (normal saline). As an alternative to 0.9% Sodium Chloride Injection, USP (normal saline), a 500 mL infusion bag of 2.5% Dextrose/0.45% Sodium Chloride Injection, USP, may be considered. The resulting final concentration of bendamustine HCl in the infusion bag should be within 0.2 – 0.6 mg/mL. After transferring, thoroughly mix the contents of the infusion bag.
- Visually inspect the filled syringe and the prepared infusion bag to ensure the lack of visible particulate matter prior to administration. The admixture should be a clear and colorless to slightly yellow solution.

Use Sterile Water for Injection, USP, for reconstitution and then either 0.9% Sodium Chloride Injection, USP, or 2.5% Dextrose/0.45% Sodium Chloride Injection, USP, for dilution, as outlined above. No other diluents have been shown to be compatible.

- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Any unused solution should be discarded according to institutional procedures for antineoplastics.

7. MARKETING AUTHORISATION HOLDER

Importer: Symgens Co.,Ltd.
Bangkok, Thailand

Manufacturer: Nang Kuang Pharmaceutical Co., Ltd.
No. 1001, 1001-1 Zhongshan Rd., Xinhua Dist, Tainan City 71243, Taiwan

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT