Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Bendamustine 25 mg/ml concentrate for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains bendamustine hydrochloride monohydrate equivalent to 25 mg bendamustine hydrochloride.
Each vial of 1 ml contains bendamustine hydrochloride monohydrate equivalent to 25 mg bendamustine hydrochloride.
Each vial of 4 ml contains bendamustine hydrochloride monohydrate equivalent to 100 mg bendamustine hydrochloride.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate)
Clear colourless to yellow solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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.

4.2 Posology and method of administration

Posology

Monotherapy for chronic lymphocytic leukaemia
100 mg/m^2 body surface area bendamustine hydrochloride on days 1 and 2; every 4 weeks up to 6 times.

Monotherapy for indolent non-Hodgkin's lymphomas refractory to rituximab
120 mg/m^2 body surface area bendamustine hydrochloride on days 1 and 2; every 3 weeks for at least 6 times.

Multiple myeloma
120-150 mg/m^2 body surface area bendamustine hydrochloride on days 1 and 2, 60 mg/m^2 body surface area prednisone i.v. or per os on days 1 to 4; every 4 weeks for at least 3 times.

Hepatic impairment
On the basis of pharmacokinetic data, no dose adjustment is necessary in patients with mild hepatic impairment (serum bilirubin < 1.2 mg/dl). A 30% dose reduction is recommended in patients with moderate hepatic impairment (serum bilirubin 1.2 - 3.0 mg/dl).

No data is available in patients with severe hepatic impairment (serum bilirubin values of > 3.0 mg/dl) (see section 4.3).

Renal impairment
On the basis of pharmacokinetic data, no dose adjustment is necessary in patients with a creatinine clearance of > 10 ml/min. Experience in patients with severe renal impairment is limited.

Paediatric population:
The safety and efficacy of bendamustine hydrochloride in children have not yet been established. Current available data is not sufficient to make a recommendation on posology.

Elderly patients
There is no evidence that dose adjustments are necessary in elderly patients (see section 5.2).

Method of administration
For intravenous infusion over 30-60 minutes (see section 6.6).

Infusion must be administered under the supervision of a physician qualified and experienced in the use of chemotherapeutic agents.

Poor bone marrow function is related to increased chemotherapy-induced haematological toxicity. Treatment should not be started if leukocyte and/or platelet values have dropped to < 3,000/µl or < 75,000/µl, respectively (see section 4.3).

Treatment should be terminated or delayed if leukocyte and/or platelet values have dropped to < 3,000/µl or < 75,000/µl, respectively. Treatment can be continued after leukocyte values have increased to > 4,000/µl and platelet values to > 100,000/µl.

The leukocyte and platelet Nadir is reached after 14-20 days with regeneration after 3-5 weeks. During therapy free intervals strict monitoring of the blood count is recommended (see section 4.4).

In case of non-haematological toxicity dose reductions have to be based on the worst CTC grades in the preceding cycle. A 50% dose reduction is recommended in case of CTC grade 3 toxicity. An interruption of treatment is recommended in case of CTC grade 4 toxicity.

If a patient requires a dose modification the individually calculated reduced dose must be given on day 1 and 2 of the respective treatment cycle.

For instructions on dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

- During breast-feeding
- Severe hepatic impairment (serum bilirubin > 3.0 mg/dl)
- Jaundice
- Severe bone marrow suppression and severe blood count alterations (leukocyte and/or platelet values dropped to < 3,000/µl or < 75,000/µl, respectively)
- Major surgery less than 30 days before start of treatment
- Infections, especially involving leukocytopenia
- Yellow fever vaccination

4.4 Special warnings and precautions for use

Myelosuppression
Patients treated with bendamustine hydrochloride may experience myelosuppression. In the event of treatment-related myelosuppression, leukocytes, platelets, haemoglobin, and neutrophils must be monitored at least weekly. Prior to the initiation of the next cycle of therapy, the following parameters are recommended: Leukocyte and/or platelet values > 4,000/µl or > 100,000/µl, respectively.

Infections
Serious and fatal infections have occurred with bendamustine hydrochloride, including bacterial (sepsis, pneumonia) and opportunistic infections such as Pneumocystis jirovecii pneumonia (PJP), varicella zoster virus (VZV) and cytomegalovirus (CMV). Cases of progressive multifocal leukoencephalopathy (PML) including fatal ones have been reported following the use of bendamustine mainly in combination with rituximab or obinutuzumab. Treatment with bendamustine hydrochloride may cause prolonged lymphocytopenia (< 600/µl) and low CD4-positive T-cell (T-helper cell) counts (< 200/µl) for at least 7–9 months

after the completion of treatment. Lymphocytopenia and CD4-positive T-cell depletion are more pronounced when bendamustine is combined with rituximab. Patients with lymphopenia and low CD4-positive T-cell count following treatment with bendamustine hydrochloride are more susceptible to (opportunistic) infections. In case of low CD4-positive T-cell counts (< 200/µl) Pneumocystis jirovecii pneumonia (PJP) prophylaxis should be considered.
All patients should be monitored for respiratory signs and symptoms throughout treatment. Patients should be advised to report new signs of infection, including fever or respiratory symptoms promptly. Discontinuation of bendamustine hydrochloride should be considered if there are signs of (opportunistic) infections.

Consider PML in the differential diagnosis in patients with new or worsening neurological, cognitive or behavioural signs or symptoms. If PML is suspected then appropriate diagnostic evaluations should be undertaken and treatment suspended until PML is excluded.

Hepatitis B reactivation
Reactivation of hepatitis B in patients who are chronic carriers of this virus has occurred after these patients received bendamustine hydrochloride. Some cases resulted in acute hepatic failure or a fatal outcome. Patients should be tested for HBV infection before initiating treatment with bendamustine hydrochloride. Experts in liver disease and in the treatment of hepatitis B should be consulted before treatment is initiated in patients with positive hepatitis B tests (including those with active disease) and for patients who test positive for HBV infection during treatment. Carriers of HBV who require treatment with bendamustine hydrochloride should be closely monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy (see section 4.8).

Skin reactions
A number of skin reactions have been reported. These events have included rash, severe cutaneous reactions and bullous exanthema. Cases of Stevens – Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN), and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), some fatal, have been reported with the use of bendamustine hydrochloride. Patients should be advised of the signs and symptoms of these reactions by their prescribers and should be told to seek medical attention immediately if they develop these symptoms.Some events occurred when bendamustine hydrochloride was given in combination with other anticancer agents, so the precise relationship is uncertain. When skin reactions occur, they may be progressive and increase in severity with further treatment. If skin reactions are progressive, bendamustine should be withheld or discontinued. For severe skin reactions with a suspected relationship to bendamustine hydrochloride, treatment should be discontinued.

Cardiac disorders
During treatment with bendamustine hydrochloride the concentration of potassium in the blood of patients with cardiac disorders must be closely monitored and potassium supplement must be given when K^+ <3.5 mEq/l, and ECG measurement must be performed. Fatal cases of myocardial infarction and cardiac failure have been reported with bendamustine hydrochloride treatment. Patients with concurrent or history of cardiac disease should be observed closely.

Nausea, vomiting
An antiemetic may be given for the symptomatic treatment of nausea and vomiting.

Tumour lysis syndrome
Tumour lysis syndrome (TLS) associated with bendamustine treatment has been reported in patients in clinical trials. The onset tends to be within 48 hours of the first dose of bendamustine and, without intervention, may lead to acute renal failure and death. Preventive measures such as adequate hydration, close monitoring of blood chemistry, particularly potassium and uric acid levels and the use of hypouricemic agents (allopurinol and rasburicase) should be considered prior to therapy. There have been a few cases of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis reported when bendamustine and allopurinol were administered concomitantly.

Anaphylaxis
Infusion reactions to bendamustine hydrochloride have occurred commonly in clinical trials. Symptoms are generally mild and include fever, chills, pruritus and rash. In rare instances severe anaphylactic and anaphylactoid reactions have occurred. Patients must be asked about symptoms suggestive of infusion reactions after their first cycle of therapy. Measures to prevent severe reactions, including antihistamines, antipyretics and corticosteroids must be considered in subsequent cycles in patients who have previously experienced infusion reactions.
Patients who experienced Grade 3 or worse allergic-type reactions were typically not re-challenged.

Contraception
Bendamustine hydrochloride is teratogenic and mutagenic.

Women should not become pregnant during treatment. Male patients should seek advice about sperm conservation prior to treatment with bendamustine hydrochloride because of possible irreversible infertility.

Extravasation
An extravasal injection should be stopped immediately. The needle should be removed after a short aspiration. Thereafter the affected area of tissue should be cooled. The arm should be elevated. Additional treatments like the use of corticosteroids are not of clear benefit.

Non-melanoma skin cancer
In clinical studies, an increased risk for non-melanoma skin cancers (basal cell carcinoma and squamous cell carcinoma) has been observed in patients treated with bendamustine containing therapies. Periodic skin examination is recommended for all patients, particularly those with risk factors for skin cancer.

Dilution
Bendamustine requires appropriate dilution before use. The concentration of bendamustine in Bendamustine 25 mg/ml concentrate for solution for infusion differs from other bendamustine products (see section 6.6 for further instructions on dilution).

4.5 Interaction with other medicinal products and other forms of interaction

No *in-vivo* interaction studies have been performed.

When bendamustine is combined with myelosuppressive agents, the effect of bendamustine and/or the co-administered medicinal products on the bone marrow may be potentiated. Any treatment reducing the patient's performance status or impairing bone marrow function can increase the toxicity of bendamustine.

Combination of bendamustine with cyclosporine or tacrolimus may result in excessive immunosuppression with risk of lymphoproliferation.

Cytostatics can reduce antibody formation following live-virus vaccination and increase the risk of infection which may lead to fatal outcome. This risk is increased in subjects who are already immunosuppressed by their underlying disease.

Bendamustine metabolism involves cytochrome P450 (CYP) 1A2 isoenzyme (see section 5.2). Therefore, potential for interaction with CYP1A2 inhibitors such as fluvoxamine, ciprofloxacin, acyclovir or cimetidine exists.

Paediatric population
Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are insufficient data from the use of bendamustine in pregnant women. In nonclinical studies bendamustine hydrochloride was embryo-/fetolethal, teratogenic and genotoxic (see section 5.3). During pregnancy bendamustine should not be used unless clearly necessary. The mother should be informed about the risk to the foetus. If treatment with bendamustine is absolutely necessary during pregnancy or if pregnancy occurs during treatment, the patient should be informed about the risks for the unborn child and be monitored carefully. The possibility of genetic counselling should be considered.

Contraception in males and females
Women of childbearing potential should be advised to avoid becoming pregnant during treatment and for at least 6 months after last dose. Men with female partners of childbearing potential should be advised to use effective contraception during treatment with bendamustine and for at least 3 months after last dose.

Fertility
Women of childbearing potential must use effective methods of contraception both before and during bendamustine therapy.

Men being treated with bendamustine are advised on conservation of sperm prior to treatment because of the possibility of irreversible infertility due to therapy with bendamustine (see section 4.4).

Breast-feeding
It is not known whether bendamustine passes into the breast milk, therefore, bendamustine is contraindicated during breast-feeding (see section 4.3). Breast-feeding must be discontinued during treatment with bendamustine.

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 (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

The most common adverse reactions with bendamustine hydrochloride are hematological adverse reactions (leukopenia, thrombopenia), dermatologic toxicities (allergic reactions), constitutional symptoms (fever), gastrointestinal symptoms (nausea, vomiting).

The table below reflects the data obtained with bendamustine hydrochloride.

MedDRA system organ class	**Very common ≥1/10**	**Common ≥1/100 to <1/10**	**Uncommon ≥1/1,000 to <1/100**	**Rare ≥1/10,000 to <1/1, 000**	**Very rare <1/10, 000**	**Not known (cannot be estimated from the available data)**
Infections and infestations	Infection NOS* Including Opportunistic infection (e.g. Herpes zoster, cytomegalovirus, hepatitis B)		Pneumocystis jirovecii pneumonia	Sepsis	Pneumonia primary atypical	
Neoplasma benign, malignant and unspecified (including cyst and polyp)		Tumour lysis syndrome	Myelodysplastic syndrome, acute myeloid leukaemia			
Blood and lymphatic system disorders	Leukopenia NOS*, Thrombocytopenia, Lymphopenia	Haemorrhage, Anaemia, Neutropenia	Pancytopenia	Bone marrow failure	Haemolysis	
Immune system disorders		Hypersensitivity NOS*		Anaphylactic reaction, Anaphylactoid reaction	Anaphylactic shock	
Nervous system disorders	Headache	Insomnia, Dizziness		Somnolence, Aphonia	Dysgeusia, Paraesthesia, Peripheral sensory neuropathy, Anticholinergic syndrome, Neurological disorders,	

					Ataxia, Encephalitis	
Cardiac disorders		Cardiac dysfunction, such as palpitations, angina pectoris, Arrhythmia	Pericardial effusion, Myocardial infarction, Cardiac failure		Tachycardia,	Atrial fibrillation
Vascular disorders		Hypotension, Hypertension		Acute circulatory failure	Phlebitis	
Respiratory, thoracic and mediastinal disorders		Pulmonary dysfunction			Pulmonary fibrosis	Pneumonitis, pulmonary alveolar haemorrhage
Gastrointestinal disorders	Nausea, Vomiting	Diarrhoea, Constipation, Stomatitis			haemorrhagic oesophagitis, Gastrointestinal haemorrhage	
Skin and subcutaneous tissue disorders		Alopecia, Skin disorders NOS*, Urticaria		Erythema, Dermatitis, Pruritus, Maculopapular rash, Hyperhidrosis		Stevens – Johnson syndrome, Toxic Epidermal Necrolysis (TEN), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)*
Reproductive system and breast disorders		Amenorrhea			Infertility	
Renal and urinary disorders						Renal failure Nephrogenic diabetes insipidus
Hepatobiliary disorders						Hepatic failure
General disorders and administration site conditions	Mucosal inflammation, Fatigue, Pyrexia	Pain, Chills, Dehydration, Anorexia			Multi organ failure	
Investigations	Haemoglobin decrease, Creatinine increase, Urea increase	AST increase, ALT increase, Alkaline phosphatase increase, Bilirubin increase, Hypokalemia				

NOS = Not otherwise specified
(*=combination therapy with rituximab)

Description of selected adverse reactions
There have been isolated reports of necrosis after accidental extra-vascular administration and tumour lysis syndrome, and anaphylaxis.

The risk of myelodysplastic syndrome and acute myeloid leukaemias is increased in patients treated with alkylating agents (including bendamustine). The secondary malignancy may develop several years after chemotherapy has been discontinued.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA pharmacovigilance, website www.hpra.ie.

4.9 Overdose

After application of a 30 min infusion of bendamustine once every 3 weeks the maximum tolerated dose (MTD) was 280 mg/m^2. Cardiac events of CTC grade 2 which were compatible with ischaemic ECG changes occurred which were regarded as dose limiting.

In a subsequent study with a 30 min infusion of bendamustine at day 1 and 2 every 3 weeks the MTD was found to be 180 mg/m^2. The dose limiting toxicity was grade 4 thrombocytopenia. Cardiac toxicity was not dose limiting with this schedule.

Counter measures
There is no specific antidote. Bone marrow transplantation and transfusions (platelets, concentrated erythrocytes) may be made or haematological growth factors may be given as effective countermeasures to control haematological side effects.

Bendamustine hydrochloride and its metabolites are dialyzable to a small extent.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, alkylating agents
ATC code: L01AA09

Bendamustine hydrochloride is an alkylating antitumour agent with unique activity. The antineoplastic and cytocidal effect of bendamustine hydrochloride is based essentially on a cross-linking of DNA single and double strands by alkylation. As a result, DNA matrix functions and DNA synthesis and repair are impaired. The antitumour effect of bendamustine hydrochloride has been demonstrated by several *in vitro* studies in different human tumour cell lines (breast cancer, non-small cell and small cell lung cancer, ovary carcinoma and different leukaemia) and *in vivo* in different experimental tumour models with tumours of mouse, rat and human origin (melanoma, breast cancer, sarcoma, lymphoma, leukaemia and small cell lung cancer).

Bendamustine hydrochloride showed an activity profile in human tumour cell lines different to that of other alkylating agents. The active substance revealed no or very low cross-resistance in human tumour cell lines with different resistance mechanisms at least in part due to a comparatively persistent DNA interaction. Additionally, it was shown in clinical studies that there is no complete cross-resistance of bendamustine with anthracyclines, alkylating agents or rituximab. However, the number of assessed patients is small.

Chronic lymphocytic leukaemia
The indication for use in chronic lymphocytic leukaemia is supported by a single open label study comparing bendamustine with chlorambucil. In the prospective, multi-centre, randomised, study, 319 previously untreated patients with chronic lymphocytic leukaemia stage Binet B or C requiring therapy were included. The first line therapy with bendamustine hydrochloride 100 mg/m^2 i.v. on days 1 and 2 (BEN) was compared to treatment with chlorambucil 0.8 mg/kg days 1 and 15 (CLB) for 6 cycles in both arms. Patients received allopurinol in order to prevent tumour lysis syndrome.
Patients with BEN have a significantly longer median progression free survival than patients with CLB treatment (21.5 versus 8.3 months, $p < 0.0001$ in the latest follow-up). Overall survival was not statistically significantly different (median not reached). The median duration of remission is 19 months with BEN and 6 months with CLB treatment ($p < 0.0001$). The safety evaluation in both treatment arms did not reveal any unexpected undesirable effects in nature and frequency. The dose of BEN was reduced in 34% of the patients. Treatment with BEN was discontinued in 3.9% of patients due to allergic reactions.

Indolent non-Hodgkin's lymphomas

The indication for indolent non-Hodgkin's lymphomas relied on two uncontrolled phase II trials.
In the pivotal prospective, multi-centre, open study 100 patients with indolent B-cell non-Hodgkin´s lymphomas refractory to rituximab mono- or combination therapy were treated with BEN single agent. Patients received a median of 3 previous chemotherapy or biologic therapy courses. The median number of previous rituximab-containing courses was 2. The patients had no response or progress within 6 months after rituximab treatment. The dose of BEN was 120 mg/m^2 i.v. on days 1 and 2 planned for at least 6 cycles. Duration of treatment depended on response (6 cycles planned). The overall response rate was 75% including 17% complete (CR and CRu) and 58% partial response as assessed by independent review committee. The median duration of remission was 40 weeks. BEN was generally well tolerated when given in this dose and schedule.

The indication is further supported by another prospective, multi-centre, open study including 77 patients. The patient population was more heterogeneous including: indolent or transformed B-cell non-Hodgkin's lymphomas refractory to rituximab mono- or combination therapy. The patients had no response or progress within 6 months or had an untoward reaction to prior rituximab treatment. Patients received a median of 3 previous chemotherapy or biological therapy courses. The median number of previous rituximab-containing courses was 2. The overall response rate was 76% with a median duration of response of 5 months (29 [95% CI 22.1, 43.1] weeks).

Multiple myeloma

In a prospective, multi-centre, randomised, open study 131 patients with advanced multiple myeloma (Durie-Salmon stage II with progress or stage III) were included. The first line therapy with bendamustine hydrochloride in combination with prednisone (BP) was compared to treatment with melphalan and prednisone (MP). Tolerability in both treatment arms was in line with the known safety profile of the respective medicinal products with significantly more dose reductions in the BP arm.The dose was bendamustine hydrochloride 150 mg/m^2 i.v. on days 1 and 2 or melphalan 15 mg/m^2 i.v. on day 1 each in combination with prednisone. Duration of treatment depended on response and averaged 6.8 in the BP and 8.7 cycles in the MP group.
Patients with BP treatment have a longer median progression free survival than patients with MP (15 [95% CI 12-21] versus 12 [95% CI 10-14] months) (p=0.0566). The median time to treatment failure is 14 months with BP and 9 months with MP treatment. The duration of remission is 18 months with BP and 12 months with MP treatment. The difference in overall survival is not significantly different (35 months BP versus 33 months MP). Tolerability in both treatment arms was in line with the known safety profile of the respective medicinal products with significantly more dose reductions in the BP arm.

5.2 Pharmacokinetic properties

Distribution

The elimination half-life $t_{1/2ß}$ after 30 min i.v. infusion of 120 mg/m^2 area to 12 subjects was 28.2 minutes.
Following 30 min i.v. infusion the central volume of distribution was 19.3 l. Under steady-state conditions following i.v. bolus injection the volume of distribution was 15.8-20.5 l.
More than 95% of the substance is bound to plasma proteins (primarily albumin).

Biotransformation

A major route of clearance of bendamustine is the hydrolysis to monohydroxy- and dihydroxy-bendamustine. Formation of N-desmethyl-bendamustine and gamma-hydroxy-bendamustine by hepatic metabolism involves cytochrome P450 (CYP) 1A2 isoenzyme. Another major route of bendamustine metabolism involves conjugation with glutathione.
In-vitro bendamustine does not inhibit CYP 1A4, CYP 2C9/10, CYP 2D6, CYP 2E1 and CYP 3A4.

Elimination

The mean total clearance after 30 min i.v. infusion of 120 mg/m^2 body surface area to 12 subjects was 639.4 ml/minute. About 20% of the administered dose was recovered in urine within 24 hours. Amounts excreted in urine were in the order monohydroxy-bendamustine > bendamustine > dihydroxy-bendamustine > oxidised metabolite > N-desmethyl bendamustine. In the bile, primarily polar metabolites are eliminated.

Hepatic impairment

In patients with 30 - 70% tumour infestation of the liver and mild hepatic impairment (serum bilirubin < 1.2 mg/dl) the pharmacokinetic behaviour was not changed. There was no significant difference to patients with normal liver and kidney function with respect to C_{max}, t_{max}, AUC, $t_{1/2ß}$, volume of distribution and clearance. AUC and total body clearance of bendamustine correlate inversely with serum bilirubin.

Renal impairment

In patients with creatinine clearance >10 ml/min including dialysis dependent patients, no significant difference to patients with normal liver and kidney function was observed with respect to C_{max}, t_{max}, AUC, $t_{1/2ß}$, volume of distribution and clearance.

Elderly subjects
Subjects up to 84 years of age were included in pharmacokinetic studies. Higher age does not influence the pharmacokinetics of bendamustine.

5.3 Preclinical safety data

Adverse reactions not observed in clinical studies, but seen in animals at exposure levels similar to clinical exposure levels and with possible relevance to clinical use were as follows:

Histological investigations in dogs showed macroscopic visible hyperaemia of the mucosa and haemorrhagia in the gastrointestinal tract. Microscopic investigations showed extensive changes of the lymphatic tissue indicating an immunosuppression and tubular changes of kidneys and testis, as well as atrophic, necrotic changes of the prostate epithelium. Animal studies showed that bendamustine is embryotoxic and teratogenic.
Bendamustine induces aberrations of the chromosomes and is mutagenic *in vivo* as well as *in vitro*. In long-term studies in female mice bendamustine is carcinogenic.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Butylhydroxytoluene (E 321)
Macrogol

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.

After opening of the vial
Chemical, physical and microbiological in use stability has been demonstrated for 28 days at 2-8°C. Once opened, the product may be stored for a maximum of 28 days at 2-8 °C.

Solution for infusion
After dilution, chemical and physical stability has been demonstrated for 3.5 hours at 25 ºC and 2 days at 2-8ºC in polyethylene bags.

From a microbiological point of view, the solution should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

Minimisation of the risk of contamination of the multidose vial during withdrawal of each dose is the responsibility of the user. Record date and time of the first dose withdrawal on the vial label. Between uses do not balance product solution with water for injection or any diluent and return the multidose vial to the recommended storage condition of 2 - 8°C.

6.4 Special precautions for storage

Store and transport refrigerated (2-8°C). Do not freeze.

For storage conditions of the diluted medicinal product, see section 6.3.

6.5 Nature and contents of container

Amber glass vials (vial volume 6 ml) with chlorobutyl rubber stopper and aluminium seal with plastic flip off cap. Vials are sheathed in a protective sleeve.

Each vial contains 4 ml concentrate for solution for infusion.

Each pack contains 1 or 5 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

When handling Bendamustine, inhalation, skin contact or contact with mucous membranes should be avoided (wear gloves and protective clothes!). Contaminated body parts should be carefully rinsed with water and soap, the eye should be rinsed with physiological saline solution. If possible, it is recommended to work on special safety workbenches (laminar flow) with liquid impermeable, absorbent disposable foil. Pregnant personnel should be excluded from handling cytotoxics.

The concentrate for solution for infusion has to be diluted with sodium chloride 9 mg/ml (0.9%) solution for injection and then administered by intravenous infusion. Aseptic technique is to be used.

1. Dilution
Aseptically withdraw the volume needed for the required dose from the Bendamustine 25 mg/ml vial. Dilute the total recommended dose of Bendamustine 25 mg/ml with sodium chloride 9 mg/ml (0.9%) solution for injection to produce a final volume of about 500 ml.

While diluting the product, it should be noted that the concentration (25 mg/ml) of bendamustine in Bendamustine 25 mg/ml concentrate for solution for infusion is higher than in usual bendamustine concentrates resulting from reconstitution of bendamustine powder containing medicinal products.

Bendamustine 25 mg/ml must be diluted with 0.9% NaCl solution and not with any other injectable solutions.

Dilution, as recommended, results in a clear colourless to yellowish solution, practically free from visible particles.

Product should be inspected before use. When inspected, visible particles in the solution or discolouration of solution is a sign of deterioration. Deteriorated medicinal product must not be used.

2. Administration
The solution is administered by intravenous infusion over 30-60 min.

The vials are for multiple dose use.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Accord Healthcare Ireland Ltd.
Euro House
Euro Business Park
Little Island
Cork T45 K857
Ireland

8 MARKETING AUTHORISATION NUMBER

PA2315/077/003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26th August 2022

10 DATE OF REVISION OF THE TEXT