

יוני 2019

רופא/ה, רוקח/ת נכבד/ה,

Demustin 25 mg, Demustin 100 mg,
Powder for concentrate for solution for infusion

מעבדות רפא מבקשת להביא לידיעתכם כי עודכן העלון לרופא של התכשיר.

המרכיב הפעיל

Demustin 25 mg contains 25 mg bendamustine hydrochloride/vial.
Demustin 100 mg contains 100 mg bendamustine hydrochloride/vial.

התוויה:

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.
Follicular non-Hodgkin's lymphoma as first line treatment in combination with rituximab.

השינויים המשמעותיים בעלון:

• **בסעיף Posology נעשה שינוי קל (מסומן בצהוב עם קו תחתון)**

Monotherapy for chronic lymphocytic leukaemia

100 mg/m² 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/m² body surface area bendamustine hydrochloride on days 1 and 2; every 3 weeks **for at least 6 times**.

• **באזהרות הנוגעות לזיהומים צויין כי:**

In case of low CD4-positive T-cell counts (< 200/μl) Pneumocystis jirovecii pneumonia (PJP) prophylaxis should be considered.

• **באזהרות לגבי תגובות עוריות:**

הוסף DRESS (Drug reaction with eosinophilia and systemic symptoms) וכן:

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.

• **תופעות לוואי: הוספו:**

Pneumonitis, Pulmonary alveolar haemorrhage, Urticaria, DRESS.

מצ"ב קישור לעלון המעודכן בו מסומנים השינויים המשמעותיים. יש לציין שהיו בעלון שינויים נוספים שאינם מהווים החמרה. למידע המלא יש לעיין בעלון בשלמותו.

העלון לרופא נשלח לפרסום במאגר התרופות שבאתר משרד הבריאות (www.health.gov.il), וניתן גם לקבלו מודפס ע"י פניה לחברת מעבדות רפא בע"מ בטל': 02-5893939 או בכתובת דוא"ל RA@rafa.co.il.

בכבוד רב,
מגר' חנה הירש,
רוקחת ממונה.

Summary of Product Characteristics

1. Name of the medicinal product

Demustin 25 mg

Demustin 100 mg

2. Qualitative and quantitative composition

One vial of Demustin 25 mg contains 25 mg bendamustine hydrochloride.

One vial of Demustin 100 mg contains 100 mg bendamustine hydrochloride.

1 ml of the concentrate contains 2.5 mg bendamustine hydrochloride when reconstituted according to section 6.6.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Powder for concentrate for solution for infusion

White, microcrystalline powder

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.

Follicular non-Hodgkin's lymphoma as first line treatment in combination with rituximab.

4.2 Posology and method of administration

Posology

Monotherapy for chronic lymphocytic leukaemia

100 mg/m² 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/m² body surface area bendamustine hydrochloride on days 1 and 2; every 3 weeks **for at least 6 times**.

Follicular non-Hodgkin's lymphoma: Combination with rituximab:

The dose is 90 mg/m² body surface area Demustin I.V. on days 1 and 2 plus 375 mg/m² rituximab on day 1; repetition every 4 weeks.

Hepatic impairment

On the basis of pharmacokinetic data, no dose adjustment is necessary in patients with mild hepatic impairment (serum bilirubin < 1.2mg/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 also 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 dropped to $< 3,000/\mu\text{l}$ or $< 75,000/\mu\text{l}$, respectively (see section 4.3).

Treatment should be terminated or delayed if leukocyte and/or platelet values dropped to $< 3,000/\mu\text{l}$ or $< 75,000/\mu\text{l}$, respectively. Treatment can be continued after leukocyte values have increased to $> 4,000/\mu\text{l}$ and platelet values to $> 100,000/\mu\text{l}$.

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 reconstitution 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 breastfeeding

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 $< 3,000/\mu\text{l}$ or $< 75,000/\mu\text{l}$, 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 $> 4,000/\mu\text{l}$ or $> 100,000/\mu\text{l}$, 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). Treatment with bendamustine hydrochloride may cause prolonged lymphocytopenia ($< 600/\mu\text{l}$) and low CD4-positive T-cell (T-helper cell) counts ($< 200/\mu\text{l}$) 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 ($< 200/\mu\text{l}$) *Pneumocystis jirovecii* pneumonia (PJP) prophylaxis should be considered. All Therefore** 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.

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, **toxic skin** **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, Demustin should be withheld or discontinued. For severe skin reactions with 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 not father a child during and up to 6 months after treatment. They 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.

4.5 Interaction with other medicinal products and other forms of interaction

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

When Demustin is combined with myelosuppressive agents, the effect of Demustin 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 Demustin.

Combination of Demustin 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, the potential for interaction with CYP1A2 inhibitors such as fluvoxamine, ciprofloxacin, acyclovir and 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 Demustin in pregnant women. In nonclinical studies bendamustine hydrochloride was embryo-/feto-lethal, teratogenic and genotoxic (see section 5.3). During pregnancy Demustin should not be used unless clearly necessary. The mother should be informed about the risk to the foetus. If treatment with Demustin 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.

Fertility

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

Men being treated with Demustin are advised not to father a child during and for up to 6 months following cessation of treatment. Advice on conservation of sperm should be sought prior to treatment because of the possibility of irreversible infertility due to therapy with Demustin.

Breast feeding

It is not known whether bendamustine passes into the breast milk, therefore, Demustin is contraindicated during

breast feeding (see section 4.3). Breast feeding must be discontinued during treatment with Demustin.

4.7 Effects on ability to drive and use machines

Demustin 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.

Table 1: Adverse reactions in patients treated with bendamustine hydrochloride.

MedDRA system organ class	Very common $\geq 1/10$	Common $\geq 1/100$ to $< 1/10$	Uncommon $\geq 1/1,000$ to $< 1/100$	Rare $\geq 1/10,000$ 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 leukemia			
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		Amenorrhoea			Infertility	
Hepatobiliary disorder						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				
Renal and urinary disorders						Renal failure

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.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form

<http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il>

4.9 Overdose

After application of a 30 min infusion of bendamustine once every 3 weeks the maximum tolerated dose (MTD) was 280 mg/m². 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/m². 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 cytotoxic 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, ovarian 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/m² 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 had 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 was 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 had received a median of 3 previous chemotherapy or biological therapy courses. The median number of previous rituximab-containing courses was 2. The patients had had no response or there had been progression within 6 months after rituximab treatment. The dose of BEN was 120 mg/m² 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 there had been progression within 6 months or had had an untoward reaction to prior rituximab treatment. Patients had received a median of 3 previous chemotherapy or biological therapy courses. The median number of previous rituximab-containing courses had been 2. The overall response rate was 76% with a median duration of response of 5 months (29 [95% CI 22.1, 43.1] weeks).

Clinical studies in patients with non-Hodgkin's lymphoma in combination with rituximab:

The pivotal randomized phase III study compared the first-line treatment of 4-week cycles of bendamustine 90 mg/m² I.V. on days 1 and 2 in combination with 375 mg/m² rituximab I.V. on day 1 (BR therapy) with 3-week cycles of rituximab 375 mg/m² I.V. on day 1 and standard-CHOP (750 mg/m² cyclophosphamide, 50 mg/m² doxorubicin, 1.4 mg/m² vincristine and 100 mg prednisone) in 549 patients with advanced indolent non-Hodgkin's lymphoma (NHL) and mantle cell lymphoma. In 82% of BR patients and 86% of R-CHOP patients the maximal of 6 cycles were administered. A statistically significant and clinically relevant improvement of progression free survival according to investigator assessment was observed for BR patients as compared to R-CHOP patients (median 61.4 months vs. 31.3 months, HR=0.607, p<0.0001). With the exception of the comparable results of marginal-zone lymphoma this significant difference of the progression free survival between the two treatments remained also in the histological sub-entities and age groups (<65 years and ≥65 years). The BR treatment also resulted in significantly higher complete response rates (43% vs. 29%, p<0.0009). After assessment by the independent review committee the progression free survival according to WHO criteria was 23.3 vs 30.6 months, HR=0.735 (0.5, 1.08), p=0.0420 and according to IWG criteria 33.1 vs. 28.2 months, HR=0.687 (0.45, 1.05), p=0.03.

The interim analysis of the independent review committee of a further randomized, open parallel group study with bendamustine hydrochloride and rituximab (BR) compared to rituximab, cyclophosphamide, vincristine and prednisone (R-CVP) or rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) in the first line treatment of 336 patients with advanced indolent NHL or mantle- cell lymphoma showed a better response in favour of BR (complete remissions 31% vs. 25%; overall response 96% vs. 91%), too. The response in the indolent NHL population was of equal dimension.

Myelosuppression (72% vs. 43%), alopecia (35% vs. 3%) as well as neuropathia (25% vs. 3%) were more common during R-CHOP/R-CVP treatment, whereas in the BR treatment arm more skin and hypersensitivity reactions were observed (16% vs. 8% and 10% vs. 4%).

5.2 Pharmacokinetic properties

Distribution

The elimination half-life $t_{1/2\beta}$ after 30 min I.V. infusion of 120 mg/m² 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 or CYP 3A4.

Elimination

The mean total clearance after 30 min I.V. infusion of 120 mg/m² 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, $t_{1/2\beta}$, 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, $t_{1/2\beta}$, 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

Mannitol

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

The expiry date of the product is indicated on the packaging materials.

The powder should be reconstituted immediately after opening of the vial.

The reconstituted concentrate should be diluted immediately with 0.9% sodium chloride solution.

Solution for infusion

After reconstitution and dilution, chemical and physical stability has been demonstrated for 3.5 hours at 25 °C and 2 days at 2 °C to 8 °C 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.

6.4 Special precautions for storage

Store below 25 °C

Keep the vial in the outer carton in order to protect from light.

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

6.5 Nature and contents of container

Dark amber tubular flat bottom vial type I glass with gray rubber stopper and an aluminium flip-off seal.

10 ml-vials contain 25 mg bendamustine hydrochloride and are supplied in packs of 5, 10 and 20 vials.

50 ml-vials contain 100 mg bendamustine hydrochloride and are supplied in packs of 1 and 5 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

When handling Demustin, 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 eyes 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 cytostatics.

The powder for concentrate for solution for infusion has to be reconstituted with water for injection, 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. Reconstitution

The powder should be reconstituted immediately after opening of the vial.

Reconstitute each vial of Demustin containing 25 mg bendamustine hydrochloride in 10 ml water for injection by shaking;

Reconstitute each vial of Demustin containing 100 mg bendamustine hydrochloride in 40 ml water for injection by shaking.

The reconstituted concentrate contains 2.5 mg bendamustine hydrochloride per ml and appears as a clear colourless solution.

2. Dilution

As soon as a clear solution is obtained (usually after 5-10 minutes) dilute the total recommended dose of Demustin immediately with 0.9% NaCl solution to produce a final volume of about 500 ml.

Demustin must be diluted with 0.9% NaCl solution and not with any other injectable solution.

3. Administration

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

The vials are for single use only.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MANUFACTURER

Intas Pharmaceuticals Ltd, India

8. REGISTRATION HOLDER

Rafa Laboratories Ltd., P.O.Box 405, Jerusalem 9100301.

Registration number:

Demustin 25 mg: 159-64-34704

Demustin 100 mg: 159-65-34706

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