For the use of a Registered Medical Practitioner or Hospital or a Laboratory only

LYMPHTOR 100

1. Generic Name

Bendamustine Injection I.P. 100 mg

2. Qualitative and quantitative Composition:

Each Vial Contains:

Bendamustine Hydrochloride I.P…… 100 mg

Excipients …… qs

The excipients are Mannitol, Tertiary Butanol and Water

3. Dosage form and strength

Dosage form:

Injection

White to off-white lyophilized powder

Strength: 100 mg/vial

4. Clinical particulars

4.1 Therapeutic indication

Lymphtor is indicated For the treatment of patients with chronic lymphocytic leukemia and For the use in Indolent B-cell Non Hodgkin's 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

- *Monotherapy for chronic lymphocytic leukaemia*
  100 mg/m^2 body surface area bendamustine hydrochloride on days 1 and 2; every 4 weeks.
- *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.
- *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.
  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/ μ l or < 75,000/ μ l, respectively.
  Treatment should be terminated or delayed if leukocyte and/or platelet values have dropped to < 3,000/ μ l or < 75,000/ μ l, respectively. Treatment can be continued after leukocyte values have increased to > 4,000/ μ l and platelet values to > 100,000/ μ 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.
  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.

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).

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.

Method of administration

For intravenous infusion over 30 - 60 minutes..

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

Precautions to be taken before handling or administering the medicinal product recommended.

4.3 Contraindications

Bendamustine hydrochloride is contraindicated in patients with a known hypersensitivity (e.g.,anaphylactic and anaphylactoid reactions) to bendamustine or mannitol.

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/ μ l or < 75,000/ μ 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

Warning: Cytotoxic Drug: To be supplied against demand from Cancer Hospitals, Institutions and against prescription of cancer specialist only.

Myelosuppression

Patients treated with Bendamustine hydrochloride are likely to experience myelosuppression. In the reported two NHL studies, 98% of patients had Grade 3-4 myelosuppresion. Three patients (2%) died from myelosuppression-related adverse reactions; one each from neutropenic sepsis, diffuse

alveolar hemorrhage with Grade3 thrombocytopenia and pneumonia from an opportunistic Infection (CMV).

In the event of treatment-related myelosuppression, monitor leukocytes, platelets, hemoglobin (Hgb), and neutrophils closely. In the reported clinical trials, blood counts were monitored every week initially. Hematologic nadirs were observed predominantly in the third week of therapy. Hematologic nadirs may require dose delays if recovery to the recommended values have 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 ≥ 1 x 109/Land the platelet count should be ≥ 75 x 109/L.

Infections

Infection, including pneumonia and sepsis, has been reported in patients in clinical trials and in post marketing reports. Infection has been associated with hospitalization, septic shock and death. Patients with myelosuppression following treatment with Bendamustine hydrochloride are more susceptible to infections. Patients with myelosuppression following Bendamustine hydrochloride treatment should be advised to contact a physician if they have symptoms or signs of infection.

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.

Tumor Lysis Syndrome

Tumor lysis syndrome associated with Bendamustine hydrochloride treatment has been reported in patients in clinical trials and in post-marketing reports. The onset tends to be within the first treatment cycle of Bendamustine hydrochloride and, without intervention, may lead to acute renal failure and death. Preventive measures include maintaining adequate volume status, close monitoring of blood chemistry, particularly potassium and uric acid levels. Allopurinol has also been used during the beginning of Bendamustine therapy. However, there may be an increased risk of severe skin toxicity when Bendamustine and allopurinol are administered concomitantly.

Skin Reactions

A number of skin reactions have been reported in clinical trials and post-marketing safety reports. These events have included rash, toxic skin reactions and bullous exanthema. Some events occurred when Bendamustine hydrochloride was given in combination with other anticancer agents, so the precise relationship to Bendamustine hydrochloride is uncertain. In a reported study of Bendamustine hydrochloride (90 mg/m^2) in combination with rituximab, one case of toxic epidermal necrolysis (TEN) occurred. TEN has been reported for rituximab. The relationship to Bendamustlne hydrochloride cannot be determined. Cases of Stevens-Johnson syndrome (SJS) and TEN, some fatal, have been reported when Bendamustine was administered concomitantly with allopurinol and other medications known to cause these syndromes. The relationship to Bendamustine cannot be determined. Where skin reactions occur, they may be progressive and increase in severity with further treatment. If skin reactions are severe or progressive, Bendamustine hydrochloride should be withheld or 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.

Anaphylaxis

Infusion reactions to bendamustine hydrochloride have occurred commonly in reported 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 Drugs interactions

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. 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 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Pregnancy

There are insufficient data from the use of bendamustine in pregnant women. In nonclinical studies bendamustine hydrochloride was embryo-/fetolethal, teratogenic and genotoxic.

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.

Fertility

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

Men being treated with bendamustine 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 bendamustine.

Breastfeeding

It is not known whether bendamustine passes into the breast milk, therefore, bendamustine is contraindicated during breastfeeding. Breastfeeding 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 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

Summary of the safety profile

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).

Tabulated list of adverse reactions

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	
Neoplasms benign, malignant		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	
Hepatobiliary disorder						Hepatic failure
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)
Renal and urinary disorders						Renal failure
Reproductive system and breast disorders		Amenorrhea			Infertility	
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

Description of 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

Torrent Pharma available at: http://www.torrentpharma.com/index.php/site/info/adverse_event_reporting.

By reporting side effects, you can help provide more information on the safety of this medicine.

4.9 Overdose

After application of a 30 min infusion of bendamustine hydrochloride 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 reported study with a 30 min infusion of bendamustine hydrochloride 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 Mechanism of Action

Bendamustine hydrochloride 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 cross links. The bifunctional covalent linkage can lead to cell death via several pathways. Bendamustine hydrochloride is active against both quiescent and dividing cells. The exact mechanism of action of Bendamustine hydrochloride remains unknown.

5.2 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 reported 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, reported 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 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 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 reported 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 was 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.

5.3 Pharmacokinetic properties

Distribution

- The elimination half-life t1/2ß 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).
- 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 Cmax, tmax, AUC, t1/2ß, 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 Cmax, tmax, AUC, t1/2ß, 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.

6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology

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

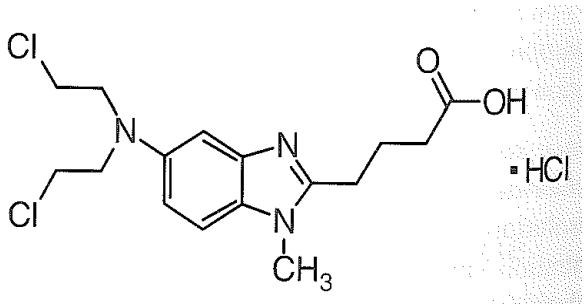
Reported histological investigations in dogs showed macroscopic visible hyperaemia of the mucosa and haemorrhagia in the gastrointestinal tract. Microscopic investigations showed extensive changes of the lymphatic tissue indicating an immunosuppression and tubular changes of kidneys and testis, as well as atrophic, necrotic changes of the prostate epithelium.

In reported 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**.**

7 Description

Bendamustine Hydrochloride is 4-[5-[bis(2-chloroethyl)amino]-1-methylbenzimidazol-2-yl] butanoic acid hydrochloride. Its empirical formula is $C_{16}H_{21}Cl_2N_3O_2$,HCl and its structural formula is:



Bendamustine Hydrochloride is a white to almost white crystalline powder with a molecular weight of 394.7. It is Freely soluble in methanol, slightly soluble in water, practically insoluble in chloroform.

LYMPHTOR 100

White to off white color, lyophilize powder. The excipients are Mannitol, Tertiary Butanol and Water.

8 Pharmaceutical particulars

8.1 Incompatibilities

Not Applicable

8.2 Shelf-life

Do not use later than date of expiry.

8.3 Packaging information

Available in 30 ml Amber color vial.

8.4 Storage and handing instructions

Store protected from Moisture at a temperature not exceeding 25°C. Protect from light.

Keep out of reach of children

9 Patient Counselling Information

LYMPHTOR 100 mgs

Package leaflet: Information for the user

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet

What is in this leaflet

9.1 What is Lymphtor and what it is used for

Lymphtor is a medicine which is used for the treatment of certain types of cancer (cytotoxic medicine). Lymphtor is used alone (monotherapy) or in combination with other medicines for the treatment of the following forms of cancer:

- Chronic lymphocytic leukaemia in cases where fludarabine combination chemotherapy is not
- appropriate for you
- Non-Hodgkin's lymphomas, which had not, or only shortly, responded to prior rituximab treatment
- Multiple myeloma in cases where high-dose chemotherapy with autologous stem cell transplantation, thalidomide or bortezomib containing therapy is not appropriate for you.

9.2 What you need to know before you take Lymphtor

Do not take Lymphtor:

- If you are allergic to Lymphtor or any of the other ingredients of this medicine
- While breastfeeding, if treatment with Lymphtor is necessary during lactation you must discontinue breastfeeding (see section warnings and precautions on breastfeeding)
- If you have severe liver dysfunction (damage to the functional cells of the liver)
- If you have yellowing of the skin or whites of the eyes caused by liver or blood problems (jaundice)
- If you have severely disturbed bone marrow function (bone marrow depression) and serious changes in your number of white blood cells and platelets in the blood

- If you have had major surgical operations less than 30 days before starting treatment
- If you have an infection, especially one accompanied by a reduction in white blood cells (leucocytopenia)
    - In combination with yellow fever vaccines.

Warnings and precautions

Warning: Cytotoxic Drug: To be supplied against demand from Cancer Hospitals, Institutions and against prescription of cancer specialist only.

Talk to your doctor or nurse before using Lymphtor:

- In case of reduced capability of the bone marrow to replace blood cells. You should have your number of white blood cells and platelets in the blood checked before starting treatment with Lymphtor, before each subsequent course of treatment and in the intervals between courses of treatment
- In case of infections. You should contact your doctor if you have signs of infection, including fever or lung symptoms
- In cases of existing heart disease (e.g. heart attack, chest pain, severely disturbed heart rhythms)
- Talk to your doctor or nurse during use of Lymphtor:
- In case you notice any pain in your side, blood in your urine or reduced amount of urine. When your disease is very severe, your body may not be able to clear all the waste products from the dying cancer cells. This is called tumour lysis syndrome and can cause kidney failure and heart problems within 48 hours of the first dose of Lymphtor. Your doctor may ensure you are adequately hydrated and give you other medicines to help prevent it
- In case of reactions on your skin during treatment with Lymphtor. The reactions may increase in severity
- In case of painful red or purplish rash that spreads and blisters and/or other lesions begin to appear in the mucous membrane (e.g. mouth and lips), in particular if you had before light sensitivity, infections of the respiratory system (e.g. bronchitis) and/or fever
- In case of severe allergic or hypersensitivity reactions. You should pay attention to infusion reactions after your first cycle of therapy
- Keep out of reach of children

Children and adolescents

There is no experience in children and adolescents with Lymphtor.

Other medicines and Lymphtor

Tell your doctor or pharmacist if you are taking or have recently taken or might take any other medicines.

If Lymphtor is used in combination with medicines which inhibit the formation of blood in the bone marrow, the effect on the bone marrow may be intensified.

If Lymphtor is used in combination with medicines which alter your immune response, this effect may be intensified. Cytostatic medicines may diminish the effectiveness of live-virus vaccination. Additionally, cytostatic medicines increase the risk of an infection after vaccination with live vaccines (e.g. viral vaccination).

Pregnancy, breast-feeding and fertility

If you are pregnant or breastfeeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before using this medicine.

Pregnancy

Lymphtor can cause genetic damage and has caused malformations in animal studies. You should not use Lymphtor during pregnancy unless clearly indicated by your doctor. In case of treatment you should have medical consultation about the risk of potential adverse effects of your therapy for the unborn child and genetic consultation is recommended. If you are a woman of childbearing potential, you must use an effective method of contraception both before and during treatment with Lymphtor. If pregnancy occurs during your treatment with Lymphtor you must immediately inform your doctor and should have genetic consultation. If you are a man, you should avoid fathering a child during treatment with Lymphtor and for up to 6 months after treatment has stopped. There is a risk that treatment with Lymphtor will lead to infertility and you may wish to seek advice on conservation of sperm before treatment starts.

Breastfeeding

Lymphtor must not be administered during breastfeeding. If treatment with Lymphtor is necessary during lactation you must discontinue breastfeeding. Ask your doctor or pharmacist for advice before taking any medicine.

Fertility

Men receiving treatment with Lymphtor are advised not to conceive a child during treatment and for up to 6 months afterwards. Before starting treatment, you should seek advice on storing sperm because of the possibility of permanent infertility.

Driving and using machines

No studies on the effects on the ability to drive and to use machines have been performed. Do not drive or operate machines if you experience side effects, such as dizziness or lack of coordination.

9.3 How to take Lymphtor

Lymphtor is administered into a vein over 30- 60 minutes in various dosages,
either alone (monotherapy) or in combination with other medicines.
Treatment should not be started if your white blood cells (leukocytes) have fallen to counts below determined levels.
Your doctor will determine these values at regular intervals.

Chronic lymphocytic leukaemia

Lymphtor 100 mg per square metre of your body surface area (based on your height and weight)	on Days 1+2
Repeat the cycle after 4 weeks up to 6 times	

Non-Hodgkin's lymphomas

Lymphtor 120 mg per square metre of your body surface area (based on your height and weight))	on Days 1+2
Repeat the cycle after 3 weeks at least 6 times	

Multiple myeloma

Lymphtor 120-150 mg per square metre of	on Days 1+2

your body surface area (based on your height and weight)	
Prednisone 60 mg per square metre of your body surface area (based on your height and weight) i.v. or per os.	on Days 1-4
Repeat the cycle after 4 weeks at least 3 times	

Treatment should be terminated if white blood cell (leukocyte) and/or platelet values drop to determined levels. Treatment can be continued after white blood cell values have increased.

Impaired liver or kidney function

Dependent on the degree of impairment of your liver function it may be necessary to adjust your dose (by 30% in case of moderate liver dysfunction). No dose adjustment is necessary in case of impairment of kidney function. Your attending doctor will decide whether a dosage adjustment is necessary.

How it is administered

Treatment with Lymphtor should be undertaken only by doctors experienced in tumour therapy. Your doctor will give you the exact dose of Lymphtor and use the necessary precautions. Your attending doctor will administer the solution for infusion after preparation as prescribed. The solution is administered into a vein as a short-term infusion over 30-60 minutes.

Duration of use

There is no time limit laid down as a general rule for treatment with Lymphtor. Duration of treatment depends on disease and response to treatment. If you are at all worried or have any questions regarding treatment with Lymphtor, please speak to your doctor or nurse.

If you forget to take Lymphtor

If a dose of Lymphtor has been forgotten, your doctor will usually retain the normal dosage schedule**.**

If you stop taking Lymphtor

The doctor treating you will decide whether to interrupt the treatment or to change over to a different preparation. If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

9.4 Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.
Some of the findings listed below may be found after tests performed by your doctor. Tissue decay (necrosis) has been observed very rarely following leakage of Lymphtor into the tissue outside the blood vessels (extravascular). A burning sensation where the infusion needle is inserted may be a sign of leakage outside the blood vessels. The consequence can be pain and poorly healing skin defects. The dose-limiting side-effect of Lymphtor is impaired bone-marrow function, which usually returns to normal after treatment. Suppressed bone marrow function may lead to low blood cells, which in turn may lead to an increased risk of infection, anaemia or a heightened risk of bleeding.

Very common side effects (may affect more than 1 in 10 people):

- low counts of white blood cells (disease-fighting cells in your blood)
- decrease in the red pigment of the blood

- (haemoglobin: a protein in red blood cells that carries oxygen throughout the body)
- low counts of platelets (colourless blood cells that help blood clot)
- infections
- feeling sick (nausea)
- vomiting
- mucosal inflammation
- headache
- increased blood level of creatinine (a chemical waste product that is produced by your muscle)
- increased blood level of urea (a chemical waste product)
- fever
- fatigue

Common side effects (may affect up to 1 in 10 people):

- bleeding (haemorrhage)
- disturbed metabolism caused by dying cancer
- cells releasing their contents into the blood stream
- reduction in red blood cells which can make the skin pale and cause weakness or breathlessness (anaemia)
- low counts of neutrophils (a common type of white blood cell important to fighting off infections)
- hypersensitivity reactions such as allergic inflammation of the skin (dermatitis), nettle rash (urticaria)
- a rise in liver enzymes AST/ALT (which may
- indicate inflammation or damage to cells in the liver)
- a rise in the enzyme alkaline phosphatase (an enzyme made mostly in the liver and bones)
- a rise in bile pigment (a substance made during the normal breakdown of red blood cells)
- low potassium blood levels (a nutrient that is necessary for the function of nerve and muscle cells, including those in your heart)
- disturbed function (dysfunction) of the heart (palpitations, angina pectoris)
- disturbed heart rhythms (arrhythmia)
- low or high blood pressure (hypotension or hypertension)
- disturbed lung function
- diarrhoea
- constipation
- sore mouth (stomatitis)
- loss of appetite
- hair loss
- skin changes
- missed periods (amenorrhoea)
- pain
- insomnia
- chills
- dehydration
- dizziness
- itchy rash (urticaria)

Uncommon side effects (may affect up to 1 in 100 people):

- accumulation of fluid in the heart sac (escape of fluid into the pericardial space)
- ineffective production of all blood cells (myelodysplastic syndrome)
- acute leukemia

- heart attack, chest pain (myocardial infarct)
- heart failure

Rare side effects (may affect up to 1 in 1,000 people):

- infection of the blood (sepsis)
- severe allergic hypersensitivity reactions (anaphylactic reactions)
- reduction in your bone marrow function, which may make you feel unwell or show up in your
- blood tests
- signs similar to anaphylactic reactions (anaphylactoid reactions)
- drowsiness
- loss of voice (aphonia)
- acute circulatory collapse (failure of blood circulation mainly from a cardiac origin with failure to maintain the supply of oxygen and other nutrients to the tissues and removing toxins)
- reddening of the skin (erythema)
- inflammation of the skin (dermatitis)
- itching (pruritus)
- skin rash (macular exanthema)
- excessive sweating (hyperhidrosis)

Very rare side effects (may affect up to 1 in 10,000 people):

- Primary atypical inflammation of the lungs (pneumonia)
- Break-down of red blood cells
- Rapid decrease in blood pressure sometimes with skin reactions or rash (anaphylactic shock)
- Disturbed sense of taste
- Altered sensations (paraesthesia) and malaise and pain in the limbs (peripheral neuropathy)
- Serious condition resulting in the blockade of specific receptor in the nervous systems
- Disorders of the nervous system
- Lack of coordination (ataxia)
- Inflammation of the brain (encephalitis)
- Increased heart rate (tachycardia)
- Inflammation of the veins (phlebitis)
- Formation of tissue in the lungs (fibrosis of the lungs)
- Bleeding inflammation of the gullet (haemorrhagic oesophagitis)
- Bleeding of stomach or gut
- Infertility
- Multiple organ failure

Not known side effects (cannot be estimated from the available data):

- Liver failure
- Renal failure
- Irregular and often rapid heart rate (atrial fibrillation)
- Painful red or purplish rash that spreads and blisters and/or other lesions begin to appear in
- the mucous membrane (e.g. mouth and lips), in particular if you had before light sensitivity,
- infections of the respiratory system (e.g. bronchitis) and/or fever
- Pneumonitis
- Bleeding from the lungs

There have been reports of tumours (myelodysplastic syndrome, acute myeloid leukaemia (AML), bronchial carcinoma) following treatment with Lymphtor. No clear relationship with Lymphtor could be determined.Contact your doctor or seek medical attention.

If you notice any of the following side effects (frequency not known):

- Serious skin rashes including Stevens-Johnson syndrome and toxic epidermal necrolysis. These can appear as reddish target-like macules or circular patches often with central blisters on the trunk, skin peeling, ulcers of mouth, throat, nose, genitals and eyes and can be preceded by fever and flu-like symptoms.
- Widespread rash, high body temperature, enlarged lymph nodes and other body organs involvement (Drug Reaction with Eosinophilia and Systemic Symptoms which is also known as DRESS or drug hypersensitivity syndrome).

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: https://www.torrentpharma.com/index.php/site/info/adverse_event_reporting.
By reporting side effects, you can help provide more information on the safety of this medicine.

9.5 How to store Lymphtor

Store protected from Moisture at a temperature not exceeding 25°C. Protect from light.

Keep out of reach of children.

9.6 Contents of the pack and other information

Each Vial Contains:

Bendamustine Hydrochloride I.P……. 100 mg

Excipients…….... q.s.

The excipients are Mannitol, Tertiary Butanol and Water

10 Details of manufacturer

Manufacture By:

BDR Pharmaceuticals International Pvt. Ltd.

Plot No 58 to 67, Sector B-1,

Umariya - Dungaria, Tehsil-Shahpura, Jabalpur, M.P.

11 Details of permission or licence number with date

Mfg Lic No.: 28-A/25/2018 issued on 29 Jun 2018

12. Date of revision

MAR 2022

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/LYMPHTOR 100 mg/MAR-22 /02/PI