



Professional Information for Medicines for Human Use

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

OMUBEN 25 mg/Vial (Powder for concentrate for solution for infusion)
OMUBEN 100 mg/Vial (Powder for concentrate for solution for infusion)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

OMUBEN 25/100 mg/Vial:
Each vial contains bendamustine hydrochloride 25 mg/100 mg powder for concentrate for solution for infusion.
Contains sugar – mannitol 42,50 mg and 170,00 mg respectively.
For the full list of excipients, (see section 6.1).

3. PHARMACEUTICAL FORM

For Lyophilised powder:
White to off-white lyophilized cake or powder in amber glass vial stoppered with gray igloo lyo rubber stopper and sealed with aluminium seal having a PP disc.

For Reconstituted solution:
A clear colourless solution essentially free from visible particles.

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.
- First-line treatment of indolent CD20 positive Non-Hodgkin's Lymphoma in combination with rituximab.
- 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

For intravenous infusion over 30 to 60 minutes.
Infusion must be administered under the supervision of a medical practitioner qualified and experienced in the use of chemotherapeutic medicines.
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 x 10 9/L or < 75 x 10 9/L, respectively (see section 4.3).

Monotherapy for chronic lymphocytic leukaemia
100 mg/m² body surface area **OMUBEN** on days 1 and 2; every 4 weeks.

Combination treatment for first-line indolent Non-Hodgkin's Lymphoma
90 mg/m² body surface area **OMUBEN** on days 1 and 2 in combination with 375 mg/m² body surface area rituximab as a slow i.v. infusion on day 1; every 4 weeks.

Monotherapy for indolent Non-Hodgkin's Lymphomas refractory to rituximab
120 mg/m² body surface area **OMUBEN** on days 1 and 2; every 3 weeks.

Multiple Myeloma
120-150 mg/m² body surface area **OMUBEN** on days 1 and 2; 60 mg/m² body surface area prednisone i.v. or orally on days 1 to 4; every 4 weeks.
Treatment should be terminated or delayed if leukocyte and/or platelet values dropped to < 3 x 10 9/L or < 75 x 10 9/L, respectively. Treatment can be continued after leukocyte values have increased to > 4 x 10 9/L and platelet values to > 100 x 10 9/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 preparation and administration instructions (see Method of administration).

Special populations
Hepatic impairment
On the basis of pharmacokinetic data, no dose adjustment is necessary in patients with mild hepatic impairment [serum bilirubin < 34,2 µmol/L (2,0 mg/dl)].
A 30 % dose reduction is recommended in patients with moderate hepatic impairment (serum bilirubin [34,2 µmol/L – 51,3 µmol/L (2 – 3,0 mg/dl)].
No data is available in patients with severe hepatic impairment [serum bilirubin values of > 51,3 µmol/L (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.

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

Paediatric patients
There is no experience in children and adolescents with **OMUBEN**.

Method of 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.

4.3. Contraindications

- Hypersensitivity to the bendamustine hydrochloride or to any of the excipients in **OMUBEN** (see section 6.1)
- Pregnancy and lactation (see section 4.6)
- Severe hepatic impairment [serum bilirubin > 34,2 µmol/L (2,0 mg/dl)]
- Jaundice
- Severe bone marrow suppression and severe blood count alterations (leukocyte and/or platelet values dropped to < 3 x 10 9/L or < 75 x 10 9/L, respectively)
- Major surgery less than 30 days before start of treatment
- Infections, especially involving leukocytopenia
- Yellow fever vaccination or any other live (attenuated) vaccination
- Congenital QT prolongation
- Concomitant medicines causing QT prolongation

4.4. Special warnings and precautions for use

Myelosuppression
Patients treated with **OMUBEN** may experience myelosuppression. In the event of treatment-related myelosuppression, leukocytes, platelets, haemoglobin, and hematocrits 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). Treatment with **OMUBEN** 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 hydrochloride as **OMUBEN** is combined with rituximab. Patients with lymphopenia and low CD4-positive T-cell count following treatment with **OMUBEN** are more susceptible to (opportunistic) infections, including tuberculosis. In case of low CD4-positive T-cell counts (< 200/µl), 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 **OMUBEN** 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 may occur after these patients received bendamustine hydrochloride as in **OMUBEN**. 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 **OMUBEN** 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 Medicine 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 medical practitioner and should be told to seek medical attention immediately if they develop these symptoms. Some events occurred when **OMUBEN** was given in combination with other anticancer medicines, 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, **OMUBEN** should be withheld or discontinued. For severe skin reactions with suspected relationship to bendamustine hydrochloride as **OMUBEN**, treatment should be discontinued.

Cardiac disorders
During treatment with **OMUBEN** 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 **OMUBEN** 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 **OMUBEN** treatment. The onset tends to be within 48 hours of the first dose of **OMUBEN** 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 medicines (allopurinol and rasburicase) should be considered prior to therapy. There have been a few cases of SJS and TEN reported when bendamustine and allopurinol were administered concomitantly.

Anaphylaxis
Infusion reactions to **OMUBEN** have been reported. Symptoms 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. **OMUBEN** should be discontinued.

Contraception
OMUBEN 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 **OMUBEN** 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. There have been reports of necrosis, tumour lysis syndrome and anaphylaxis.
There have been reports of secondary tumours, including myelodysplastic syndrome, myeloproliferative disorders, acute myeloid leukaemia and bronchial carcinoma.

OMUBEN contains mannitol, people who are allergic to mannitol should not take **OMUBEN**.

4.5. Interaction with other medicines and other forms of interaction

No *in-vivo* interaction studies have been performed.
When **OMUBEN** is combined with myelosuppressive medicines, the effect of **OMUBEN** 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 **OMUBEN**.
Combination of **OMUBEN** with ciclosporine 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 hydrochloride as in **OMUBEN** 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 exist.

4.6. Fertility, pregnancy and lactation

Fertility
Women of childbearing potential must use effective methods of contraception both before and during **OMUBEN** therapy. Men being treated with **OMUBEN** 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 **OMUBEN**.

Pregnancy
There are insufficient data from the use of **OMUBEN** in pregnant women. In nonclinical studies bendamustine hydrochloride was embryo-fetolethal, teratogenic and genotoxic. Therefore, **OMUBEN** is contraindicated during pregnancy. The mother should be informed about the risk to the foetus. 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.

Breastfeeding
It is not known whether bendamustine passes into the breast milk, therefore, **OMUBEN** is contraindicated during breastfeeding (see section 4.3). Breastfeeding must be discontinued during treatment with **OMUBEN**.

4.7. Effects on ability to drive and use machines

OMUBEN has major influence on the ability to drive and use machines. Ataxia, peripheral neuropathy and somnolence have been reported during treatment with **OMUBEN** (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

a. Summary of the safety profile
The most common adverse reactions with **OMUBEN** are hematological adverse reactions (leukopenia, thrombopenia), dermatologic toxicities (allergic reactions), constitutional symptoms (fever), gastrointestinal symptoms (nausea, vomiting).

b. Tabulated list of adverse reactions
For patients who received only **OMUBEN**, the following adverse reactions were reported during therapy plus follow-up for 14 days after treatment was stopped:

SYSTEM ORGAN CLASS	FREQUENCY
Infections and infestations	
Infection not otherwise specified (NOS), including opportunistic infection (e.g. Herpes zoster, Cytomegalovirus, Hepatitis B)	Frequent
PJP, Sepsis, Tuberculosis	Less Frequent
Pneumonia primary atypical	Frequency Not Known
Neoplasma benign, malignant and unspecified (including cyst and polyp)	
Tumour lysis syndrome	Frequent
Myelodysplastic syndrome, acute myeloid leukemia	Less Frequent
Blood and lymphatic system disorders	
Leukopenia NOS, Thrombocytopenia, Lymphopenia, Haemorrhage, Anaemia, Neutropenia	Frequent
Pancytopenia Bone marrow failure	Less Frequent
Haemolysis	Frequency Not Known

↟DETACH BEFORE DISPENSING

SCHEDULING STATUS

S4

PATIENT INFORMATION LEAFLET
OMUBEN 25 mg/Vial (Powder for concentrate for solution for Infusion)
Contains sugar - mannitol 42,50 mg
OMUBEN 100 mg/Vial (Powder for concentrate for solution for Infusion)
Contains sugar - mannitol 170,00 mg
Bendamustine hydrochloride

Read all of this leaflet carefully before you start taking OMUBEN
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- **OMUBEN** has been prescribed for you personally and you should not share your medicine with other people. It may harm them, even if their symptoms are the same as yours.

What is in this leaflet:

1. What **OMUBEN** is and what it is used for.
2. What you need to know before you use **OMUBEN**.
3. How to use **OMUBEN**.
4. Possible side effects.
5. How to store **OMUBEN**.
6. Contents of the pack and other information.

1. What OMUBEN is and what it is used for
OMUBEN is used for the treatment of certain types of cancer (cytostatic medicine).
OMUBEN is used alone (monotherapy) or in combination with other medicines for the treatment of the following forms of cancer:
- chronic lymphocytic leukaemia
- Non-Hodgkin Lymphoma which was not treated before, in combination treatment with rituximab or which had not, or only shortly, responded to prior rituximab treatment (monotherapy)
- multiple myeloma

2. What you need to know before you take OMUBEN
Do not take OMUBEN:
- If you are hypersensitive (allergic) to the active ingredient Bendamustine hydrochloride or any other ingredients of this medicine;
- If you are a pregnant woman or breastfeeding your baby;
- If you have severe liver damage (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 the number of white blood cells and platelets in your blood (white blood cells and/or thrombocyte values drop to < 3 x 10 9/L or < 75 x 10 9/L, respectively);
- If you have had major surgical operations less than 30 days before starting treatment;
- If you have an infection, especially accompanied by a reduction in white blood cells (leucopenia);
- In combination with yellow fever vaccines or other live attenuated vaccines.

Warnings and precautions OMUBEN
- 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 **OMUBEN** 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 including respiratory signs and symptoms.
- In case of reactions on your skin during treatment with **OMUBEN**. The skin 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 cases of existing heart disease (e.g. heart attack, chest pain, severely disturbed heart rhythms).
- 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 **OMUBEN**. Your doctor may ensure you are adequately hydrated and give you other medicines to help prevent it.
- In case of severe allergic or hypersensitivity reactions. You should pay attention to infusion reactions after your first cycle of therapy.
- Hepatitis B reactivation. Cases of patients with history diagnosis of hepatitis B.
- Contraception.

Taking other medicines with OMUBEN:
Always tell your healthcare professional if you are taking any other medicine (this includes complementary or traditional medicines). See Do not take **OMUBEN**.

Tell your doctor before taking **OMUBEN** if you are taking any of the medicines listed below:
- If **OMUBEN** 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 **OMUBEN** is used in combination with medicines which alter your immune response, this effect may be intensified.
  - Cytostatic medicines (medicine that slows or stops the growth of cells, including cancer cells, without killing them) 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, breastfeeding and fertility
If you are pregnant, breastfeeding your baby or planning to have a baby, please consult your doctor, pharmacist or other healthcare professional for advice before **OMUBEN** is administered to you.

Pregnancy
OMUBEN can cause genetic damage and has caused malformations in animal studies. You should not use **OMUBEN** during pregnancy unless certainly indicated by your doctor.
In case of treatment you should use 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 **OMUBEN**. If pregnancy occurs during your treatment with **OMUBEN** you must immediately inform your doctor and should use genetic consultation.

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

Fertility
Men receiving treatment with **OMUBEN** are advised not to father 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. If you are a man, you should avoid fathering a child during treatment with **OMUBEN** and for up to 6 months after treatment has stopped. There is a risk that treatment with **OMUBEN** will lead to infertility and you may wish to seek advice on conservation of sperm before treatment starts.

Driving and using machines
OMUBEN has major influence on the ability to drive and to use machines. Do not drive or operate machines if you experience side effects, such as, somnolence (sleepiness or state of being drowsy) dizziness or lack of coordination.

OMUBEN contains mannitol:
DO NOT USE **OMUBEN** if you had an allergic reaction when you took the medicines contained in mannitol.

3. How to take OMUBEN
You will not be expected to give yourself **OMUBEN**. It will be given to you by a person who is qualified to do so.
OMUBEN 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) and/or your blood platelets have fallen to counts below determined levels.
Your doctor will determine these values at regular intervals.

Chronic Lymphocytic Leukaemia

OMUBEN 100 mg per square meter of your body surface area (based on your height and weight) on days 1 and 2, every 4 weeks.	on Days 1+2
Repeat the cycle after 4 weeks up to 6 times	

Non-Hodgkin Lymphomas

OMUBEN 90 mg per square meter of your body surface area (based on your height and weight) on days 1 and 2 in combination with 375 mg per square area rituximab as a slow i.v. infusion on day 1; every 4 weeks.	on Days 1 + 2
Repeat the cycle after 3 weeks at least 6 times	

Multiple Myeloma

OMUBEN 120 - 150 mg per square meter of your body surface area (based on your height and weight) on days 1 and 2.	on Days 1 + 2
Prednisone 60 mg per square meter of your body surface area (based on your height and weight) by injection or orally on days 1 to 4; every 4 weeks.	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 dropped to determined levels. Treatment can be continued after white blood cell and platelet 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 **OMUBEN** should be undertaken only by doctors experienced in tumour therapy. Your doctor will give you the exact dose of **OMUBEN** 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 **OMUBEN**. Duration of treatment depends on disease and response to treatment.
If you are at all worried or have any questions regarding treatment with **OMUBEN**, please speak to your doctor or nurse.

OMUBEN will be given to you, by injection, by your doctor or another health care professional. You should check with your doctor or pharmacist if you are unsure. If you have the impression that the effect of **OMUBEN** is too strong or too weak, talk to your doctor or pharmacist.

If you take more OMUBEN than you should
Since a healthcare professional will administer this medicine, he/she will control the dosage. However, in the event of over dosage your doctor will manage the over dosage.

If you are concerned that you may take more **OMUBEN**, contact your doctor or another healthcare professional immediately.

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

If you stop using OMUBEN
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 product, ask your doctor or pharmacist.

4. Possible side effects
OMUBEN can have side effects:
Not all side effects reported for **OMUBEN** are included in this leaflet. Should your general health worsen or if you experience any untoward effects while taking this medicine, please consult your doctor, pharmacist or other healthcare professional for advice.
Tissue decay (necrosis) has been observed very rarely following leakage of **OMUBEN** 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 **OMUBEN** is impaired bone marrow function, which usually returns to normal after treatment. Suppressed bone marrow function may lead to low counts of blood cells, which in turn may lead to an increased risk of infection, anaemia or a heightened risk of bleeding.

If any of the following happens, stop taking/over **OMUBEN** and tell your doctor immediately or go to the casualty department at your nearest hospital:
- Swelling of your hands, feet, ankles, face, mouth or throat, which may cause difficulty in swallowing or breathing.
- Rash or itching.
- Fainting.

These are all very serious side effects. If you have them, you may have had a serious allergic reaction to **OMUBEN**. You may need urgent medical attention or hospitalisation.

Tell your doctor immediately or go to the casualty department at your nearest hospital if you notice any of the following:
Frequent side effects:
- Chest pain (angina)
- Disturbed function (dysfunction) of the heart
- Disturbed heart rhythms (arrhythmia)
- Disturbed lung function

Less frequent effects:
- Primary atypical inflammation of the lungs (pneumonia)
- Severe allergic hypersensitivity reactions (anaphylactic reactions)
- Signs similar to anaphylactic reactions (anaphylactoid reactions)
- Accumulation of fluid in the heart sac (escape of fluid into the pericardial space)
- Heart attack, chest pain (myocardial infarction)
- Heart failure
- Increased heart rate (tachycardia)
- Acute circulatory collapse (failure of blood circulation mainly from the heart with failure to maintain the supply of oxygen and other nutrients to the tissues and removing toxins)
- *Pneumocystis jirovecii pneumonia* (a fungal infection of the lungs, causing cough, often mild and dry and fever)

Frequency not known side effects:
- 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).

These are all serious side effects. You may need urgent medical attention.

Tell your doctor if you notice any of the following:
Frequently side effects:
- 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) causing shortness of breath, irregular heartbeats, dizziness, unusual tiredness
- Low counts of platelets (colourless blood cells that help blood clot)
- Infections (including shingles, cytomegalovirus, hepatitis B virus infection)
- 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 (unusual weakness or tiredness)
- Bleeding (haemorrhage)
- Disturbed metabolism caused by dying cancer cells releasing their contents into the blood stream (Tumour lysis syndrome)
- 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)
- A rise in liver enzymes aspartate aminotransferase/alanine aminotransferase (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)
- Low or high blood pressure (hypotension or hypertension)
- Diarrhoea
- Constipation
- Sore mouth (stomatitis)
- Loss of appetite
- Hair loss
- Skin changes
- Missed periods (amenorrhoea)
- Pain
- Insomnia
- Chills
- Dehydration
- Dizziness
- Itchy rash (urticaria)

Less frequent side effects
- Tuberculosis (TB) (a persistent cough, constant tiredness, loss of body mass, loss of appetite, fever, coughing up blood, night sweats)
- Ineffective production of all blood cells in the bone marrow (the spongy material inside your bones where blood cells are made)
- Acute leukaemia, (a cancer of the myeloid line of blood cells, characterised by the rapid growth of abnormal cells that build up in the bone marrow and blood and interfere with normal blood cells)
- Infection of the blood (sepsis)
- Reduction in your bone marrow function, which may make you feel unwell or show up in your blood tests
- Drowsiness
- Loss of voice (aphonia)
- Reddening of the skin (erythema)
- Inflammation of the skin (dermatitis)
- Itching (pruritus)
- Skin rash (macular exanthema)
- Excessive sweating (hyperhidrosis)
- Break-down of red blood cell (haemolysis)
- Raised decrease in blood pressure sometimes with skin reactions or rash (anaphylactic shock)
- Disturbed sense of taste
- Altered sensations (paraesthesia)
- 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
- Anticholinergic syndrome (leading to dilated pupils, decreased sweating, elevated temperature or rapid heartbeat)
- Lack of coordination (ataxia)
- Inflammation of the brain (encephalitis)
- 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

Frequency not known side effects:
- 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
- Drug rash in combination therapy with rituximab
- Pneumonitis
- Bleeding from the lungs

There have been reports of tumours (myelodysplastic syndrome, angiomyolipomas, bronchial carcinoma following treatment with **OMUBEN**. No clear relationship with **OMUBEN** could be determined.
If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

Reporting of side effects
If you get 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 via the " 6.04 Adverse Drug reaction Reporting Form found online under SAHPRA's publications https://www.sahpra.org.za/Publications/Index/8. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store OMUBEN
STORE ALL MEDICINES OUT OF REACH OF CHILDREN.
Store at or below 25 °C. Keep it in a dry place.
Do not use after expiry date stated on the label.
Keep the container in the outer carton to protect the content from light.

Return all unused medicine to your pharmacist.
Do not dispose of unused medicine in drains or sewerage systems (e.g. toilets).

6. Contents of the pack and other information
What OMUBEN contains
Bendamustine Hydrochloride
Mannitol
Tert-Butanol
Nitrogen
Water for injection

What OMUBEN looks like and contents of the pack
OMUBEN 25/100 mg Vial:
25 mg/Vial:
Lyophilised powder is filled in glass vials sealed with 20 mm aluminium seal having white colour PP disc. These vials are packed in pre-printed carton with a packaging leaflet.

100 mg/Vial:
Lyophilised powder is filled in glass vials with 20 mm aluminium seal having grey colour PP disc. These vials are packed in pre-printed carton with a packaging leaflet.

NAME, BUSINESS ADDRESS AND TELEPHONE NUMBER OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION
AUROGEN SA (PTY) LTD
Woodhill Office Park, Building 1,
First Floor, 53 Phillip Engelbrecht Avenue
Meyerstal, Ext. 12, 1448,
Johannesburg
South Africa

Registration numbers
OMUBEN 25 MG: 55/26/0657.655
OMUBEN 100 MG: 55/26/0658.656

This leaflet was last revised in
29 January 2025

SYSTEM ORGAN CLASS	FREQUENCY
Immune system disorders	
Hypersensitivity NOS	Frequent
Anaphylactic reaction, Anaphylactoid reaction	Less Frequent
Anaphylactic shock	Frequency Not Known
Nervous system disorders	
Headache, Insomnia, Dizziness	Frequent
Somnolence, Aphonia	Less Frequent
Dysgeusia, Paraesthesia, Peripheral sensory neuropathy, Anticholinergic syndrome, Neurological disorders, Ataxia, Encephalitis	Frequency Not Known
Cardiac disorders	
Cardiac dysfunction such as palpitations, angina pectoris, Dysrhythmia, QT prolongation	Frequent
Pericardial effusion, Myocardial infarction, Cardiac failure	Less Frequent
Tachycardia, Atrial fibrillation	Frequency Not Known
Vascular disorders	
Hypotension, Hypertension	Frequent
Acute circulatory failure	Less Frequent
Phlebitis	Frequency Not Known
Respiratory, thoracic and media-stinal disorders	
Pulmonary Dysfunction	Frequent
Pulmonary fibrosis, Pneumonitis Pulmonary alveolar haemorrhage	Frequency Not Known
Gastrointestinal disorders	
Nausea, Vomiting, Diarrhoea, Constipation, Stomatitis	Frequent
Hemorrhagic oesophagitis, Gastrointestinal haemorrhage	Frequency Not Known
Skin and subcutaneous tissue disorders	
Alopecia, Skin disorders NOS, Urticaria	Frequent
Erythema, Dermatitis, Pruritus, Maculopapular Rash, Hyperhidrosis	Less Frequent
SJS, TEN, DRESS (combination therapy with rituximab)	Frequency Not Known
Reproductive system and breast disorders	
Amenorrhea	Frequent
Infertility	Frequency Not Known
Hepatobiliary disorder	
Hepatic failure	Frequency Not Known
General disorders and administration site conditions	
Mucosal inflammation, Fatigue, Pyrexia Pain, Chills, Dehydration, Anorexia	Frequent
Multi-organ failure	Frequency Not Known
Investigations	
Haemoglobin decrease, Creatinine increase, Urea increase, aspartate aminotransferase (AST) increase, alanine aminotransferase (ALT) increase, Alkaline phosphatase increase, Bilirubin increase, Hypokalemia	Frequent
Renal and urinary disorders	
Renal failure	Frequency Not Known

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. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the '6.04 Adverse Drug Reactions Reporting Form,' found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9. Overdose
After application of a 30 min infusion of **OMUBEN** 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 **OMUBEN** 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.

Treatment
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. **OMUBEN** and its metabolites are dialyzable to a small extent.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties
Pharmacotherapeutic group: Antineoplastic medicines, alkylating medicines,

ATC code: L01AA09

Bendamustine hydrochloride is an alkylating antitumor medicine 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 antitumor 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 leukaemias) and *in vivo* in different experimental tumour models with tumours of animal (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 medicines. 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.

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
Amajor 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 clearance 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.

Special populations

Hepatic impairment
In patients with 30 - 70 % tumour infestation of the liver and mild hepatic or moderate hepatic impairment (serum bilirubin < 34,2 µmol/L (2,0 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, $t_{1/2\beta}$, 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 Cmax, tmax, AUC, $t_{1/2\beta}$, volume of distribution and clearance.

Elderly
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
Not applicable.

Environmental Risk Assessment
OMUBEN is a well-established active ingredient used in pharmaceutical preparations for human use. Given the anticipated pattern of use and disposal of the product, the environmental exposure of the active substance and metabolites are expected to be very limited. The use of **OMUBEN** 25/100 mg vial is not considered warranting any environmental concerns or requiring any special product labelling.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients
Mannitol Ph.Eur
Tert-Butanol HIS
Nitrogen USNF/Ph.Eur/IHS
Water for injection USP/Ph.Eur/IHS

6.2. Incompatibilities
Not applicable.

6.3. Shelf life
24 months

6.4. Special precautions for storage
Store at or below 25 °C. Keep in a dry place.
STORE OUT OF REACH OF CHILDREN.

6.5. Nature and contents of container

25 mg/Vial:
Lyophilised powder is filled in glass vial tubular Type-I, 26 mL amber with 20 mm neck (20R ISO vial) stoppered with 20 mm grey bromobutyl rubber stopper (LYO-IGLOO) and sealed with 20 mm aluminum seal having White colour PP disc. These vials shall be packed in pre-printed carton with a packaging leaflet.

100 mg/Vial:
Lyophilised powder is filled in glass vial moulded Type-I, 60 mL (50 H) amber with 20 mm neck stoppered with 20 mm grey bromobutyl rubber stopper (LYO-IGLOO) and sealed with 20 mm aluminum seal having Grey colour PP disc. These vials shall be packed in pre-printed carton with a packaging leaflet.

6.6. Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product
When handling **OMUBEN**, 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.

Instructions for use
When handling **OMUBEN**, 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
- Reconstitute each vial of **OMUBEN** containing 25 mg **OMUBEN** in 10 mL water for injection by shaking.
- Reconstitute each vial of **OMUBEN** containing 100 mg **OMUBEN** in 40 mL water for injection by shaking.

The reconstituted concentrate contains 2,5 mg **OMUBEN** 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 **OMUBEN** immediately with 0,9 % NaCl solution to produce a final volume of about 500 mL.
OMUBEN must be diluted with 0,9 % NaCl solution only and not with any other injectable solution.

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8. REGISTRATION NUMBER
OMUBEN 25 MG: 55/26/0657.655
OMUBEN 100 MG: 55/26/0658.656

9. DATE OF FIRST AUTHORISATION
29 January 2025

P1538756

↟DETACH BEFORE DISPENSING

SKEDULERINGSTATUS

S4

PASIËNTINLIGTINGSBLAD
OMUBEN 25 mg/flessie (poeier vir konsentraat vir oplossing vir infusie)
Bevat suiker - mannitol 42,50 mg
OMUBEN 100 mg/flessie (poeier vir konsentraat vir oplossing vir infusie)
Bevat suiker - mannitol 170,00 mg
Bendamustiendihidrochloried

Lees hierdie inligtingsblad noukeurig deur voordat jy begin om OMUBEN te neem
- Hou hierdie inligtingsblad. Dit mag nodig wees om dit later weer te lees.
- Indien jy enige verdere vrae het, vra jou dokter of apteker.
- **OMUBEN** is vir jou persoonlik voorgeskryf en jy moenie jou medisyne met ander persone deel nie. Dit kan skadelik wees vir hulle, al is hulle simptome dieselfde as joune.

Wat is in hierdie inligtingsblad:
1. Wat is **OMUBEN** en waarvoor word dit gebruik.
2. Wat jy moet weet voordat jy **OMUBEN** gebruik.
3. Hoe om **OMUBEN** te neem.
4. Moontlike newe-effekte.
5. Hoe om **OMUBEN** te berg.
6. Inhoud van die verpakking en ander inligting.

1. Wat is OMUBEN en waarvoor word dit gebruik
OMUBEN word gebruik vir die behandeling van sekere soorte kanker (silostatiese medisyne).
OMUBEN word alleen gebruik (monoterapie) of in kombinasie met ander medisynes vir die behandeling van die volgende soorte kanker:
- chroniese limfositiese leukemie
- nie-Hodgkin-limfoom wat nog nie voorheen behandel is nie, in kombinasiebehandeling met rituksimab, of wat nie, of slegs vir 'n kort tydperk, gereageer het op vorige rituksimab-behandeling (monoterapie)
- veelvuldige miëloom

2. Wat jy moet weet voordat jy OMUBEN neem
Moenie OMUBEN neem nie:
- Indien jy hipersensitief (allergies) vir die aktiewe bestanddeel bendamustiendihidrochloried of vir enige van die ander bestanddele van hierdie medisyne is;
- Indien jy swanger is of jou baba borsvoed.
- Indien jy ernge lewerskade het (skade aan die funksionele selle van die lewer);
- Indien jou vel of dit wit van jou oë vergeel weens probleme met jou lewer of bloed (geelsug);
- Indien jou beenmurgfunksie erg aangetas is (beenmurgonderdrukking) met groot wysigings in die getal witbloedselle en plaatjies in jou bloed (witbloedselle en/of trombosietwaardes val tot < 3 x 10 ^{9}/L of < 75 x 10 ^{9}/L, onderskeidelik);
- Indien jy 'n groot operasie ondergaan het minder as 30 dae voor aanvang van behandeling;
- Indien jy 'n infeksie het, veral een wat gepaard gaan met 'n verlaging in witbloedselle (leukopenie);
- In kombinasie met geelkoorsentstowwe of ander lewende, verswakte entstowwe.

Waarskuwings en voorsorgmaatreëls OMUBEN
- In geval die beenmurg se vermoë om bloedselle te vervang, belemmer is. Die getal witbloedselle en bloedplaatjies in jou bloed behoort nagegaan te word voordat behandeling met **OMUBEN** begin word, voor elke daaropvolgende kursus van behandeling en in die tussenposes tussen kursusse van behandeling.
- In geval van infeksies. Jy moet jou dokter kontak indien jy tekens van infeksie het, insluitende koors of longsimptome (insluitende respiratoriese tekens en simptome).
- In geval jy velreaksies ondervind tydens behandeling met **OMUBEN**. Die velreaksies kan toeneem in ernstigheidsgraad.
- In geval van pynlike rooi of perserige uitslag wat versprei en blase en/of ander letsels begin verskyn in die slymvlies (bv. mond en lippe), veral indien jy voorheen ligaamsiktwiteit, infeksies van die asemhalingsisteel (bv. bronghs) en/ of koors gehad het.
- In geval van bestaande hartsiekte (bv. hartaanval, bonspyn, erg versteurde hartritme).
- In geval jy enige pyn in jou sy, bloed in jou urine of dat 'n kleiner volume urine gevorm word, opmerk. Wanneer jou siekte baie hewig is, is dit moontlik dat jou liggaam nie al die afvalprodukte van die afsterwende kankerselle kan opruim nie. Dit word tumorlisesindroom genoem en kan nierversaking en hartprobleme veroorsaak binne 48 uur na die eerste dosis **OMUBEN**. Jou dokter kan seker maak dat jy voldoende gehidreer is en vir jou ander medisynes gee om dit te help voorkom.
- In geval van hewige allergiese of hipersensitiwiteitsreaksies. Jy moet attent wees op infusiereaksies na jou eerste siklus van terapie.
- Hepatitis B-heraktivering. Gevalle van pasiënte met 'n geskiedenis van 'n diagnose van hepatitis B.
- Voorbehoeding.

Die neem van ander medisynes met OMUBEN:

Sê altyd vir jou geneesheer/bedekundige indien jy enige ander medisyne neem (dit sluit komplementêre of tradisionele medisynes in). Sien Moenie **OMUBEN** neem nie.

Voordat jy **OMUBEN** neem, sê vir jou dokter indien jy enige van die medisynes wat hier onder gelys word, neem:
- Indien **OMUBEN** gebruik word in kombinasie met medisynes wat die vorming van bloed in die beenmurg onderdruk, kan die uitwerking op die beenmurg versterk word.
- Indien **OMUBEN** gebruik word in kombinasie met medisynes wat jou immuunrespons wysig, kan hierdie effek versterk word.
  - Silostatiese medisynes (medisyne wat die groei van selle vertraag of stop, insluitende kankerselle, sonder om die selle dood te maak) kan die doeltreffendheid van inenting met lewende virus verminder. Bykomend verhoog silostatiese medisynes die risiko van 'n infeksie na inenting met lewende entstowwe (bv. virale inenting).

Swangerskap, borsvoeding en vrugbaarheid

Indien jy swanger is, jou baba borsvoed of beplan om swanger te raak, raadpleeg asseblief jou dokter, apteker of ander geesondheidsorgbeskikundige voordat **OMUBEN** aan jou toegedien word.

Swangerskap
OMUBEN kan genetiese skade veroorsaak en het miskomings in dierestudies veroorsaak. Jy moenie **OMUBEN** tydens swangerskap gebruik nie, behalwe as dit spesifiek deur jou dokter aangedui is.
In geval van behandeling behoort jy mediese konsultasie te kry rakende die risiko van potensiële ongunste effekte wat jou terapie vir die ongebore kind inhou en genetiese konsultasie word aanbeveel.
Indien jy 'n vrou is wat nog kan swanger raak, moet jy beslis voor en tydens behandeling met **OMUBEN** 'n doeltreffende voorbehoedmetode gebruik. Indien jy tydens jou behandeling met **OMUBEN** swanger raak, moet jy onmiddellik jou dokter inlig en jy behoort geriefsiese berading te kry.

Borsvoeding
OMUBEN moenie tydens borsvoeding toegedien word nie.
Indien behandeling met **OMUBEN** nodig is tydens laktasie, moet jy ophou om jou baba te borsvoed.
Vra jou dokter of apteker se advies voordat jy enige medisyne neem.

Vrugbaarheid
Mans wat behandeling met **OMUBEN** ontvang, word aangeraai om tydens behandeling en vir tot 6 maande daarna nie 'n kind te verwek nie. Voordat met behandeling begin word, behoort jy advies in te win rakende spermbewaring weens die moontlikheid van permanente onvrugbaarheid.
Indien jy 'n man is, moet jy dit vermy om 'n kind te verwek tydens behandeling met **OMUBEN** en vir tot 6 maande nadat behandeling gestaak is. Daar is 'n risiko dat behandeling met **OMUBEN** tot onvrugbaarheid sal lei en jy mag verkies om advies rakende bewaring van sperm in te win voordat behandeling begin.

Bestuur en gebruik van masjiene
OMUBEN het 'n groot invloed op die vermoë om te bestuur en masjiene te gebruik. Moenie bestuur of masjiene hanteer indien jy newe-effekte, soos slaperigheid (lomerigheid), duiseligheid of gebrek aan koördinasie, ondervind nie.

OMUBEN bevat mannitol:
MOENIE **OMUBEN** GEBRUIK NIE indien jy 'n allergiese reaksie gehad het toe jy medisynes geneem het wat mannitol bevat.

3. Hoe om OMUBEN te neem
Daar sal nie van jou verwag word om **OMUBEN** self toe te dien nie. Dit sal vir jou gegee word deur 'n persoon wat gekwalifiseerd is om dit te doen.
OMUBEN word in 'n aar toegedien oor 'n tyd van 30 – 60 minute in verskeie doserings, of alleen (monoterapie) of in kombinasie met ander medisynes.
Behandeling moet nie begin word indien jou witbloedselle (leukosiete) en/of jou bloedplaatjies geval het tot tellings wat onder bepaalde vlakke is nie.
Jou dokter gaan hierdie waardes met gereelde intervalle bepaal.

Chroniese Limfositiese Leukemie

OMUBEN 100 mg per vierkante meter van jou liggaamsoppervlakte (gebaseer op jou lengte en gewig) op dae 1 en 2; elke 4 weke.	op Dae 1 + 2
Herhaal die siklus na 4 weke vir tot 6 keer.	

Nie-Hodgkin-Limfome

OMUBEN 90 mg per vierkante meter van jou liggaamsoppervlakte (gebaseer op jou lengte en gewig) op dae 1 en 2 in kombinasie met 375 mg/m² liggaamsoppervlakte rituksimab as 'n stadige IV-infusie op dag 1; elke 4 weke.	op Dae 1 + 2
Herhaal die siklus na 3 weke ten minste 6 keer.	

Veelvuldige Miëloom

OMUBEN 120 – 150 mg per vierkante meter van jou liggaamsoppervlakte (gebaseer op jou liggaamsoppervlakte) op dae 1 en 2.	op Dae 1 + 2
Prednison 60 mg per vierkante meter van jou liggaamsoppervlakte (gebaseer op jou lengte en gewig) deur inspuiting of mondeliks toegedien op dae 1 tot 4; elke 4 weke.	op Dae 1 – 4
Herhaal die siklus na 4 weke ten minste 3 keer.	

Behandeling moet getermineer word indien witbloedsel- (leukosiet) en/of plaatjiewaardes tot bepaalde vlakke val. Behandeling kan voortgesit word nadat witbloedsel- en plaatjiewaardes weer gestyg het.

Belemmerde lewer- of nierfunksie
Afhangende van die mate van belemmering van jou lewerfunksie kan dit nodig wees om jou dosis aan te pas (met 30 % in geval van matige lewerdisfunksie). Geen dosisaanpassing is nodig in geval van belemmerde nierfunksie nie. Die dokter wat jou behandel gaan besluit of dit nodig is om die dosis aan te pas.

Hoe dit toegedien word
Slegs dokters wat ervare is in tumorterapie behoort behandeling met **OMUBEN** te onderneem. Jou dokter sal vir jou die presiese dosis **OMUBEN** gee en die nodige voorsorgmaatreëls gebruik.
Die dokter wat jou behandel sal die oplossing vir infusie toedien nadat dit voorberei is soos wat voorgeskryf is. Die oplossing word in 'n aar toegedien as 'n korttermyn-infusie oor 30 – 60 minute.

Duur van gebruik
Daar is geen tydsbeperking as 'n algemene reël vir behandeling met **OMUBEN** nie. Duur van behandeling hang af van die siekte en respons op behandeling.
Indien jy enigiins bekommerd is of enige vrae het rakende behandeling met **OMUBEN**, praat asseblief met jou dokter of verpleegkundige daaroor.

Jou dokter of 'n ander geesondheidsorgbeskundige sal **OMUBEN** deur 'n inspuiting aan jou toedien. Vra gerus jou dokter of apteker indien jy onseker is. Indien jy die indruk kry dat die effek van **OMUBEN** te sterk of te swak is, bespreek dit met jou dokter of apteker.

Indien jy meer OMUBEN neem as wat jy behoort te neem

Aangesien 'n gesondheidsorgdeskundige hierdie medisyne gaan toedien, sal hy/sy die dosis beheer. Indien oordosering egter wel voorkom, sal jou dokter dit hanteer.

Indien jy bekommerd is dat meer **OMUBEN** geneem het, kontak onmiddellik jou dokter of ander gesondheidsorgbeskundige.

Indien jy 'n dosis OMUBEN oorgeslaan het
Indien 'n dosis van **OMUBEN** gemis word, sal jou dokter gewoonlik by die normale doseringskedule hou.

Indien jy ophou om OMUBEN te gebruik
Die dokter wat jou behandel sal besluit of dit nodig is om die behandeling te onderbreek of om oor te slaan na 'n verskillende middel.
Indien jy enige verdere vrae het rakende die gebruik van hierdie produk, vra gerus jou dokter of apteker.

4. Moontlike newe-effekte
OMUBEN kan newe-effekte hê:
Nie alle newe-effekte van **OMUBEN** geraapporteer is, word in hierdie inligtingsblad ingesluit nie. Indien jou algemene gesondheid sou verswak of indien jy enige ongunstige effekte ondervind terwyl jy hierdie medisyne neem, moet jy asseblief jou dokter, apteker of ander gesondheidsorgdeskundige raadpleeg.

Ontbinding van weefsel (nekrose) is baie seldsaam waargeneem nadat **OMUBEN** ingeluk het in die weefsel buite die bloedvate (ekstravaskulêr). 'n Brandgevoel waar die infusiemaald ingeplaas is, kan 'n teken wees van lekkasie buite die bloedvate. Die gevolge kan pyn en veldefekte wat swak genees, wees.
Die dosisbeperkende newe-effek van **OMUBEN** is belemmerde beenmurgfunksie, wat gewoonlik nà behandeling terugkeer na normaal. Onderdrukte beenmurgfunksie kan lei tot lae bloedsetellings, wat dan weer kan lei tot 'n verhoogde risiko van infeksie, anemie of 'n groter risiko van bloeding.

Indien enige van die volgende voorkom, hou op om **OMUBEN** te neem/gebruik en sê onmiddellik vir jou dokter of gaan na die ongevalleafdeling by jou naaste hospitaal:
- Swelling van jou hande, voete, enkels, gesig, mond of keel, wat probleme met sluk en asemhaling kan veroorsaak.
- Uitslag of gejeuk.
- Floute.

Hierdie is baie ernstige newe-effekte. Indien jy enige daarvan ondervind, mag jy 'n ernstige allergiese reaksie op **OMUBEN** gehad het. Jy mag dringend mediese bystand of hospitaalsaise benodig.

Indien jy enige van die volgende opmerk, sê onmiddellik vir jou dokter of gaan na die ongevalleafdeling by jou naaste hospitaal:

Newe-effekte wat dikwels voorkom:
- Pyn in die bors (angina).
- Versteurde funksie (disfunksie) van die hart.
- Versteurde hartritme (aritmie).
- Versteurde longfunksie.

Newe-effekte wat minder dikwels voorkom:
- Primêre atipiese inflammasie van die longe (pneumonie).
- Hewige allergiese hipersensitiwiteitsreaksies (anafilaktiese reaksies).
- Tekens soortgelyk aan anafilaktiese reaksies (anafilaktoïede reaksies).
- Opeenhoping van vog in die ruimte om die hart (vloeistof tek uit in die perikardiale spasie in).
- Hartaanval, borspyn (miokardiale infarksie).
- Hartversaking.
- Versnelde hartempo (tagikardie).
- Akute sirkulatoriese ineenstorting (bloedsirkulasie faal, hoofsaaklik van die hart af en kan nie voorsiening van suurstof en ander voedingstowwe na die weefsels volhou nie. en faal om gifstowwe te verwyder).
- *Pneumocystis jiroveci-pneumonie* ('n swaminfeksie van die longe, wat hoes, gewoonlik gering en droog, en koors veroorsaak).

Newe-effekte waarvan die frekwensie onbekend is:
- Ernstige velsiklase insluitende Stevens-Johnsonsindroom en toksiese epidermale nekrolise. Dit kan voorkom as rooierige, teikenagtige vlekke of ronde kolle met blase in die middel op die romp, afskilfering van die vel, ulkusse in die mond, keel, neus, op die geslagsdele en oë en kan voorafgegaan word deur koors en griepagtige simptome.
- Wydverspreide uitslag, hoë liggaamstemperatuur, vergrote limfknope en waarby ander liggaamsorgane betrokke is (medisynereaksie met eosinofilie en sistemiese simptome, wat ook bekend is as DRESS of medisynehipersensitiwiteitsindroom).

Hierdie is baie ernstige newe-effekte. Jy mag dringend mediese bystand benodig.

Sê vir jou dokter indien jy enige van die volgende opmerk:
Newe-effekte wat dikwels voorkom:
- Lae witbloedseltellings (die selle in jou bloed wat teen siektes veg).
- Abnarme in die rooi pigment in die bloed (hemoglobien; 'n proteïen in roobloedselle wat suurstof deur die liggaam vervoer) wat kortasemheid, onegallige hartklop, duiseligheid en ongewone moegheid veroorsaak.
- Lae plaatjietellings (kleurlose bloedselle wat die bloed help om te stol).
- Infeksies (insluitende gordelroos, sitomegalovirus, hepatitis B-virusinfeksie).
- Voel misilik (naarheid).
- Braking.
- Slymvliesontsteking.
- Hoofpyn.
- Verhoogde kreatinienvlak in die bloed ('n chemiese afvalproduk wat deur jou spiere gevorm word).
- Verhoogde vlak van ureum in jou bloed ('n chemiese afvalproduk).
- Koors.
- Uitputting (ongewone swakheid of moegheid).
- Bloeding (hemorragie).
- Versteurde metabolisme wat veroorsaak word deur kankerselle wat afsterf en hul inhoud in die bloedstroom vrystel (tumorlisesindroom).
- Verlaging in rooibloedselle, wat die vel bleek kan laat vertoon en swakheid of kortasemheid kan veroorsaak (anemie).
- Lae neutrofieltellings ('n algemene tipe witbloedsel wat belangrik is om infeksies te beveg).
- 'n Styging in die leweransieme aspartaat aminotransferase/alanien aminotransferase (wat inflammasie of skade aan lewerselle kan aandui).
- 'n Styging in die ensiem alkaliese fosfatase ('n ensiem wat grootliks in die lewer en bene vervaardig word).
- 'n Styging in galpigment (gevorm tydens normale afbraak van roobloedselle).
- Lae kalsiumvlakke in die bloed ('n voedingstof wat nodig is vir die werking van senuwee- en spierselle, insluitende dié in jou hart).
- Lae of hoë bloeddruk (hipotensie of hipertensie).
- Diarree.
- Hardlywigheid.
- Seer mond (stomatitis).
- Verlies van eetlus.
- Haarverlies.
- Veranderings in jou vel.
- Slaan maandstondes oor (amenoree).
- Pyn.
- Slaaploosheid.
- Kouekoors.
- Ontwatering.
- Duiseligheid.
- Jeukende uitslag (urtikarie).

Newe-effekte wat minder dikwels voorkom
- Tuberkulose (TB) ('n aanhoudende hoes, gedurige moegheid, verloor liggaamsmassa, verlies aan eetlus, koors, hoes bloed op, nagsweet).
- Ondoeltreffende produksie van al die tipes bloedselle in die beenmurg (die sponsagtige materiaal binne in jou bene, waar bloedselle gemaak word).
- Akute leukemie ('n kanker van die mieliokele lyn van bloedselle, gekenmerk deur die vinnige groei van abnormale selle wat optree in die beenmurg en bloed, en dan inneeg met normale bloedselle).
- Infeksie van die bloed (sepsis).
- Vermindering van jou beenmurgfunksie, wat jou ongesteld kan laat voel of in jou bloedtoetse waargeneem word.
- Lomerigheid.
- Verloor jou stem (afonie).
- Vel word rooi (eriteem).
- Inflammasie van die vel (dermatitis).
- Gejeuk (pruritus).
- Velutslag (makulêre eksanteem).
- Buitensporige sweting (hiperhidrose).
- Afbraak van roobloedselle (hemolise).
- Vinnige daling in bloeddruk, soms met velreaksies of uitslag (anafilaktiese skok).
- Versteurde smaaksensasie.
- Gewysigde sensasies (parestesie).
- Malaise en pyn in die ledemate (perifere neuropatie).
- Ernstige toestand wat lei tot blokkade van 'n spesifieke reseptor in die senuweesteisel.
- Versteurings van die senuweesteisel.
- Antcholinergiese sindroom (se tot verwyde pupille, verminderde sweetafskeiding, verhoogde liggaamstemperatuur of vinnige hartklop).
- Gebrek aan koördinasie (ataksie).
- Inflammasie van die brein (enkefalitis).
- Inflammasie van die are (flebitis).
- Vorming van weefsel in die longe (fibrose van die longe).
- Bloeiende inflammasie van die sluiderm (hemorragiese esofagitis).
- Bloeding in die maag of derms.
- Onwelsgevoeldheid.
- Veelvuldige orgaanversaking.

Newe-effekte waarvan die frekwensie onbekend is:
- Lewerversaking.
- Nierversaking.
- Onegallige en dikwels vinnige hartspoed (atriale fibrillasie).
- Pynlike rooi of perserige uitslag wat versprei en blase en/of ander letsels begin verskyn in die slymvlies (bv. mond en lippe), veral indien jy voorheen ligaamsiktwiteit, infeksies van die respiratoriese stelsel (bv. bronghs) en/of koors gehad het.
- Mediasyne-uitslag in kombinasieterapie met rituksimab.
- Pneumonitis.
- Bloeding in die longe.

Daar was ook nie van tumors (miëlodisplastiese sindroom, angiomiolipome, bronginale karsinoom) nà behandeling met **OMUBEN**. Geen duidelike verwantskap met **OMUBEN** kon bepaal word nie.
Indien jy enige newe-effekte opmerk wat nie in hierdie inligtingsblad genoem word nie, lig asseblief jou dokter of apteker daaroor in.

Rapportering van newe-effekte
Indien jy newe-effekte ondervind, bespreek dit met jou dokter, apteker of verpleegkundige. Dit sluit enige moontlike newe-effekte wat nie in hierdie inligtingsblad gelys word nie, in.

Jy kan ook newe-effekte aan SAHPRA rapporteer via die "6.04 Adverse Drug Reaction Reporting Form" wat aanlyn onder SAHPRA se publikasies beskikbaar is by https://www.sahpra.org.za/Publications/Index/8. Deur newe-effekte te rapporteer, kan jy help om meer inligting rakende die veiligheid van hierdie medisyne te verskaf.

5. Hoe om OMUBEN te berg
BERG ALLE MEDISYNES BUITE BEREIK VAN KINDERS.
Bêre by of onder 25 °C. Hou op 'n droë plek.
Moenie gebruik nà die vervaldatum wat op die etiket voorkom nie.
Hou die flesse in die buitenste karton om die inhoud teen lig te beskerm.

Neem alle ongebruikte medisyne terug na jou apteker.
Moenie ongebruikte medisyne in dreine en rioolsteisels (bv. toilette) wegdoen nie.

6. Inhoud van die verpakking en ander inligting
Wat OMUBEN bevat
Bendamustiendihidrochloried
Mannitol
Tert-butanol
Stikstof
Water vir inspuiting

Hoe OMUBEN lyk en inhoud van die verpakking
OMUBEN 25/100 mg flessie:
25 mg/flessie:
Gevriesdroogde poeier gevul in 'n glasflessie met 'n 20 mm aluminiumseël met 'n wit PP-skyfie. Hierdie flessies word in 'n bedrukte karton saam met 'n inligtingsblad verpak.

100 mg/flessie:
Gevriesdroogde poeier gevul in 'n glasflessie met 'n 20 mm aluminiumseël met 'n grys PP-skyfie. Hierdie flessies word in 'n bedrukte karton saam met 'n inligtingsblad verpak.

HOUER VAN DIE REGISTRASIESERTIFIKAAT
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Suid-Afrika

Registrasienommers
OMUBEN 25 mg: 55/26/0657.655
OMUBEN 100 mg: 55/26/0658.656

Hierdie inligtingsblad is laas hersien
29 Januarie 2025

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