

PATIENT INFORMATION LEAFLET

SCHEDULING STATUS: S4

PROPRIETARY NAME, STRENGTH AND PHARMACEUTICAL FORM:

RIBOMUSTIN (**bendamustine hydrochloride**) 25 mg Powder for concentrate for solution
for infusion – For single use only

RIBOMUSTIN (**bendamustine hydrochloride**) 100 mg Powder for concentrate for solution
for infusion – For single use only

Read all of this leaflet carefully before you receive RIBOMUSTIN

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- RIBOMUSTIN 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.

1. WHAT RIBOMUSTIN CONTAINS

- The active substance is bendamustine hydrochloride.

RIBOMUSTIN 25 mg: 1 vial contains 25 mg of bendamustine hydrochloride (sterile active ingredient).

RIBOMUSTIN 100 mg: 1 vial contains 100 mg of bendamustine hydrochloride (sterile active ingredient).

After reconstitution 1 ml of the concentrate contains 2,5 mg bendamustine hydrochloride.

- The other ingredients are: mannitol.

2. WHAT RIBOMUSTIN IS USED FOR

RIBOMUSTIN is a medicinal product which is used for the treatment of certain types of cancer (cytostatic medicine).

RIBOMUSTIN 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

3. BEFORE YOU ARE GIVEN RIBOMUSTIN

You should not receive RIBOMUSTIN:

- if you are hypersensitive (allergic) to the active ingredient bendamustine hydrochloride or to mannitol;
- during pregnancy, or if you are 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 $< 3 \times 10^9/\ell$ or $< 75 \times 10^9/\ell$, respectively);
- 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 (leucopenia).
- in combination with yellow fever vaccines or other live attenuated vaccines.

Take special care with RIBOMUSTIN:

- if you get severe allergic or hypersensitivity reactions. You should pay attention to infusion reactions after your first cycle of therapy.
- if you have a reduced capability of the bone marrow to replace blood cells. You should have your full blood count checked before starting treatment with RIBOMUSTIN, before each subsequent course of treatment and in the intervals between courses of treatment.
- if you have any infections which may include TB (tuberculosis). You should contact your doctor if you have signs of infection, including fever or lung symptoms.
- if you get reactions on your skin during treatment with RIBOMUSTIN. These reactions may increase in severity with subsequent courses.
- if you have an existing heart disease (e.g. heart attack, chest pain, disturbed heart rhythm).
- if you notice blood in your urine or a 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 RIBOMUSTIN. Your doctor will be aware of this and may give you medicines to help prevent it.

If you are a man receiving treatment with RIBOMUSTIN you should not father a child during your treatment and for up to 6 months afterwards. Before starting treatment, you should seek advice on storing your sperm cells because of the possibility of permanent infertility (see Pregnancy and Breastfeeding).

Unintentional injection into the tissue outside blood vessels (extravasal injection) may cause local tissue damage. Your doctor will treat this.

Pregnancy and Breastfeeding

You should not receive RIBOMUSTIN if you are pregnant or breastfeeding your baby.

If you are pregnant or breastfeeding your baby, please inform your doctor.

Pregnancy:

RIBOMUSTIN can cause genetic damage and has caused malformations in animal studies. You should not use RIBOMUSTIN if you are pregnant.

If you are a woman of childbearing potential you must use an effective method of contraception both before and during treatment with RIBOMUSTIN. If you become pregnant during your treatment with RIBOMUSTIN you must immediately inform your doctor and should get genetic consultation.

If you are a man, you should not father a child during treatment with RIBOMUSTIN and for up to 6 months after treatment has stopped. There is a risk that treatment with RIBOMUSTIN will lead to infertility and you may wish to seek advice on conservation of your sperm cells before your treatment starts.

Breastfeeding:

RIBOMUSTIN must not be administered if you are breastfeeding your baby. If treatment with RIBOMUSTIN is necessary, you must stop breastfeeding your baby until your treatment with RIBOMUSTIN has been completed.

Driving and using machinery:

Do not drive or operate machines if you experience side effects such as dizziness or lack of coordination.

Using other medicines with RIBOMUSTIN:

Always tell your healthcare professional if you are taking any other medicine.

(This includes complementary or traditional medicines.)

If RIBOMUSTIN 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.

You should not be immunised with live attenuated vaccines if you are being treated with RIBOMUSTIN.

RIBOMUSTIN may diminish the effectiveness of live-virus vaccination. Additionally RIBOMUSTIN increases the risk of an infection after vaccination with live vaccines (e.g. viral vaccination).

4. HOW RIBOMUSTIN IS GIVEN

RIBOMUSTIN 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 $3 \times 10^9/\ell$ and/or your blood platelets have fallen to counts below $75 \times 10^9/\ell$. Your doctor will determine these values at regular intervals.

Treatment should be terminated if white blood cell (leukocyte) and/or platelet values drop to $< 3 \times 10^9/\ell$ or $< 75 \times 10^9/\ell$, respectively. Treatment can be continued after white blood cell values have increased to $> 4 \times 10^9/\ell$ and platelet values to $> 100 \times 10^9/\ell$.

Impaired liver or kidney function

Dependent on the degree of impairment of your liver or kidney function it may be necessary to adjust your dose. Your attending doctor will decide whether a dosage adjustment is necessary.

How it is administered

Treatment with RIBOMUSTIN should be undertaken only by doctors experienced in cancer therapy. Your doctor will give you the exact dose of RIBOMUSTIN 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 RIBOMUSTIN.

Duration of treatment depends on your disease and your response to treatment.

If you are at all worried or have any questions regarding treatment with RIBOMUSTIN, please speak to your doctor.

5. POSSIBLE SIDE EFFECTS

RIBOMUSTIN can have side effects.

Not all side effects reported for RIBOMUSTIN are included in this leaflet. Should your general health worsen or if you experience any untoward effects while taking RIBOMUSTIN, please consult your doctor, pharmacist or other healthcare professional for advice.

Tissue death (necrosis) has been less frequently observed following unintentional injection into the tissue outside blood vessels (extravascular). A burning sensation where the infusion needle is inserted may be a sign of injection into tissue outside the blood vessels. This can cause pain and poorly healing skin defects.

RIBOMUSTIN can cause impaired bone-marrow function, which usually returns to normal after treatment. Suppressed bone-marrow function increases the risk of infection.

Frequent:

- Low counts of white blood cells (leucocytopenia)
- Decrease in the red cells of the blood (haemoglobin)
- Low counts of platelets (thrombocytopenia)
- Low counts of neutrophils (neutropenia)
- Infections including TB
- Hypersensitivity reactions such as allergic inflammation of the skin (dermatitis), nettle rash (urticaria)
- Fatigue
- Feeling sick (nausea)
- Vomiting
- Fever
- Mucosal inflammation
- Bleeding (haemorrhage)
- Increased blood level of creatinine
- Increased blood level of urea
- A rise in liver enzymes AST/ALT
- A rise in the enzyme alkaline phosphatase
- A rise in bile pigment
- Low potassium blood levels
- Impaired function (dysfunction) of the heart
- Palpitations
- Low or high blood pressure (hypotension or hypertension)
- Impaired lung function
- Disturbed metabolism caused by dying cancer cells releasing their contents into the bloodstream

- Reduction in red blood cells which can make the skin pale and cause weakness (anaemia)
- Diarrhoea
- Constipation
- Dehydration
- Sore mouth (stomatitis)
- Loss of appetite
- Hair loss
- Skin changes
- Missed periods (amenorrhoea)
- Pain
- Insomnia
- Chills

Less frequent:

- Accumulation of fluid in the heart sac (escape of fluid into the pericardial space)
- Infection of the blood (sepsis)
- Severe allergic hypersensitivity reactions (anaphylactic reactions)
- Signs similar to anaphylactic reactions (anaphylactoid reactions)
- Drowsiness
- Loss of voice (aphonia)
- Acute circulatory collapse
- Reddening of the skin (erythema)
- Inflammation of the skin (dermatitis)
- Itching (pruritus)
- Skin rash (macular exanthema)

- Excessive sweating (hyperhidrosis)
- Primary atypical inflammation of the lungs (pneumonia)
- Break-down of red blood cells (haemolytic anaemia)
- Rapid 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)
- Disease of the nervous system (anticholinergic syndrome)
- Neurological disorders
- Lack of coordination (ataxia)
- Inflammation of the brain (encephalitis)
- Increased heart rate (tachycardia)
- Heart attack, chest pain (myocardial infarct)
- Heart failure
- Inflammation of the veins (phlebitis)
- Formation of scar tissue in the lungs (fibrosis of the lungs)
- Inflammation and bleeding of the gullet (haemorrhagic oesophagitis)
- Bleeding of stomach or gut
- Infertility
- Multiple organ failure

There have been reports of secondary tumours (myelodysplastic syndrome, acute myeloid leukaemia, bronchial carcinoma) following treatment with RIBOMUSTIN.

Severe skin reactions (Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis) have been reported.

6. STORING AND DISPOSING OF RIBOMUSTIN

Keep out of the reach and sight of children.

Storage conditions:

Store at or below 25 °C.

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

Note on shelf-life after opening or preparing the solution

Solutions for infusions prepared according to the directions listed are stable in polyethylene bags at 25 °C for 3,5 hours, and in a refrigerator they are stable for 2 days.

RIBOMUSTIN contains no preservatives. The solutions should therefore not be used after these lengths of time.

7. PRESENTATION OF RIBOMUSTIN

RIBOMUSTIN 25 mg is available in Type I brown glass vials of 26 ml with 20 mm grey bromobutyl/silicate rubber stopper and an aluminium flip-off cap with a blue polypropylene disc. 26 ml vials contain 25 mg bendamustine hydrochloride and are supplied in packs of 1, 5, 10 and 20 vials.

RIBOMUSTIN 100 mg is available in Type I brown glass vials of 60 ml with 20 mm grey bromobutyl/silicate rubber stopper and an aluminium flip-off cap with a blue polypropylene disc. 60 ml vials contain 100 mg bendamustine hydrochloride and are supplied in packs of 1 and 5 vials.

8. IDENTIFICATION OF RIBOMUSTIN

White, microcrystalline lyophilisate (powder).

9. REGISTRATION NUMBER/REFERENCE NUMBER

RIBOMUSTIN 25 mg: 45/26/1127

RIBOMUSTIN 100 mg: 45/26/1128

10. NAME AND ADDRESS OF REGISTRATION HOLDER

Astellas Pharma (Pty) Ltd, EOH Business Park, Gillooly's View, 5 Osborne Lane,
Bedfordview, 2007

11. DATE OF PUBLICATION

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Date of most recently revised package insert as approved by Council :

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