PROPOSED PATIENT INFORMATION LEAFLET

SCHEDULING STATUS S4

PRODUCT NAME, strength and pharmaceutical form

RIBEND (bendamustine hydrochloride) 25 mg: Powder for concentrate for solution for infusion – For single use only.

RIBEND (bendamustine hydrochloride) 100 mg: Powder for concentrate for solution for infusion – For single use only.

For fill list of excipients: **see section 6**

Sugar free

Read all this leaflet carefully before you are given RIBEND

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

What is in this leaflet

1. What RIBEND is and what is it used for:

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

RIBEND 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 RIBEND:

RIBEND should not be administered to you:

- if you are hypersensitive (allergic) to the active ingredient bendamustine hydrochloride or to any of the other ingredients of **RIBEND** (listed in section 6).
- 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 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 one accompanied by a reduction in white blood cells (leucopenia).
- in combination with yellow fever vaccines or other live attenuated vaccines.

Warnings and precautions

Special care should be taken with RIBEND:

Tell your doctor or health care provider before being given **RIBEND** if you have or had:

- 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 **RIBEND**, 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 **RIBEND**. 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 **RIBEND**. Your doctor will be aware of this and may give you medicines to help prevent it.
- If you have or had hepatitis B virus

If you are a man receiving treatment with **RIBEND** 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.

Other medicines and RIBEND

Always tell your health care provider if you are taking any other medicine. (This includes all complementary or traditional medicines.)

If **RIBEND** 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 **RIBEND**.

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

Pregnancy and breastfeeding and fertility:

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

Pregnancy:

RIBEND can cause genetic damage and has caused malformations in animal studies. You should not use **RIBEND** 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 **RIBEND**. If you become pregnant during your treatment with **RIBEND** 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 **RIBEND** and for up to 6 months after treatment has stopped. There is a risk that treatment with **RIBEND** will lead to infertility and you may wish to seek advice on conservation of your sperm cells before your treatment starts.

Breastfeeding:

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

Driving and using machines:

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

It is not always possible to predict to what extent **RIBEND** may interfere with the daily activities of a patient. Patients should ensure that they do not engage in the above activities until they are aware of the measure to which **RIBEND** affects them.

3. How to use RIBEND:

You will not be expected to give yourself **RIBEND**. It will be given to you by a person who is qualified to do so.

RIBEND 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 x 10^9/L and/or your blood platelets have fallen to counts below 75 x 10^9/L.

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 x 10^9/L or < 75 x 10^9/L, respectively. Treatment can be continued after white blood cell values have increased to > 4 x 10^9/L and platelet values to > 100 x 10^9/L.

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 **RIBEND** should be undertaken only by doctors experienced in cancer therapy. Your doctor will give you the exact dose of **RIBEND** 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 **RIBEND**. 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 **RIBEND**, please speak to your doctor.

4. Possible side effects

RIBEND can have side effects.

Not all side effects reported for **RIBEND** are included in this leaflet. Should your general health worsen or if you experience any untoward effects while taking **RIBEND**, please consult your health care provider for advice.

If any of the following happens, tell your doctor immediately or go to the casualty department at your nearest hospital:

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.

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

Tell your doctor if you notice any of the following:

Frequent side effects:

- Infections (including shingles, cytomegalovirus, hepatitis B virus infection).
- Tumor lysis syndrome (disturbed metabolism caused by dying cancer cells releasing their contents into the bloodstream).
- Headache, insomnia (sleeping problems), dizziness.
- 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 side effects:

- Acute myeloid 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).
- 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)
- Feeling unwell 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
- Irregular heartbeats
- A rare type of anaemia in which red blood cells, white blood cells and platelets are reduced (pancytopenia).
- Bleeding or bruising more easily than normal (bone marrow failure)

Frequency not known side effects:

- Liver failure.

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

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

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 or pharmacist or nurse. You can also report side effects to SAHPRA 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 **RIBEND.**

5. How to store RIBEND

Storage conditions:

Store at or below 25 °C.

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

STORE ALL MEDICINE OUT OF REACH OF CHILDREN

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

6. Contents of the pack and other information

What RIBEND contains:

The active substance in **RIBEND** is bendamustine hydrochloride.

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

RIBEND 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.

What RIBEND looks like and contents of the pack

RIBEND 25 mg: White, microcrystalline lyophilisate.

RIBEND 100 mg: White, microcrystalline lyophilizate.

Holder of Certificate of Registration

Innovata Pharmaceuticals (Pty) LTD

Crownwood Office Park

100 Northern Parkway

Ormonde

Johannesburg

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South Africa

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New

Registration number

TBI

Access to the corresponding Professional information.

A copy of the professional Information is contained in the packaging of **RIBEND**.