1.6.3 Patient information leaflet (PIL)

The Patient information leaflet (PIL) for the product - **RILAST 500** (Rituximab 500 mg/50 mL, Single use vial) is enclosed in the following pages.

PATIENT INFORMATION LEAFLET

Rituximab 100 mg and 500 mg concentrate for solution for infusion

1. Composition

Each mL contains 10 mg of Rituximab

50 mL vial: Each single-use vial contains 500 mg of Rituximab

10 mL vial: Each single-use vial contains 100 mg of Rituximab

2. Product description

Rituximab is a type of protein called a “monoclonal antibody”. It sticks to the surface of a type of white blood cell called “B-Lymphocyte”. When rituximab sticks to the surface of this cell, the cell dies.

3. Presentation

Rituximab is 10/50 ml injection clear glass vial, supplied as a concentrate for solution for infusion.

- 10 mL vial is available as a pack of 1 vial
- 50 mL vial is available as a pack of 1 vial

4. What it is used for indication

Rituximab is used to treat non-Hodgkin’s lymphoma, chronic lymphocytic leukaemia (both are types of blood cancer) and rheumatoid arthritis (inflammatory disorder affecting many joints), Granulomatosis with polyangiitis and microscopic polyangiitis (GPA & MPA).

5. How to use: method of administration, route of administration, dosage

Rituximab is given by infusion through a needle placed in a vein (intravenous infusion), in your arm by a healthcare professional. The usual dose of rituximab when it is given on its own is 375 mg per square metre body surface area, once a week for four to eight weeks.

For non-Hodgkin’s lymphoma rituximab is usually given in combination with chemotherapy medicines. The usual dose of rituximab is 375 mg per square metre body surface area on day one of each chemotherapy cycle, for up to eight cycles depending on the type of chemotherapy.

For chronic lymphocytic leukaemia rituximab is given in combination with chemotherapy medicines at a dose of 375 mg per square metre body surface area on day one of the first chemotherapy cycle, followed by 500 mg per square metre body surface area for each subsequent chemotherapy cycle, for six cycles in total.

For rheumatoid arthritis, each course of treatment is made up of two separate infusions which are given 2 weeks apart. Repeated courses of treatment with Rituximab are possible. Depending on the signs and symptoms of your disease, your doctor will decide when you should receive more Rituximab.

For Granulomatosis with polyangiitis and microscopic polyangiitis (GPA & MPA), treatment with Rituximab uses four separate infusions given at weekly intervals. Corticosteroids will usually be given by

injection before the start of Rituximab treatment. Corticosteroids given by mouth may be started at any time by your doctor to treat your condition.

Your physician may decide to change your treatment or give you more courses of treatment with rituximab, depending on your condition and your response to the medicine.

6. When do not take this drug: contraindication

Do not take Rituximab if:

- you are allergic to rituximab, other proteins which are like rituximab
- you have history of progressive multifocal leukoencephalopathy (inflammation of the white matter in brain)
- you have a severe active infection at the moment
- you have a weak immune system.
- you have severe heart failure or severe uncontrolled heart disease and have rheumatoid arthritis, granulomatosis with polyangiitis or microscopic polyangiitis.

7. Adverse reaction

Like all medicines, this medicine can cause side effects, although not everybody gets them. Most side effects are mild to moderate but some may be serious and require treatment. Rarely, some of these reactions have been fatal.

Infusion reactions

During or within the first 2 hours of the first infusion you may develop fever, chills and shivering. Less frequently, some patients may experience pain at the infusion site, blisters, itching, sickness, tiredness, headache, breathing difficulties, tongue or throat swelling, itchy or runny nose, vomiting, flushing or palpitations, heart attack or low number of platelets. If you have heart disease or angina, these reactions might get worse. Tell the person giving you the infusion immediately if you develop any of these symptoms, as the infusion may need to be slowed down or stopped. You may require additional treatment such as an antihistamine or paracetamol. When these symptoms go away, or improve, the infusion can be continued. These reactions are less likely to happen after the second infusion. Your physician may decide to stop your rituximab treatment if these reactions are serious.

Infections

Tell your physician immediately if you get signs of an infection including:

- fever, cough, sore throat, burning pain when passing urine or feeling weak or generally unwell
- memory loss, trouble thinking, difficulty walking or sight loss – these may be due to a very rare, serious brain infection, which has been fatal (Progressive Multifocal Leukoencephalopathy or PML).

You might get infections more easily during your treatment with rituximab.

These are often colds, but there have been cases of pneumonia or urinary infections. These are listed below under “Other side effects”.

Skin Reactions

Very rarely, severe blistering skin conditions that can be life-threatening may occur. Redness, often associated with blisters, may appear on the skin or on mucous membranes, such as inside the mouth, the genital areas or the eyelids, and fever may be present. Tell your physician immediately if you experience any of these symptoms.

Other side effects include:

If you are being treated for non-Hodgkin's Lymphoma or chronic lymphocytic leukaemia

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

- bacterial or viral infections, bronchitis
- low number of white blood cells, with or without fever or blood cells called "platelets"
- feeling sick (nausea)
- bald spots on the scalp, chills, headache
- lower immunity – because of lower levels of anti-bodies called "immunoglobulins" (IgG) in the blood which help protect against infection

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

- infections of the blood (sepsis), pneumonia, shingles, cold, bronchial tube infections, fungal infections, infections of unknown origin, sinus inflammation, hepatitis B
- low number of red blood cells (anaemia), low number of all blood cells
- allergic reactions (hypersensitivity)
- high blood sugar level, weight loss, swelling in the face and body, high levels of the enzyme "LDH" in the blood, low calcium levels in the blood
- unusual feelings of the skin – such as numbness, tingling, pricking, burning, a creeping skin feeling, reduced sense of touch
- feeling restless, problems falling asleep
- becoming very red in the face and other areas of the skin as a consequence of dilation of the blood vessels
- feeling dizzy or anxious
- producing more tears, tear duct problems, inflamed eye (conjunctivitis)
- ringing sound in the ears, ear pain
- heart problems – such as heart attack, uneven or fast heart rate
- high or low blood pressure (low blood pressure especially when standing upright)
- tightening of the muscles in the airways which causes wheezing (bronchospasm), inflammation, irritation in the lungs, throat or sinuses, being short of breath, runny nose
- being sick (vomiting), diarrhoea, pain in the stomach, irritation or ulcers in the throat and mouth, problems swallowing, constipation, indigestion
- eating disorders, not eating enough, leading to weight loss
- hives, increased sweating, night sweats
- muscle problems – such as tight muscles, joint or muscle pain, back and neck pain
- general discomfort or feeling uneasy or tired, shaking, signs of flu
- multiple-organ failure.

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

- blood clotting problems, decrease of red blood cell production and increase of red blood cell destruction (aplastic haemolytic anaemia), swollen or enlarged lymph nodes
- low mood and loss of interest or enjoyment in doing things, feeling nervous
- taste problems – such as changes in the way things taste
- heart problems – such as reduced heart rate or chest pain (angina) asthma, too little oxygen reaching the body organs
- swelling of the stomach.

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

- short term increase in the amount of some types of anti-bodies in the blood (called immunoglobulins – IgM), chemical disturbances in the blood caused by break-down of dying cancer cells
- nerve damage in arms and legs, paralysed face
- heart failure
- inflammation of blood vessels including those leading to skin symptoms
- respiratory failure
- damage to the intestinal wall (perforation)
- Severe skin problems causing blisters that can be life-threatening. Redness, often associated with blisters, may appear on the skin or on mucous membranes, such as inside the mouth, the genital areas or the eyelids, and fever may be present.
- kidney failure
- severe vision loss
- Not known (it is not known how often these side effects happen): a reduction in white blood cells which does not happen straight away
- reduced platelets number just after the infusion – this can be reversed, but can be fatal in rare cases
- hearing loss, loss of other senses

b) If you are being treated for rheumatoid arthritis

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

- Infections such as pneumonia (bacterial)
- Pain on passing water (urinary tract infection)
- Allergic reactions that are most likely to occur during an infusion, but can occur up-to 24-hours after infusion
- Changes in blood pressure, nausea, rash, fever, feeling itchy, runny or blocked nose and sneezing, shaking, rapid heart beat, and tiredness
- Headache
- Changes in laboratory tests carried out by your physician. These include a decrease in the amount of some specific proteins in the blood (immunoglobulins) which help protect against infection.

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

- Infections such as bronchial tube inflammation (bronchitis)
- A feeling of fullness or a throbbing pain behind the nose, cheeks and eyes (sinusitis), pain in the abdomen, vomiting and diarrhoea, breathing problems
- Fungal foot infection (athlete's foot)
- High cholesterol levels in the blood
- Abnormal sensations of the skin, such as numbness, tingling, pricking or burning, sciatica, migraine, dizziness
- Loss of hair
- Anxiety, depression
- Indigestion, diarrhoea, acid reflux, irritation and /or ulceration of the throat and the mouth
- Pain in the tummy, back, muscles and/or joints

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

- Excess fluid retention in the face and body
- Inflammation, irritation and / or tightness of the lungs, and throat, coughing
- Skin reactions including hives, itching and rash
- Allergic reactions including wheezing or shortness of breath, swelling of the face and tongue, collapse

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

- A complex of symptoms occurring within a few weeks of an infusion of rituximab including allergic like reactions such as rash, itching, joint pain, swollen lymph glands and fever
- severe blistering skin conditions that can be life-threatening. Redness, often associated with blisters, may appear on the skin or on mucous membranes, such as inside the mouth, the genital areas or the eyelids, and fever may be present.

Other rarely-reported side-effects due to rituximab include a decreased number of white cells in the blood (neutrophils) that help to fight against infection.

c) If you are being treated for granulomatosis with polyangiitis or microscopic polyangiitis

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

- infections, such as chest infections, urinary tract infections (pain on passing water), colds and herpes infections
- allergic reactions that are most likely to occur during an infusion, but can occur up-to 24-hours after infusion
- diarrhoea
- coughing or shortness of breath
- nose bleeds
- raised blood pressure
- painful joints or back
- muscle twitches or shakiness
- feeling dizzy
- tremors (shakiness, often in the hands)
- difficulty sleeping (insomnia)
- swelling of the hands or ankles

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

- indigestion
- constipation
- skin rashes, including acne or spots
- flushing or redness of the skin
- blocked nose
- tight or painful muscles
- pain in the muscles or in the hands or feet
- low number of red blood cells (anaemia)
- low numbers of platelets in the blood
- an increase in the amount of potassium in the blood
- changes in the rhythm of the heart, or the heart beating faster than normal

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

- severe blistering skin conditions that can be life-threatening. Redness, often associated with blisters, may appear on the skin or on mucous membranes, such as inside the mouth, the genital areas or the eyelids, and fever may be present.
- recurrence of a previous Hepatitis B infection

Rituximab may also cause changes in laboratory tests carried out by your doctor.
If you are having Rituximab with other medicines, some of the side effects you may get may be due to the other medicines.

8. What you should avoid to use with this drug: interaction with other medicines and food

Tell your physician or pharmacist if you are taking, have recently taken or might take any other medicines. This includes medicines obtained without a prescription and herbal medicines. This is because rituximab can affect the way some other medicines work. Also some other medicines can affect the way rituximab works.

Concomitant administration of methotrexate or cyclophosphamide did not alter the pharmacokinetics of Rituximab. Rituximab have no or negligible influence on the ability to drive and use machines.

9. What to do if missing a dose

Do not take a double dose to make up for a missed dose.

10. Storage condition: temperature

Keep this medicine out of the sight and reach of children. Store in a refrigerator (2 °C – 8 °C). Keep the container in the outer carton in order to protect from light.

11. Overdosage handling: signs and symptoms of overdose, what should you do if you overdose

Overdosage with rituximab was not observed. In case of overdose, medication should be stopped and contact your physician or pharmacist.

12. Warning and precaution

Talk to your physician or pharmacist, before you are given rituximab if:

- you have ever had or might now have a hepatitis infection. This is because in a few cases, rituximab could cause hepatitis B to become active again, which can be fatal in very rare cases. Patients who have ever had hepatitis B infection will be carefully checked by their physician for signs of this infection
- you have ever had heart problems (such as angina, palpitations or heart failure) or breathing problems.

If any of the above apply to you (or you are not sure), talk to your physician or pharmacist before you are given Rituximab. Your physician may need to take special care of you during your treatment with Rituximab.

If you have rheumatoid arthritis, granulomatosis with polyangiitis or microscopic polyangiitis also tell your physician

- if you think you may have an infection, even a mild one like a cold. The cells that are affected by rituximab help to fight infection and you should wait until the infection has passed before you are given rituximab. Also please tell your physician if you had a lot of infections in the past or suffer from severe infections.
- if you think you may need any vaccinations in the near future, including vaccinations needed to travel to other countries. Some vaccines should not be given at the same time as rituximab or in the months after you receive rituximab. Your physician will check if you should have any vaccines before you receive rituximab.

Tell to your physician:

- if you are taking medicines for high blood pressure. You may be asked not to take these other medicines 12 hours before you are given rituximab. This is because some people have a fall in their blood pressure while they are being given rituximab.
- if you have ever taken medicines which affect your immune system – such as chemotherapy or immune-suppressive medicines.

If any of the above apply to you (or you are not sure), talk to your physician or pharmacist before you are given rituximab.

Children and adolescents

Talk to your physician or pharmacist before you are given this medicine if you, or your child, are under 18 years of age. This is because there is not much information about the use of rituximab in children and young people.

Pregnancy and breast-feeding

You must tell your physician if you are pregnant, think that you might be pregnant or are planning to become pregnant. This is because rituximab can cross the placenta and may affect your baby.

If you can get pregnant, you and your partner must use an effective method of contraception while using rituximab. You must also do this for 12 months after your last treatment with rituximab.

Do not breast-feed while you are being treated with rituximab. Also do not breast-feed for 12 months after your last treatment with rituximab. This is because rituximab may pass into breast milk.

13. When to consult a physician, pharmacist

Consult your physician or pharmacist, in case of any problems with the product.

14. Shelf-life

30 Months

15. Name, address, logo (if have) of manufacture

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