B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Ituxredi 100 mg concentrate for solution for infusion
Ituxredi 500 mg concentrate for solution for infusion
rituximab

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Ituxredi is and what it is used for

What Ituxredi is
Ituxredi contains the active substance "rituximab". This 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.

What Ituxredi is used for
Ituxredi may be used for the treatment of several different conditions in adults and children. Your doctor may prescribe rituximab for the treatment of:

a) Non-Hodgkin's Lymphoma
This is a disease of the lymph tissue (part of the immune system) that affects a type of white blood cell called B-Lymphocytes.
In adults rituximab can be given alone or with other medicines called "chemotherapy".
In adult patients where the treatment is working, rituximab may be used as a maintenance treatment for 2 years after completing the initial treatment.
In children and adolescents, rituximab is given in combination with "chemotherapy".

b) Chronic lymphocytic leukaemia
Chronic lymphocytic leukaemia (CLL) is the most common form of adult leukaemia. CLL affects a particular lymphocyte, the B cell, which originates from the bone marrow and develops in the lymph nodes. Patients with CLL have too many abnormal lymphocytes, which accumulate mainly in the bone marrow and blood. The proliferation of these abnormal B-lymphocytes is the cause of symptoms you may have. Rituximab in combination with chemotherapy destroys these cells which are gradually removed from the body by biological processes.

c) Rheumatoid arthritis

Rituximab is used for the treatment of rheumatoid arthritis. Rheumatoid arthritis is a disease of the joints. B lymphocytes are involved in the cause of some of the symptoms you have. Rituximab is used to treat rheumatoid arthritis in people who have already tried some other medicines which have either stopped working, have not worked well enough or have caused side effects. Rituximab is usually taken together with another medicine called methotrexate.
Rituximab slows down the damage to your joints caused by rheumatoid arthritis and improves your ability to do normal daily activities.
The best responses to rituximab are seen in those who have a positive blood test to rheumatoid factor (RF) and/or anti-Cyclic Citrullinated Peptide (anti-CCP). Both tests are commonly positive in rheumatoid arthritis and aid in confirming the diagnosis.

d) Granulomatosis with polyangiitis or microscopic polyangiitis
Rituximab is used for the treatment of adults and children 2 years of age and older with granulomatosis with polyangiitis (formerly called Wegener's granulomatosis) or microscopic polyangiitis, taken in combination with corticosteroids.
Granulomatosis with polyangiitis and microscopic polyangiitis are two forms of inflammation of the blood vessels which mainly affects the lungs and kidneys, but may affect other organs as well. B lymphocytes are involved in the cause of these conditions.

e) Pemphigus vulgaris
Rituximab is used for the treatment of patients with moderate to severe pemphigus vulgaris.
Pemphigus vulgaris is an autoimmune condition that causes painful blisters on the skin and lining of the mouth, nose, throat and genitals.

2. What you need to know before you use Ituxredi

Do not take Ituxredi if
- you are allergic to rituximab, other proteins which are like rituximab, or any of the other ingredients of this medicine (listed in section 6)
- 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, microscopic polyangiitis or pemphigus vulgaris.

Do not have rituximab if any of the above apply to you. If you are not sure, talk to your doctor, pharmacist or nurse before you are given rituximab.

Warnings and precautions
Talk to your doctor, pharmacist or nurse 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 doctor 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 doctor, pharmacist or nurse before you are given rituximab. Your doctor may need to take special care of you during your treatment with rituximab.

Also talk to your doctor 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 doctor will check if you should have any vaccines before you receive rituximab.

If you have rheumatoid arthritis, granulomatosis with polyangiitis, microscopic polyangiitis orpemphigus vulgaris also tell your doctor
- 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 doctor if you had a lot of infections in the past or suffer from severe infections.

Children and adolescents
Non-Hodgkin's lymphoma
Rituximab can be used for the the treatment of children and adolescents, 6 months of age and older, with non-Hodgkin's lymphoma, specifically CD20 positive diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma (BL)/Burkitt leukaemia (mature B-cell acute leukaemia) (BAL) or Burkitt-like lymphoma (BLL).
Talk to your doctor, pharmacist or nurse before you are given this medicine if you, or your child, are under 18 years of age.

Granulomatosis with polyangiitis or microscopic polyangiitis
Rituximab can be used for treatment of children and adolescents, 2 years of age and older, with granulomatosis with polyangiitis (formerly called Wegener's granulomatosis) or microscopic polyangiitis. There is not much information about the use of rituximab in children and adolescents with other diseases.

Talk to your doctor, pharmacist or nurse before you are given this medicine if you, or your child, are under 18 years of age.

Other medicines and Ituxredi
Tell your doctor, pharmacist or nurse 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.

In particular, tell your doctor:
- 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 doctor, pharmacist or nurse before you are given rituximab.

Pregnancy and breast-feeding
You must tell your doctor or nurse 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.
Rituximab passes into breast milk in very small amounts. As the long-term effects on breastfed infants are not known, for precautionary reasons, breast-feeding is not recommended during treatment with rituximab and for 6 months after the treatment.

Driving and using machines
It is not known whether rituximab has an effect on you being able to drive or use any tools or machines.

Ituxredi contains sodium
This medicine contains 52.2 mg sodium (main component of the cooking/table salt) in each 10 ml vial and 261.2 mg in each 50 ml vial.
This is equivalent to 2.6% (for 10ml vial) and 13.2% (for 50ml vial) of the recommended maximum daily dietary intake of sodium for an adult.

3. How Ituxredi is given

How it is given
Ituxredi will be given to you by a doctor or nurse who is experienced in the use of this treatment. They will watch you closely while you are being given this medicine. This is in case you get any side effects.
You will always be given Ituxredi as a drip (intravenous infusion).

Medicines given before each Ituxredi administration
Before you are given Ituxredi, you will be given other medicines (pre-medication) to prevent or reduce possible side effects.

How much and how often you will receive your treatment

a) If you are being treated for non-Hodgkin's Lymphoma
- *If you are having Ituxredi alone*
  Ituxredi will be given to you once a week for 4 weeks. Repeated treatment courses with rituximab are possible.
- *If you are having Ituxredi with chemotherapy*
  Ituxredi will be given to you on the same day as your chemotherapy. This is usually given every 3 weeks up to 8 times.
- If you respond well to treatment, you may be given Ituxredi as a maintenance treatment every 2 or 3 months for two years. Your doctor may change this, depending on how you respond to the medicine.
- If you are less than 18 years of age, you will be given Ituxredi with chemotherapy. You will receive Ituxredi up to 6 times over a 3.5 – 5.5 month period.

b) If you are being treated for chronic lymphocytic leukaemia
When you are treated with rituximab in combination with chemotherapy, you will receive Ituxredi infusions on day 0 cycle 1 then day 1 of each cycle for 6 cycles in total. Each cycle has a duration of 28 days. The chemotherapy should be given after the rituximab infusion. Your doctor will decide if you should receive concomitant supportive therapy.

c) If you are being treated 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. This may be months from now.

d) If you are being treated for granulomatosis with polyangiitis or microscopic polyangiitis
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 mouthmay be started at any time by your doctor to treat your condition.
If you are 18 years of age and older and respond well to treatment, you may be given rituximab as a maintenance treatment. This will be administered as 2 separate infusions which are given 2 weeks apart, followed by 1 infusion every 6 months for at least 2 years. Your doctor may decide to treat you longer with rituximab (up to 5 years), depending on how you respond to the medicine.

e) If you are being treated for pemphigus vulgaris
Each course of treatment is made up of two separate infusions which are given 2 weeks apart. If you respond well to treatment, you may be given rituximab as a maintenance treatment. This will be administered 1 year and 18 months after the initial treatment and then every 6 months as needed or your doctor may change this, depending on how you respond to the medicine.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

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 24 hours of the infusion you may develop fever, chills and shivering. Less frequently, some patients may experience pain at the infusion site, blisters, itching, sickness (nausea), tiredness, headache, breathing difficulties, blood pressure raised, wheezing, throat discomfort, 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 or your child develops 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 doctor may decide to stop your rituximab treatment if these reactions are serious.

Infections
Tell your doctor immediately if you or your child gets 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).
- fever, headache and stiff neck, incoordination (ataxia), personality change, hallucinations, altered consciousness, seizures or coma – these may be due to a serious brain infection (enteroviral meningoencephalitis), which can be fatal.

You might get infections more easily during your treatment with rituximab.
These are often colds, but there have been cases of pneumonia, urinary infections and serious viral infections. These are listed below under “Other side effects”.

If you are being treated for rheumatoid arthritis, granulomatosis with polyangiitis, microscopic polyangiitis or pemphigus vulgaris, you will also find this information in the Patient Alert Card you have been given by your doctor. It is important that you keep this Alert Card and show it to your partner or caregiver.

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 doctor immediately if you experience any of these symptoms.

Other side effects include:

a) If you or your child 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
- tumour 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
- brain and meningeal infection/inflammation (enteroviral meningoencephalitis)

Children and adolescents with non-Hodgkin's lymphoma:
In general, side effects in children and adolescents with non-Hodgkin's lymphoma were similar to those in adults with non-Hodgkin's lymphoma or chronic lymphocytic leukaemia. The most common side effects seen were fever associated with low levels of a type of white blood cell (neutrophil), inflammation or sores in the lining of the mouth, and allergic reactions (hypersensitivity).

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 doctor. 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

Not known (frequency cannot be estimated from the available data):
- Serious viral infection
- brain and meningeal infection/inflammation (enteroviral meningoencephalitis)

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. Some infections may be severe (please see information on *Infections* within this section).

c) If you or your child 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
- Fever
- Blocked or runny 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

Not known (frequency cannot be estimated from the available data):
- Serious viral infection
- brain and meningeal infection/inflammation (enteroviral meningoencephalitis)

Children and adolescents with granulomatosis with polyangiitis or microscopic polyangiitis
In general, side effects in children and adolescents with granulomatosis with polyangiitis or microscopic polyangiitis were of a similar type to those in adults with granulomatosis with polyangiitis or microscopic polyangiitis. Most common side effects seen were infections, allergic reactions and feeling sick (nausea).

d) If you are being treated for pemphigus vulgaris

Very common side effects (may affect more than 1 in 10 people):
- Allergic reactions that are most likely to occur during an infusion, but can occur up to 24 hours after infusion
- Headache
- Infections such as chest infections
- Long lasting depression
- Loss of hair

Common side effects (may affect up to 1 in 10 people):
- Infections such as common cold, herpes infections, eye infection, oral thrush and urinary tract infections (pain on passing urine)
- Mood disorders such as irritability and depression
- Skin disorders such as itching, hives, and benign lumps
- Feeling tired or dizzy
- Fever
- Painful joints or back
- Pain in the tummy
- Pain in the muscles
- Heart beating faster than normal

Not known (frequency cannot be estimated from the available data):
- Serious viral infection
- brain and meningeal infection/inflammation (enteroviral meningoencephalitis)

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.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist, or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the Yellow Card Scheme website www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Ituxredi

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C – 8°C). Do not freeze. Keep the container in the outer carton in order to protect from light.

- After aseptic dilution in sodium chloride solution

The prepared infusion solution of Ituxredi in 0.9% sodium chloride solution is physically and chemically stable for 60 days at 5±3°C and 30 days at 25±2°C.

- After aseptic dilution in Dextrose solution

The prepared infusion solution of Ituxredi in 5% Dextrose solution is physically and chemically stable for 48 hours at 2°C - 8°C and 25±2ºC.

From a microbiological point of view, the prepared infusion solution should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C – 8°C.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines that you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Ituxredi contains

The active ingredient in Ituxredi is called rituximab. The 10 ml vial contains 100 mg of rituximab (10 mg/ml). The 50 ml vial contains 500 mg of rituximab (10 mg/ml).

The other ingredients are sodium citrate (E331), citric acid (E330), polysorbate 80 (E433), sodium chloride, and water for injections.

What Ituxredi looks like and contents of the pack

Ituxredi is a clear to opalescent, colourless to yellowish solution, supplied as a concentrate for solution for infusion in a glass vials.
Each pack contains either 1 vial or 2 vials of Ituxredi.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

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