Blitzima®

Patient information leaflet BLITZIMA

SCHEDULING STATUS S4

PROPRIETARY NAME, STRENGTH AND PHARMACEUTICAL FORM
BLITZIMA 100 mg concentrate for solution for infusion
BLITZIMA 500 mg concentrate for solution for infusion

Read all of this leaflet carefully before you start using BLITZIMA
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- **BLITZIMA** 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 BLITZIMA CONTAINS
Each ml contains 10 mg rituximab.
Each vial contains 100 mg (in 10 ml) or 500 mg (in 50 ml) rituximab.
The other ingredients are polysorbate 80, sodium chloride, tri-sodium citrate dihydrate, water for injections.
Sugar free.

2. WHAT BLITZIMA IS USED FOR
BLITZIMA may be used for the treatment of several different conditions in adults. Your doctor may prescribe **BLITZIMA** for the treatment of:
- Non-Hodgkin's Lymphoma
- Chronic lymphocytic leukaemia
- Granulomatosis with polyangiitis or microscopic polyangiitis

3. BEFORE YOU USE BLITZIMA
Do not use BLITZIMA if:
- you are hypersensitive (allergic) to rituximab, other proteins which are like rituximab, or any of the other ingredients of **BLITZIMA** (see **WHAT BLITZIMA CONTAINS**).
- you have a severe active infection at the moment, infection with tuberculosis (TB), or have recently been in close contact with someone who has a tuberculosis (TB) infection.
- you have a weak immune system
- you have severe heart failure or severe uncontrolled heart disease and have granulomatosis with polyangiitis or microscopic polyangiitis.

Do not use **BLITZIMA** if any of the above apply to you. If you are not sure, talk to your doctor, pharmacist or nurse before you use **BLITZIMA.**

Take special care with BLITZIMA:
Talk to your doctor, pharmacist or nurse before you use **BLITZIMA** if:
- you have ever been diagnosed with or might currently have a tuberculosis (TB) infection. This is because **BLITZIMA** could cause the tuberculosis infection to become active again. For this reason, your doctor may test for tuberculosis and indicate that you require preventative treatment for tuberculosis infection before using **BLITZIMA.** If the test is negative your doctor may monitor and periodically test for TB infection during your treatment with **BLITZIMA.**
- you have ever had or might now have a hepatitis infection. This is because in a few cases, **BLITZIMA** 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 use **BLITZIMA.** Your doctor may need to take special care during your treatment with **BLITZIMA.**

If you have granulomatosis with polyangiitis or microscopic polyangiitis 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 **BLITZIMA** help to fight infection and you should wait until the infection has passed before you use **BLITZIMA**. Also tell your doctor if you have 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 for travel to other countries. Some vaccines should not be given at the same time as **BLITZIMA** or in the months after you receive **BLITZIMA.** Your doctor will check if you should have any vaccines before you use **BLITZIMA.**

Children and adolescents
Talk to your doctor, pharmacist or nurse 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 **BLITZIMA** in children and young people.

Pregnancy and breastfeeding:
If you are pregnant or breastfeeding your baby, please consult your doctor, pharmacist or other healthcare professional for advice before taking **BLITZIMA.**
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 **BLITZIMA** can transfer across 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 **BLITZIMA.** You must also do this for 12 months after your last treatment with **BLITZIMA.**
Do not breastfeed while you are being treated with **BLITZIMA.**
Do not breastfeed for 12 months after your last treatment with **BLITZIMA.** This is because **BLITZIMA** may pass into breast milk.

Driving and using machinery:
BLITZIMA may impair your ability to drive a vehicle or use machines. Take special care before performing tasks requiring your attention, until you know how **BLITZIMA** will affect you.

Taking other medicines with BLITZIMA:
Always tell your healthcare professional if you are taking any other medicine. (This includes complementary or traditional medicines.)
Tell your doctor or pharmacist if you are currently using:
- 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 **BLITZIMA.** This is because some people have a fall in their blood pressure while they are being given **BLITZIMA.**
- if you have ever taken medicines which affect your immune system, such as chemotherapy or immune-suppressive medicines.

4. HOW TO TAKE BLITZIMA
Do not share medicines prescribed for you with any other person.
Always take **BLITZIMA** exactly as your doctor has instructed you.
You should check with your doctor or pharmacist if you are unsure.

How it is given
BLITZIMA 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 **BLITZIMA** as a drip (intravenous infusion).

Medicines given before each BLITZIMA administration
Before you are given **BLITZIMA**, 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 **BLITZIMA** alone*
  BLITZIMA will be given to you once a week for 4 weeks. Repeated treatment courses with **BLITZIMA** are possible.
- *If you are having **BLITZIMA** with chemotherapy*
  BLITZIMA 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 **BLITZIMA** every 2 or 3 months for two years. Your doctor may change this, depending on how you respond to the medicine.

b) If you are being treated for chronic lymphocytic leukaemia
When you are treated with **BLITZIMA** in combination with chemotherapy, you will receive **BLITZIMA** every 28 days until you have received 6 doses. The chemotherapy should be given after the **BLITZIMA** infusion. Your doctor will decide if you should receive other treatment at the same time.

c) If you are being treated for granulomatosis with polyangiitis or microscopic polyangiitis
Treatment with **BLITZIMA** uses four separate infusions given at weekly intervals. A corticosteroid medicine will usually be given by injection before the start of **BLITZIMA** treatment. Corticosteroid medicine given by mouth may be started at any time by your doctor to treat your condition.

If you receive more BLITZIMA than you should:
Since **BLITZIMA** is administered by your doctor or nurse, it is unlikely that you will be given too much. There are no known side effects of receiving too much **BLITZIMA.**

If you forget or miss your BLITZIMA infusion:
If you forget or miss an appointment to receive **BLITZIMA**, make another appointment as soon as possible

5. POSSIBLE SIDE EFFECTS
BLITZIMA can have side effects.
Not all side effects reported for **BLITZIMA** are included in this leaflet.
Should your general health worsen or if you experience any untoward effects while taking **BLITZIMA**, please consult your doctor, pharmacist or other healthcare professional for advice.

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 get 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 infusion 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 doctor may decide to stop your **BLITZIMA** treatment if these reactions are serious.

Infections
Tell your doctor 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 **BLITZIMA.** These are often colds, but there have been cases of pneumonia or urinary infections.

If you are being treated for granulomatosis with polyangiitis or microscopic polyangiitis, 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 have any of these symptoms.

Tell your doctor as soon as possible if you notice any of the following:
a) If you are being treated for non-Hodgkin's Lymphoma or chronic lymphocytic leukaemia
Frequent:
- bacterial or viral infections, bronchitis
- low number of white blood cells sometimes with fever, or low number of 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
- 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 and 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.

Less frequent:
- 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
- short term increase in the amount of some types of antibodies 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

Frequency not known:
- 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 granulomatosis with polyangiitis or microscopic polyangiitis
Frequent:
- 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
- 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

Less frequent:
- 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

BLITZIMA may also cause changes in laboratory tests carried out by your doctor.

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

6. STORING AND DISPOSING OF BLITZIMA
- Store at 2 °C to 8 °C.
- Keep the container in the outer carton in order to protect from light.

- **Diluted product**

The prepared infusion solution of rituximab is physically and chemically stable for 24 hours at 2 °C to 8 °C and subsequently 12 hours at room temperature (not more than 30 °C).
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 to 8 °C, unless dilution has taken place in controlled and validated aseptic conditions.
- **STORE ALL MEDICINES OUT OF REACH OF CHILDREN.**
- Do not use after the expiry date printed on the carton.
- Return all unused medicine to your pharmacist.
- Do not dispose of unused medicine in drains and sewerage systems (e.g. toilets).

7. PRESENTATION OF BLITZIMA
BLITZIMA 100 mg: Clear, colourless, type I glass vial with a chlorobutyl rubber stopper and an aluminium seal with a yellow flip-off cap. Pack of 2 vials.
BLITZIMA 500 mg: Clear, colourless, type I glass vial with a chlorobutyl rubber stopper and an aluminium seal with a dark grey flip-off cap. Pack of 1 vial.

8. IDENTIFICATION OF BLITZIMA
Clear, colourless solution.

9. REGISTRATION NUMBERS
BLITZIMA 100 mg: 53/26/0506
BLITZIMA 500 mg: 53/26/0507

10. NAME AND ADDRESS OF REGISTRATION HOLDER
Adcock Ingram Limited
1 New Road
Erand Gardens
Midrand, 1685
South Africa

11. DATE OF PUBLICATION
25 August 2020

adcock Ingram

HEALTHCARE CELLTRION™

PasiëntInligtingstuk vir BLITZIMA

SKEDULERINGSTATUS S4

EIENDOMSNAAM, STERKTE EN DOSEERVORM
BLITZIMA 100 mg konsentrasie vir oplossing vir infusie
BLITZIMA 500 mg konsentrasie vir oplossing vir infusie

Lees hierdie inligtingstuk sorgvuldig deur voordat u begin om BLITZIMA te gebruik:
- Hou hierdie inligtingstuk. Dit mag nodig wees om dit weer te lees.
- Raadpleeg asseblief u dokter of apteker indien u verdere vrae het.
- **BLITZIMA** is vir u persoonlik voorgeskryf en u moet nie u medisyne met ander persone deel nie. Dit mag skadelik vir hulle wees, selfs al is hul simptome dieselfde as u s'n.

1. WAT BLITZIMA BEVAT
Elke ml bevat 10 mg rituximab.
Elke flessie bevat 100 mg (in 10 ml) of 500 mg (in 50 ml) rituximab.
Die ander bestanddele is polisorbaat 80, natriumchloried, tri-natriumsitraatdihidraat, water vir inspuitings.
Suikervry.

2. WAARVOOR BLITZIMA GEBRUIK WORD
BLITZIMA kan gebruik word vir die behandeling van verskillende toestande in volwassenes. U dokter kan **BLITZIMA** vir die behandeling van die volgende voorskryf:
- Nie-Hodgkin's Limfoom
- Chroniese limfositiese leukemie
- Granulomatose met poliangiitis of mikroskopiese poliangiitis

3. VOORDAT U BLITZIMA GEBRUIK
Moenie BLITZIMA gebruik:
- Indien u hipersensitief (allergies) vir rituximab, ander proteïene wat soos rituximab is, of enige van die ander bestanddele van **BLITZIMA** (sien **WAT BLITZIMA BEVAT**) is nie.
- Indien u tans 'n erge aktiewe infeksie het, infeksie met tuberkulose (TB) het of onlangs in noue kontak was met iemand wat tuberkulose (TB) het nie.
- Indien u 'n swak immuunstelsel het nie.
- Indien u ernstige hartversaking of ernstige ongekontroleerde hartsiekte en granulomatose met poliangiitis of mikroskopies poliangiitis het nie.

Moenie **BLITZIMA** gebruik indien enige van bogenoemde op u van toepassing is nie. Indien u nie seker is nie, raadpleeg u dokter, apteker of verpleegster voordat u **BLITZIMA** gebruik.

Neem spesiale sorg met BLITZIMA:
Raadpleeg u dokter, apteker of verpleegster voordat u **BLITZIMA** gebruik:
- Indien u al ooit asbesdiagnoseer is met tuberkulose (TB) infeksie of dit tans dalk het. Dit is omdat **BLITZIMA** kan veroorsaak dat die tuberkulose infeksie weer aktief word. Vir hierdie rede kan u dokter u toets vir tuberkulose en aandui dat u voorkomende behandeling vir tuberkulose infeksie benodig voordat u begin om **BLITZIMA** te gebruik. Indien die toets negatief is, kan u dokter u monitor en periodiek toets vir TB-infeksie tydens u behandeling met **BLITZIMA.**
- Indien u ooit 'n hepatitis infeksie gehad of dit dalk tans het. Dit is omdat **BLITZIMA** in 'n paar gevalle kan veroorsaak dat hepatitis-B weer aktief word, wat in baie seldsame gevalle noodlottig kan wees. Pasiënte wat ooit hepatitis-B infeksie gehad het, sal sorgvuldig deur hul dokter nagagaan word vir tekens van hierdie infeksie.
- Indien u ooit hartprobleme (soos angina, hartkloppping of harversaking) of asemhalingsprobleme gehad het.

Indien enige van die bogenoemde van u van toepassing is (of indien u nie seker is nie), raadpleeg u dokter, apteker of verpleegster voordat u **BLITZIMA** gebruik. U dokter moet dalk spesiale sorg neem tydens u behandeling met **BLITZIMA.**

Indien u granulomatose met poliangiitis of mikroskopiese poliangiitis het, vertel ook u dokter:
- Indien u dink dat u 'n infeksie het, selfs al is dit 'n ligte een soos verkoue. Die selle wat deur **BLITZIMA** beïnvloed word, help om infeksie te beveg en u moet wag totdat die infeksie verby is voordat u **BLITZIMA** gebruik. Vertel ook u dokter indien u in die verlede baie infeksies gehad het of indien u aan ernstige infeksies ly.
- Indien u dink dat u binnekort enige inentings mag benodig, insluitend inentings vir reis na ander lande. Sommige inentings moet nie gelyktydig saam met **BLITZIMA** gegee word nie, asook nie in die maande nadat u **BLITZIMA** ontvang het nie. U dokter sal seker maak of u enige inentings moet hê voordat u **BLITZIMA** gebruik.

Kinders en adolessente
Raadpleeg u dokter, apteker of verpleegster voordat u hierdie medisyne kry, indien u of u kind jonger as 18 jaar is. Dit is omdat daar nie veel inligting oor die gebruik van **BLITZIMA** by kinders en jongmense is nie.

Swangerskap en borsvoeding:
Indien u swanger is of u baba borsvoed, raadpleeg asseblief u dokter, apteker of ander gesondheidsorgkundige vir advies voordat u **BLITZIMA** begin neem.
U moet u dokter of verpleegster vertel indien u swanger is, dink dat u dalk swanger is of beplan om swanger te raak. Dit is omdat **BLITZIMA** oor die plasenta kan beweeg en u baba kan beïnvloed.
Indien u swanger kan raak, moet u en u maat 'n doeltreffende voorbehoedmetode gebruik terwyl u **BLITZIMA** gebruik. U moet dit ook 12 maande na u laaste behandeling met **BLITZIMA** doen.
Moenie borsvoed terwyl u met **BLITZIMA** behandel word nie.
Moenie borsvoed vir 12 maande na u laaste behandeling met **BLITZIMA** nie. Dit is omdat **BLITZIMA** in borsmelk oorgedra word.

Bestuur en gebruik van masjinerie:
BLITZIMA kan u vermoë om voertuie te bestuur of masjiene te gebruik benadeel. Neem spesiale sorg voordat u take uitvoer wat u aandag verg, totdat u weet hoe **BLITZIMA** u sal beïnvloed.

Neem van ander medisyne met BLITZIMA:
Vertel altyd u gesondheidsorgkundige indien u enige ander medisyne gebruik. (Dit sluit komplementêre of tradisionele medisyne in.)
Vertel u dokter of apteker indien u die volgende tans gebruik:
- Vertel u dokter indien u medisyne vir hoë bloeddruk neem. U kan gevra word om nie hierdie ander medisyne 12 uur voordat **BLITZIMA** toegedien word te neem nie. Dit is omdat sommige mense se bloeddruk daal terwyl hulle **BLITZIMA** ontvang.
- Indien u ooit medisyne neem wat u immuunstelsel beïnvloed, soos chemoterapie of immuunonderdrukkende medisyne.

4. HOE OM BLITZIMA TE NEEM
Moenie medisyne wat vir u voorgeskryf is met enige ander persoon deel nie.
Neem **BLITZIMA** altyd presies soos u dokter voorgeskryf het.
Raadpleeg u dokter of apteker indien u onseker is.

Hoe dit gegee word
BLITZIMA sal aan u gegee word deur 'n dokter of verpleegkundige wat ervare is in die gebruik van hierdie behandeling. Hulle sal u noukeurig dophou terwyl u hierdie medisyne ontvang. Dit is ingeval u enige newe-effekte kry.
U sal altyd **BLITZIMA** as 'n drip (binneaarste infusie) ontvang.

Medisyne wat voor elke BLITZIMA toediening gegee word
Voordat u **BLITZIMA** ontvang, sal u ander medisyne (pre-medisyne) ontvang om moontlike newe-effekte te voorkom of te verminder.

Hoeveel en hoe gereeld sal u behandeling ontvang
a) Indien u vir nie-Hodgkin's Limfoom behandel word
- *Indien u **BLITZIMA** alleenlik ontvang*
  BLITZIMA sal een keer per week vir 4 weke aan u gegee word. Herhaalde behandelingskursusse met **BLITZIMA** is moontlik.
- *Indien u **BLITZIMA** saam met chemoterapie ontvang*
  BLITZIMA sal op dieselfde dag as u chemoterapie aan u gegee word. Dit word gewoonlik elke 3 weke gegee tot en met 8 keer.
- Indien u goed reageer op behandeling, kan u **BLITZIMA** elke 2 of 3 maande vir twee jaar gegee word. U dokter kan dit verander, afhangende hoe u op die medisyne reageer.

b) Indien u vir chroniese limfositiese leukemie behandel word
Wanneer u met **BLITZIMA** in kombinasie met chemoterapie behandel word, sal u **BLITZIMA** elke 28 dae ontvang totdat u 6 dosisse ontvang het. Die chemoterapie moet na die **BLITZIMA**-infusie gegee word. U dokter sal besluit of u ander behandeling terselfdertyd moet ontvang.

c) Indien u vir granulomatose met poliangiitis of mikroskopiese poliangiitis behandel word
Behandeling met **BLITZIMA** maak gebruik van vier afsonderlike infusies wat weekliks gegee word. 'n Kortikosteroïedmedisyne sal gewoonlik met 'n inspuiting toegedien word voordat die **BLITZIMA** behandeling begin. 'n Kortikosteroïedmedisyne wat per mond gegee word, kan enige tyd deur u dokter begin word om u toestand te behandel.

Indien u meer BLITZIMA ontvang as wat u moet:
Aangesien **BLITZIMA** deur u dokter of verpleegster toegedien word, is dit onwaarskynlik dat u te veel gegee sal word. Daar is geen newe-effekte bekend indien u te veel **BLITZIMA** ontvang nie.

Indien u, u BLITZIMA-infusie vergeet of mis:
Indien u 'n afspraak om **BLITZIMA** te ontvang vergeet of mis, moet u so gou moontlik 'n ander afspraak maak.

5. MOONTLIKE NEWE-EFFEKTE
BLITZIMA kan newe-effekte hê.
Nie alle newe-effekte wat vir **BLITZIMA** gerapporteer is, is in hierdie inligtingstuk ingesluit nie.
Indien u algemene gesondheid versleg of indien u enige ongewenste effekte ervaar terwyl u **BLITZIMA** ontvang, raadpleeg asseblief u dokter, apteker of ander gesondheidsorgkundige vir advies.

Infusie-reaksies
Gedurende of binne die eerste 2 uur van die eerste infusie kan u koors, kouekoors en bewing ontwikkel. Minder dikwels, kan sommige pasiënte pyn kry op die infusieplek, blase, jeuk, siek voel, moegheid, hoofpyn, asemhalingsprobleme, swelling van die tong of keel, jeuk- of loopneus, braking, blosing of hartkloppings, hartaanval of lae aantal bloedplaatjies. Indien u hartsiekte of angina het, kan hierdie infusie-reaksies erger word. **Vertel die persoon wat die infusie toedien onmiddellik** indien u enige van hierdie simptome ontwikkel, aangesien die infusie dalk vertraag of gestaak moet word. U mag aanvullende behandeling benodig, soos antihistamiene of parasetamol. Wanneer hierdie simptome verdwyn, of verbeter, kan die infusie voortgesit word. Hierdie reaksies is minder waarskynlik om te gebeur na die tweede infusie.
U dokter kan besluit om u **BLITZIMA** behandeling te staak indien hierdie reaksies ernstig is.

Infeksies
Vertel jou dokter onmiddellik indien u tekens van 'n infeksie kry, insluitend:
- koors, hoes, seer keel, brandpyn as u urineer of swak voel of algemeen sleg voel
- geheueverlies, probleme met denke, loopprobleme of sigverlies – dit kan wees as gevolg van 'n baie seldsame, ernstige breininfeksie, wat noodlottig was (progressiewe multifokale leuko-enkefalopatie of PML)

U kan dalk infeksies makliker kry gedurende u behandeling met **BLITZIMA.** Hierdie is dikwels verkoue, maar daar was gevalle van longontsteking of urinêre infeksies.

Indien u behandel word vir granulomatose met poliangiitis of mikroskopiese poliangiitis, sal u hierdie inligting ook vind in die Pasiënt Waarskuwingskaart wat u dokter ontvang het. Dit is belangrik dat u hierdie Waarskuwingskaart hou en dit aan u maat of versorger wys.

Velreaksies
Baie selde, kan ernstige blaasvormende veltoestande wat lewensgevaarlik kan wees voorkom. Rooiheid, wat dikwels met blase gepaard gaan, kan verskyn op die vel of op die slymvliese, soos binne die mond, die geslagsdele of die ooglede, en koors kan voorkom.
Vertel u dokter onmiddellik indien u enige van hierdie simptome het.

Vertel u dokter so gou as moontlik indien u enige van die volgende opmerk:
a) Indien u vir nie-Hodgkin's Limfoom of chroniese limfositiese leukemie behandel word:
Dikwels:
- bakteriële of virale infeksies, brongitis
- lae aantal witbloedselle soms met koors, of lae aantal bloedselle genaamd "bloedplaatjies"
- siek voel (naarheid)
- kaal kolle op die kopvel, kouekoors, hoofpyn
- laer immuniteit – as gevolg van laer vlakke van anti-liggame genaamd "immunoglobuliene" (IgG) in die bloed wat help beskerm teen infeksie
- infeksies van die bloed (sepsis), longontsteking, gordelroos, verkoue, brongiale buisinfeksies, swaminfeksies, infeksies van onbekende oorsprong, sinusontsteking, hepatitis-B
- lae aantal rooibloedselle (bloedarmoede), lae aantal van alle bloedselle
- allergiese reaksies (hipersensitiwiteit)
- hoë bloedsuikervlak, gewigsverlies, swelling in die gesig en lyf, hoë vlakke van die ensiem LDH in die bloed, lae kalsiumvlakke in die bloed
- ongewone gevoelens van die vel – soos gevoelloosheid, tinteling, brand, 'n kriewelende vel gevoel, verminderde sensasie van aanraking
- rusteloos voel, probleme om aan die slaap te raak
- word baie rooi in die gesig en ander velareas as gevolg van verwyding van die bloedvate
- duiselig of angstig voel
- die vervaardiging van meer trane, probleme met traankanale, ontsteekte oog (konjunktivitis)
- lui geluid in die ore, oorpyn
- hartprobleme – soos hartaanval of ongelyke of vinnige hartklop
- hoë of lae bloeddruk (lae bloeddruk veral as u regop staan)
- vernouing van die spiere in die lugweë wat hyging (brongospasma) veroorsaak, ontsteking, irritasie in die longe, keel of sinusse, kortasem, loopneus
- siek word (braking), diarree, pyn in die maag, irritasie of sere in die keel en mond, slukprobleme, hardlywigheid, slegte spysvertering
- eetversteurings: nie genoeg eet nie, wat tot gewigsverlies lei
- velbulte, verhoogde sweet, nagsweet
- spierprobleme – soos stywe spiere, gewrigs- of spierpyn, rug- of nekpyn
- algemene ongemak of ongemaklik voel of moegheid, skud, tekens van griep
- veelvuldige orgaanversaking

Minder dikwels:
- bloedstollingsprobleme, afname in rooibloedselproduksie en toename in vernietiging van rooibloedselle (aplastiese hemolitiese anemie), swelling of vergrote limfknope
- lae gemoed en verlies aan belangstelling of plesier om dinge te doen, senuweeagtig voel
- smaakprobleme – soos veranderinge in die manier hoe dinge smaak
- hartprobleme – soos verminderde hartklop of borspyn (angina)
- asma, te min suurstof wat die liggaamsorgane bereik
- swelling van die maag
- korttermyn toename in die hoeveelheid van sommige soort teenliggaampies in die bloed (genaamd immunoglobuliene – IgM), chemiese versteurings in die bloed veroorsaak deur die afbreek van sterwende kankerselle
- senuweeskade in arms en bene, verlamde gesig
- hartversaking
- ontsteking van bloedvate insluitend dié wat tot velsimptome lei
- respiratoriese versaking
- skade aan die dermwand (perforasie)
- ernstige velprobleme wat blase veroorsaak wat lewensgevaarlik kan wees. Rooiheid, wat dikwels met blase gepaard gaan, kan op die vel of op slymvliese verskyn, soos in die mond, geslagsdele of ooglede, en koors kan voorkom
- nierversaking
- ernstige sigverlies

Frekwensie onbekend:
- 'n vermindering in witbloedselle wat nie dadelik plaasvind nie
- verminderde aantal bloedplaatjies net na die infusie – dit kan omgekeer word, maar kan in seldsame gevalle noodlottig wees
- gehoorverlies, verlies van ander sintuie

b) Indien u vir granulomatose met poliangiitis of mikroskopiese poliangiitis behandel word
Dikwels:
- infeksies, soos borsinfeksies, urienweginfeksies (pyn tydens urinering), verkoue en herpesinfeksies
- allergiese reaksies wat waarskynlik tydens 'n infusie kan voorkom, maar wat tot 24 uur na infusie kan voorkom
- diarree
- hoes of kortasem
- neusbloeding
- verhoogde bloeddruk
- pynlike gewrigte of rug
- spiertrekkings of bewerigheid
- duiselig voel
- bewing (bewerigheid, dikwels in die hande)
- probleme met slaap (slapeloosheid)
- swelling van die hande of enkels
- slegte spysvertering
- hardlywigheid
- veluitslag, insluitend aknee of kolle
- blosing of rooiheid van die vel
- verstopte neus
- stywe of pynlike spiere
- pyn in die spiere of in die hande of voete
- lae aantal rooibloedselle (bloedarmoede)
- lae aantal plaatjies in die bloed
- 'n toename in die hoeveelheid kalium in die bloed
- veranderinge in die hartritme, of die hart klop vinniger as normaal

Minder dikwels:
- ernstige blasvormende veltoestande wat lewensgevaarlik kan wees. Rooiheid, dikwels geassosieer met blase, kan op die vel of slymvlies verskyn, soos in die mond, die geslagsdele of die ooglede, en koors kan voorkom,
- herhaling van 'n vorige Hepatitis-B infeksie

BLITZIMA kan ook verandering in laboratoriumtoetse veroorsaak wat deur u dokter uitgevoer is.

Indien u enige newe-effekte opmerk wat nie in hierdie inligtingstuk genoem word nie, moet u asseblief u dokter of apteker in kennis stel.

6. BERGING EN WEGDOENING VAN BLITZIMA
- Bêre teen 2 °C tot 8 °C.
- Hou die houer in die buiteste karton om te beskerm teen lig.

- **Verdunde produk**

Die voorbereide infusie-oplossing van rituximab is fisies en chemies stabiel vir 24 uur teen 2 °C tot 8 °C en daarna 12 uur teen kamertemperatuur (nie meer as 30 °C). Van 'n mikrobiologiese oogpunt, moet die voorbereide oplossing onmiddellik gebruik word. Indien nie onmiddellik gebruik, is die in-gebruik bergingstye en toestande voor die gebruik die verantwoordelikheid van die gebruiker en is dit gewoonlik nie langer as 24 uur teen 2 °C tot 8 °C nie, behalwe as die verdunning in gekontroleerde en gevalideerde aseptiese toestande plaasgevind het.
- **BÊRE ALLE MEDISYNE BUITE BEHEER VAN KINDERS**
- Moenie gebruik na die vervaldatum wat op die karton aangedui is nie.
- Neem alle ongebruikte medisyne terug na u apteker.
- Moenie ongebruikte medisyne in dreine en rioolstelsels (e.g. toilette) weggooi nie.

7. VOORSTELLING VAN BLITZIMA
BLITZIMA 100 mg: Helder, kleurlose, tipe I glas flessie met 'n chloorbutielrubberstop en 'n aluminiumseël met 'n geel af-flip doppie. Pak met 2 flessies.
BLITZIMA 500 mg: Helder, kleurlose, tipe I glas flessie met 'n chloorbutielrubberstop en 'n aluminiumseël met 'n donkergrys af-flip doppie. Pak met 1 flessie.

8. IDENTIFIKASIE VAN BLITZIMA
Helder, kleurlose oplossing.

9. REGISTRASIENOMMERS
BLITZIMA 100 mg: 53/26/0506
BLITZIMA 500 mg: 53/26/0507

10.NAAM EN ADRES VAN REGISTRASIEHOUER
Adcock Ingram Limited
New Road 1
Erand Gardens
Midrand, 1685
South Africa

adcock Ingram

HEALTHCARE CELLTRION™

11.DATUM VAN PUBLIKASIE
25 Augustus 2020

10/2020

Blitzima®

Professional Information for BLITZIMA.

SCHEDULING STATUS **S4**

PROPRIETARY NAME AND DOSAGE FORM
BLITZIMA 100 mg concentrate for solution for infusion
BLITZIMA 500 mg concentrate for solution for infusion

Infusion related reactions: Infusion related deaths (death within 24 hours of infusion) have been associated with rituximab. These events appear as manifestations of an infusion related complex and include hypoxia, pulmonary infiltrates, adult respiratory distress syndrome, myocardial infarction, ventricular fibrillation or cardiogenic shock. Nearly all fatal infusion related events occurred in relation to the first infusion.
Tumour lysis syndrome (TLS): In the setting of TLS, acute renal failure requiring dialysis, with instances of fatal outcome, has been associated with rituximab. Assessment of renal function and serum electrolytes are indicated in patients with a rapid decrease in tumour volume (see **WARNINGS AND SPECIAL PRECAUTIONS**).

COMPOSITION
Each vial contains 100 mg (in 10 ml) or 500 mg (in 50 ml) rituximab.
Inactive Ingredients:
Polysorbate 80, sodium chloride, tri-sodium citrate dihydrate, water for injections.
Sugar free.

PHARMACOLOGICAL CLASSIFICATION
A 26 Cytostatic agents

PHARMACOLOGICAL ACTION
Pharmacodynamic properties
Rituximab is a chimeric mouse/human monoclonal antibody that binds specifically to the trans-membrane antigen CD20. CD20 is found on both normal and malignant B cells, but not on haematopoietic stem cells, pro-B cells, normal plasma cells or other normal tissue. This antigen does not internalise upon antibody binding and is not shed from the cell surface. CD20 does not circulate in the plasma as a free antigen and, thus, does not compete for antibody binding.
The Fab domain of rituximab binds to the CD20 antigen on B lymphocytes and the Fc domain can recruit immune effector functions to mediate B cell lysis. Possible mechanisms of effector-mediated cell lysis include complement-dependent cytotoxicity (CDC) resulting from C1q binding, and antibody-dependent cellular cytotoxicity (ADCC) mediated by one or more of the Fcγ receptors on the surface of granulocytes, macrophages and NK cells. Rituximab binding to CD20 antigen on B lymphocytes has also been demonstrated to induce cell death via apoptosis Rituximab binding was observed on lymphoid cells in the thymus, the white pulp of the spleen, and a majority of B lymphocytes in peripheral blood and lymph nodes. Little or no binding was observed in the non-lymphoid tissues examined.
In clinical studies, peripheral B cell counts declined below normal following completion of the first dose of rituximab. In patients treated for haematological malignancies, B cell recovery began within 6 months of treatment and generally returned to normal levels within 12 months after completion of therapy, although in some patients this may take longer (up to a median recovery time of 23 months post-induction therapy).

In patients with granulomatosis with polyangiitis or microscopic polyangiitis, the number of peripheral blood B cells decreased to <10 cells/µl after two weekly infusions of rituximab 375 mg/m², and remained at that level in most patients up to the 6 month time point. The majority of patients (81 %) showed signs of B cell return, with counts >10 cells/µl by month 12, increasing to 87 % of patients by month 18.

Pharmacokinetic properties
Non-Hodgkin's lymphoma
Based on a population pharmacokinetic analysis in 298 NHL patients who received single or multiple infusions of rituximab as a single agent or in combination with CHOP therapy (applied rituximab doses ranged from 100 to 500 mg/m²), the typical population estimates of nonspecific clearance (CL1), specific clearance (CL2) likely contributed by B cells or tumour burden, and central compartment volume of distribution (V1) were 0,14 l/day, 0,59 l/day, and 2,7 l, respectively. The estimated median terminal elimination half-life of rituximab was 22 days (range, 6,1 to 52 days) Baseline CD19-positive cell counts and size of measurable tumour lesions contributed to some of the variability in CL2 of rituximab in data from 161 patients given 375 mg/m² as an intravenous infusion for 4 weekly doses. Age, gender and WHO performance status had no effect on the pharmacokinetics of rituximab. This analysis suggests that dose adjustment of rituximab with any of the tested covariates is not expected to result in a meaningful reduction in its pharmacokinetic variability.

Rituximab, administered as an intravenous infusion at a dose of 375 mg/m² at weekly intervals for 4 doses to 203 patients with NHL naive to rituximab, yielded a mean C_{max} following the fourth infusion of 486 µg/ml (range, 77,5 to 996,6 µg/ml). Rituximab was detectable in the serum of patients 3 – 6 months after completion of last treatment.
Upon administration of rituximab at a dose of 375 mg/m² as an intravenous infusion at weekly intervals for 8 doses to 37 patients with NHL, the mean C_{max} increased with each successive infusion, spanning from a mean of 243 µg/ml (range, 16 – 582 µg/ml) after the first infusion to 550 µg/ml (range, 171 – 1 177 µg/ml) after the eighth infusion.
The pharmacokinetic profile of rituximab when administered as 6 infusions of 375 mg/m² in combination with 6 cycles of CHOP chemotherapy was similar to that seen with rituximab alone.

Chronic lymphocytic leukaemia
Rituximab was administered as an intravenous infusion at a first-cycle dose of 375 mg/m² increased to 500 mg/m² each cycle for 5 doses in combination with fludarabine and cyclophosphamide in CLL patients. The mean C_{max} (N=15) was 408 µg/ml (range, 97 – 764 µg/ml) after the fifth 500 mg/m² infusion and the mean terminal half-life was 32 days (range, 14 – 62 days).

Granulomatosis with polyangiitis and microscopic polyangiitis
Based on the population pharmacokinetic analysis of data in 97 patients with granulomatosis with polyangiitis and microscopic polyangiitis who received 375 mg/m² rituximab once weekly for four doses, the estimated median terminal elimination half-life was 23 days (range, 9 to 49 days). Rituximab mean clearance and volume of distribution were 0,313 l/day (range, 0,116 to 0,726 l/day) and 4,50 l (range 2,25 to 7,39 l) respectively.

INDICATIONS
Non-Hodgkin's lymphoma (NHL)
BLITZIMA is indicated for the treatment of previously untreated patients with stage III-IV follicular lymphoma in combination with chemotherapy.
BLITZIMA maintenance therapy is indicated for the treatment of follicular lymphoma patients responding to induction therapy.
BLITZIMA monotherapy is indicated for treatment of patients with stage III-IV follicular lymphoma who are chemo-resistant or are in their second or subsequent relapse after chemotherapy.
BLITZIMA is indicated for the treatment of patients with CD20 positive diffuse large B cell non-Hodgkin's lymphoma in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) chemotherapy.

Chronic lymphocytic leukaemia (CLL)
BLITZIMA in combination with chemotherapy is indicated for the treatment of patients with previously untreated and relapsed/refractory CLL. Only limited data are available on efficacy and safety for patients previously treated with monoclonal antibodies including **BLITZIMA** or patients refractory to previous **BLITZIMA** plus chemotherapy.

Granulomatosis with polyangiitis and microscopic polyangiitis
BLITZIMA, in combination with glucocorticoids, is indicated for the induction of remission in adult patients with severe, active granulomatosis with polyangiitis (Wegener's) (GPA) and microscopic polyangiitis (MPA).

CONTRAINDICATIONS
Contraindications for use in non-Hodgkin's lymphoma and chronic lymphocytic leukaemia
Known hypersensitivity to rituximab, murine proteins or any inactive ingredient of **BLITZIMA** (see **COMPOSITION**).
Active, severe infections.
Patients in a severely immunocompromised state

Contraindications for use in granulomatosis with polyangiitis and microscopic polyangiitis
Known hypersensitivity to rituximab, murine proteins or any inactive ingredient of **BLITZIMA** (see **COMPOSITION**).
Active, severe infections.
Patients in a severely immunocompromised state
Severe heart failure (New York Heart Association Class IV) or severe, uncontrolled cardiac disease (see **WARNINGS AND SPECIAL PRECAUTIONS**).

WARNINGS AND SPECIAL PRECAUTIONS
Tuberculosis (TB)
A diagnosis of any form of active tuberculosis should be explicitly excluded in patients considered for treatment with **BLITZIMA**. Furthermore, a history of previous tuberculosis, HIV-infection, or a diagnosis of latent TB infection pose a risk for reactivation of tuberculosis disease and appropriate preventive therapy is indicated, regardless of HIV-status. Diagnosis and treatment of latent infection, following national guidelines, should be initiated prior to use of **BLITZIMA**.

People initiating **BLITZIMA** / anti-TNF treatment, who initially tested negative for active or latent tuberculosis, should be systematically tested for latent TB infection during treatment with **BLITZIMA**, and preventive treatment instituted if indicated.

Progressive multifocal leukoencephalopathy (PML)
All patients treated with rituximab for granulomatosis with polyangiitis and microscopic polyangiitis must be given the patient alert card with each infusion. The alert card contains important safety information for patients regarding potential increased risk of infections, including PML.
Very rare cases of fatal PML have been reported following the use of rituximab. Patients must be monitored at regular intervals for any new or worsening neurological symptoms or signs that may be suggestive of PML. If PML is suspected, further dosing must be suspended until PML has been excluded. The clinician should evaluate the patient to determine if the symptoms are indicative of neurological dysfunction, and if so, whether these symptoms are possibly suggestive of PML. Consultation with a neurologist should be considered as clinically indicated.
If any doubt exists, further evaluation, including MRI scan preferably with contrast, cerebrospinal fluid (CSF) testing for JC Viral DNA and repeat neurological assessments, should be considered.
The physician should be particularly alert to symptoms suggestive of PML that the patient may not notice (e.g. cognitive, neurological or psychiatric symptoms). Patients should also be advised to inform their partner or caregivers about their treatment, since they may notice symptoms that the patient is not aware of.
If a patient develops PML the dosing of rituximab must be permanently discontinued.
Following reconstitution of the immune system in immunocompromised patients with PML, stabilisation or improved outcome has been seen. It remains unknown if early detection of PML and suspension of rituximab therapy may lead to similar stabilisation or improved outcome.

Non-Hodgkin's lymphoma and chronic lymphocytic leukaemia
Infusion related reactions
Rituximab is associated with infusion-related reactions, which may be related to release of cytokines and/or other chemical mediators. Cytokine release syndrome may be clinically indistinguishable from acute hypersensitivity reactions.
This set of reactions which includes syndrome of cytokine release, tumour lysis syndrome and anaphylactic and hypersensitivity reactions are described below. They are not specifically related to the route of administration of rituximab and can be observed with both formulations.
Severe infusion-related reactions with fatal outcome have been reported during post-marketing use of the rituximab intravenous formulation, with an onset ranging within 30 minutes to 2 hours after starting the first rituximab intravenous infusion. They were characterised by pulmonary events and in some cases included rapid tumour lysis and features of tumour lysis syndrome in addition to fever, chills, rigors, hypotension, urticaria, angioedema and other symptoms.
Severe cytokine release syndrome is characterised by severe dyspnoea, often accompanied by bronchospasm and hypoxia, in addition to fever, chills, rigors, urticaria, and angioedema. This syndrome may be associated with some features of tumour lysis syndrome such as hyperuricaemia, hyperkalaemia, hypocalcaemia, hyperphosphataemia, acute renal failure, elevated lactate dehydrogenase (LDH) and may be associated with acute respiratory failure and death. The acute respiratory failure may be accompanied by events such as pulmonary interstitial infiltration or oedema, visible on a chest X-ray. The syndrome frequently manifests itself within one or two hours of initiating the first infusion. Patients with a history of pulmonary insufficiency or those with pulmonary tumour infiltration may be at greater risk of poor outcome and should be treated with increased caution. Patients who develop severe cytokine release syndrome should have their infusion interrupted immediately and should receive aggressive symptomatic treatment. Since initial improvement of clinical symptoms may be followed by deterioration, these patients should be closely monitored until tumour lysis syndrome and pulmonary infiltration have been resolved or ruled out. Further treatment of patients after complete resolution of signs and symptoms has rarely resulted in repeated severe cytokine release syndrome.
Patients with a high tumour burden or with a high number (≥ 25 x 10^9/l) of circulating malignant cells such as patients with CLL, who may be at higher risk of especially severe cytokine release syndrome, should be treated with extreme caution. These patients should be very closely monitored throughout the first infusion. Consideration should be given to the use of a reduced infusion rate for the first infusion in these patients or a split dosing over two days during the first cycle and any subsequent cycles if the lymphocyte count is still > 25 x 10^9/l.
Infusion related adverse reactions of all kinds have been observed in 77 % of patients treated with rituximab (including cytokine release syndrome accompanied by hypotension and bronchospasm in 10 % of patients). These symptoms are usually reversible with interruption of rituximab infusion and administration of an anti-pyretic, an antihistaminic, and, occasionally, oxygen, intravenous saline or bronchodilators, and glucocorticoids if required. Please see cytokine release syndrome above for severe reactions.
Anaphylactic and other hypersensitivity reactions have been reported following the intravenous administration of proteins to patients. In contrast to cytokine release syndrome, true hypersensitivity reactions typically occur within minutes after starting infusion. Medicines for the treatment of hypersensitivity reactions, e.g., epinephrine (adrenaline), antihistamines and glucocorticoids, should be available for immediate use in the event of an allergic reaction during administration of rituximab. Clinical manifestations of anaphylaxis may appear similar to clinical manifestations of the cytokine release syndrome. Reactions attributed to hypersensitivity have been reported less frequently than those attributed to cytokine release.
Additional reactions reported in some cases were myocardial infarction, atrial fibrillation, pulmonary oedema and acute reversible thrombocytopenia.
Since hypotension may occur during rituximab administration, consideration should be given to withholding antihypertensive medicines 12 hours prior to the rituximab infusion.

Cardiac disorders
Angina pectoris, cardiac arrhythmias such as atrial flutter and fibrillation, heart failure and/or myocardial infarction have occurred in patients treated with rituximab. Therefore patients with a history of cardiac disease and/or cardiotoxic chemotherapy should be monitored closely.

Haematological toxicities
Although rituximab is not myelosuppressive in monotherapy, caution should be exercised when considering treatment of patients with neutrophils < 1.5 x 10^9/l and/or platelet counts < 75 x 10^9/l as clinical experience in this population is limited. Rituximab has been used in 21 patients who underwent autologous bone marrow transplantation and other risk groups with a presumable reduced bone marrow function without inducing myelotoxicity.
Regular full blood counts, including neutrophil and platelet counts, should be performed during rituximab therapy.

Infections
Serious infections, including fatalities, can occur during therapy with rituximab (see **SIDE EFFECTS**). Rituximab should not be administered to patients with an active, severe infection e.g. tuberculosis, sepsis and opportunistic infections (see **CONTRAINDICATIONS**) or severely immunocompromised patients (e.g. where levels of CD4 or CD8 are very low).
Medical practitioners should exercise caution when considering the use of rituximab in patients with a history of recurring or chronic infections or with underlying conditions which may further predispose patients to serious infection (see **SIDE EFFECTS**).
Patients being treated with rituximab should avoid exposure to patients with tuberculosis and contact with children and adults recently vaccinated with attenuated live vaccines.
Following rituximab therapy, patients who develop infection should be evaluated promptly and treated appropriately. Prior to initiating treatment with rituximab, it is recommended that immunoglobulin levels are determined.
Cases of hepatitis B reactivation have been reported in subjects receiving rituximab including fulminant hepatitis with fatal outcome. The majority of these subjects were also exposed to cytotoxic chemotherapy. Limited information from one study in relapsed/refractory CLL patients suggests that rituximab treatment may also worsen the outcome of primary hepatitis B infections. Hepatitis B virus (HBV) screening should be performed in all patients before initiation of treatment with rituximab. At minimum this should include HBsAg-status and HBcAb-status. These can be complemented with other appropriate markers as per local guidelines. Patients with active hepatitis B disease should not be treated with rituximab. Patients with positive hepatitis B serology (either HBsAg or HBcAb) should consult liver disease experts before start of treatment and should be monitored and managed following local medical standards to prevent hepatitis B reactivation.
Very rare cases of progressive multifocal leukoencephalopathy (PML) have been reported during post-marketing use of rituximab in NHL and CLL (see **SIDE EFFECTS**). The majority of patients had received rituximab in combination with chemotherapy or as part of a hematopoietic stem cell transplant.

Immunisations
The safety of immunisation with live viral vaccines, following rituximab therapy has not been studied for NHL and CLL patients and vaccination with live virus vaccines is not recommended. Patients treated with rituximab may receive non-live vaccinations. However with non-live vaccines response rates may be reduced. In a non-randomised study, patients with relapsed low-grade NHL who received rituximab monotherapy when compared to healthy untreated controls had a lower rate of response to vaccination with tetanus recall antigen (16 % vs. 81 %) and Keyhole Limpet Haemocyanin (KLH) neoantigen (4 % vs. 76 % when assessed for > 2-fold increase in antibody titer). For CLL patients similar results are assumable considering similarities between both diseases but that has not been investigated in clinical trials.
Mean pre-therapeutic antibody titres against a panel of antigens (Streptococcus pneumoniae, influenza A, mumps, rubella, varicella) were maintained for at least 6 months after treatment with rituximab.

Skin reactions
Severe skin reactions such as toxic epidermal necrolysis (Lyell's syndrome) and Stevens-Johnson syndrome, some with fatal outcome, have been reported (see **SIDE EFFECTS**). In case of such an event, with a suspected relationship to rituximab, treatment should be permanently discontinued.

Granulomatosis with polyangiitis and microscopic polyangiitis
Infusion related reactions
Rituximab is associated with infusion related reactions (IRRs), which may be related to release of cytokines and/or other chemical mediators. Premedication consisting of an analgesic/anti-pyretic medicine and an anti-histaminic medicine, should always be administered before each infusion of rituximab. Premedication with glucocorticoids should also be administered before each infusion of rituximab in order to reduce the frequency and severity of IRRs (see **DOSAGE AND DIRECTIONS FOR USE and SIDE EFFECTS**).
The most common symptoms were allergic reactions like headache, pruritus, throat irritation, flushing, rash, urticaria, hypertension, and pyrexia. In general, the proportion of patients experiencing any infusion reaction was higher following the first infusion than following the second infusion of any treatment course. The incidence of IRR decreased with subsequent courses (see **SIDE EFFECTS**). The reactions reported were usually reversible with a reduction in rate, or interruption, of rituximab infusion and administration of an anti-pyretic, an antihistamine, and, occasionally, oxygen, intravenous saline or bronchodilators, and glucocorticoids if required. Closely monitor patients with pre-existing cardiac conditions and those who experienced prior cardiopulmonary adverse reactions. Depending on the severity of the IRR and the required interventions, temporarily or permanently discontinue rituximab. In most cases, the infusion can be resumed at a 50 % reduction in rate (e.g. from 100 mg/h to 50 mg/h) when symptoms have completely resolved.
Medicines for the treatment of hypersensitivity reactions, e.g. epinephrine (adrenaline), antihistamines and glucocorticoids, should be available for immediate use in the event of an allergic reaction during administration of rituximab.
There are no data on the safety of rituximab in patients with moderate heart failure (NYHA class III) or severe, uncontrolled cardiovascular disease. In patients treated with rituximab, the occurrence of pre-existing ischemic cardiac conditions becoming symptomatic, such as angina pectoris, has been observed, as well as atrial fibrillation and flutter. Therefore, in patients with a known cardiac history, and those who experienced prior cardiopulmonary adverse reactions, the risk of cardiovascular complications resulting from infusion reactions should be considered before treatment with rituximab and patients closely monitored during administration. Since hypotension may occur during rituximab infusion, consideration should be given to withholding anti-hypertensive medications 12 hours prior to the rituximab infusion.

Cardiac disorders
Angina pectoris, cardiac arrhythmias such as atrial flutter and fibrillation, heart failure and/or myocardial infarction have occurred in patients treated with rituximab. Therefore patients with a history of cardiac disease should be monitored closely.

Infections
Based on the mechanism of action of rituximab and the knowledge that B cells play an important role in maintaining normal immune response, patients have an increased risk of infection following rituximab therapy (see **Pharmacodynamic properties**).
Serious infections, including fatalities, can occur during therapy with rituximab (see **SIDE EFFECTS**). **BLITZIMA** should not be administered to patients with an active, severe infection (e.g. tuberculosis, sepsis and opportunistic infections, see **CONTRAINDICATIONS**) or severely immunocompromised patients (e.g. where levels of CD4 or CD8 are very low).
Medical practitioners should exercise caution when considering the use of rituximab in patients with a history of recurring or chronic infections or with underlying conditions which may further predispose patients to serious infection, e.g. hypogammaglobulinaemia (see **SIDE EFFECTS**). It is recommended that immunoglobulin levels are determined prior to initiating treatment with rituximab.
Patients reporting signs and symptoms of infection following rituximab therapy should be promptly evaluated and treated appropriately. Before giving a subsequent course of rituximab treatment, patients should be re-evaluated for any potential risk for infections.
Very rare cases of fatal progressive multifocal leukoencephalopathy (PML) have been reported following use of rituximab for the treatment of autoimmune diseases including Systemic Lupus Erythematosus (SLE) and vasculitis.

Hepatitis B Infections
Cases of hepatitis B reactivation, including those with a fatal outcome, have been reported in granulomatosis with polyangiitis and microscopic polyangiitis patients receiving rituximab.
Hepatitis B virus (HBV) screening should be performed in all patients before initiation of treatment with rituximab. At minimum this should include HBsAg-status and HBcAb-status. These can be complemented with other appropriate markers as per local guidelines. Patients with active hepatitis B disease should not be treated with rituximab. Patients with positive hepatitis B serology (either HBsAg or HBcAb) should consult liver disease experts before start of treatment and should be monitored and managed following local medical standards to prevent hepatitis B reactivation.

Late neutropenia
Measure blood neutrophils prior to each course of rituximab, and regularly up to 6-months after cessation of treatment, and upon signs or symptoms of infection (see **SIDE EFFECTS**).

Skin reactions
Severe skin reactions such as toxic epidermal necrolysis (Lyell's syndrome) and Stevens-Johnson syndrome, some with fatal outcome, have been reported (see **SIDE EFFECTS**). In case of such an event with a suspected relationship to rituximab, treatment should be permanently discontinued.

Immunisation
Medical practitioners should review the patient's vaccination status and follow current immunisation guidelines prior to rituximab therapy. Vaccination should be completed at least 4 weeks prior to first administration of rituximab.
The safety of immunisation with live viral vaccines following rituximab therapy has not been studied. Therefore vaccination with live virus vaccines is not recommended whilst on rituximab or whilst peripherally B cell depleted.
Patients treated with rituximab may receive non-live vaccinations. However, response rates to non-live vaccines may be reduced. Should non-live vaccinations be required whilst receiving rituximab therapy, these should be completed at least 4 weeks prior to commencing the next course of rituximab.

Malignancy
Immunomodulatory medicines may increase the risk of malignancy. The possible risk for the development of solid tumours cannot be excluded at this time.

Effects on ability to drive and use machines:
No studies on the effects of rituximab on the ability to drive and use machines have been performed. rituximab may cause dizziness and influence the ability to drive and use machines.

INTERACTIONS
Currently, there are limited data on possible interactions with **rituximab**
In CLL patients, co-administration with rituximab did not appear to have an effect on the pharmacokinetics of fludarabine or cyclophosphamide. In addition, there was no apparent effect of fludarabine and cyclophosphamide on the pharmacokinetics of rituximab.
Patients with human anti-mouse antibody or human anti-chimeric antibody (HAMA/HACA) titres may have allergic or hypersensitivity reactions when treated with other diagnostic or therapeutic monoclonal antibodies.

HUMAN REPRODUCTION
Safety and efficacy during pregnancy and lactation have not been established.
Pregnancy:
IgG immunoglobulins are known to cross the placental barrier.
B cell levels in human neonates following maternal exposure to **rituximab** have not been studied in clinical trials. There are no adequate and well-controlled data from studies in pregnant women, however transient B-cell depletion and lymphocytopenia have been reported in some infants born to mothers exposed to rituximab during pregnancy. For these reasons rituximab should not be administered to pregnant women unless the possible benefit outweighs the potential risk.
Women of childbearing potential:
Due to the long retention time of rituximab in B cell depleted patients, women of childbearing potential should use effective contraceptive methods during and for 12 months following treatment with rituximab.
Lactation:
Whether rituximab is excreted in human milk is not known. However, because maternal IgG is excreted in human milk, and rituximab was detectable in milk from lactating monkeys, women should not breastfeed while treated with rituximab and for 12 months following rituximab treatment.
Fertility:
Animal studies did not reveal deleterious effects of rituximab on reproductive organs.

DOSAGE AND DIRECTIONS FOR USE
BLITZIMA should be administered under the close supervision of an experienced medical practitioner, and in an environment where full resuscitation facilities are immediately available.

Premedication consisting of an anti-pyretic and an antihistamine, e.g. paracetamol and diphenhydramine, should always be given before each administration of **BLITZIMA**.

In patients with non-Hodgkin's lymphoma and CLL, premedication with glucocorticoids should be considered if **BLITZIMA** is not given in combination with glucocorticoid-containing chemotherapy.

In patients with granulomatosis with polyangiitis (Wegener's) or microscopic polyangiitis, methylprednisolone given intravenously for 1 to 3 days at a dose of 1 000 mg per day is recommended prior to the first infusion of **BLITZIMA** (the last dose of methylprednisolone may be given on the same day as the first infusion of **BLITZIMA**). This should be followed by oral prednisone 1 mg/kg/day (not to exceed 80 mg/day, and tapered as rapidly as possible based on clinical need) during and after **BLITZIMA** treatment.

Non-Hodgkin's lymphoma
Follicular non-Hodgkin's lymphoma
Combination therapy
The recommended dose of **BLITZIMA** in combination with chemotherapy for induction treatment of previously untreated or relapsed/ refractory patients with follicular lymphoma is: 375 mg/m² body surface area per cycle, for up to 8 cycles.
BLITZIMA should be administered on day 1 of each chemotherapy cycle, after intravenous administration of the glucocorticoid component of the chemotherapy if applicable.

Maintenance therapy
Previously untreated follicular lymphoma:
The recommended dose of **BLITZIMA** used as a maintenance treatment for patients with previously untreated follicular lymphoma who have responded to induction treatment is: 375 mg/m² body surface area once every 2 months (starting 2 months after the last dose of induction therapy) until disease progression or for a maximum period of two years.
Relapsed/refractory follicular lymphoma:
The recommended dose of **BLITZIMA** used as a maintenance treatment for patients with relapsed/refractory follicular lymphoma who have responded to induction treatment is: 375 mg/m² body surface area once every 3 months (starting 3 months after the last dose of induction therapy) until disease progression or for a maximum period of two years.

Monotherapy
Relapsed/refractory follicular lymphoma:
The recommended dose of **BLITZIMA** monotherapy used as induction treatment for adult patients with stage III-IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy is: 375 mg/m² body surface area, administered as an intravenous infusion once weekly for four weeks.
For retreatment with **BLITZIMA** monotherapy for patients who have responded to previous treatment with **BLITZIMA** monotherapy for relapsed/refractory follicular lymphoma, the recommended dose is: 375 mg/m² body surface area, administered as an intravenous infusion once weekly for four weeks (see **Pharmacodynamic properties**).

Diffuse large B cell non-Hodgkin's lymphoma
BLITZIMA should be used in combination with cyclophosphamide, doxorubicin (hydroxydaunomycin), vincristine (Oncovin), prednisolone (CHOP) chemotherapy. The recommended dosage is 375 mg/m² body surface area, administered on day 1 of each chemotherapy cycle for 8 cycles after intravenous infusion of the glucocorticoid component of CHOP. Safety and efficacy of **BLITZIMA** have not been established in combination with other chemotherapies in diffuse large B cell nonHodgkin's lymphoma

Dose adjustments during treatment
No dose reductions of **BLITZIMA** are recommended. When **BLITZIMA** is given in combination with chemotherapy, standard dose reductions for the chemotherapeutic medicines should be applied.

Chronic lymphocytic leukaemia
Prophylaxis with adequate hydration and administration of uricostatics starting 48 hours prior to start of therapy is recommended for CLL patients to reduce the risk of tumour lysis syndrome. For CLL patients whose lymphocyte counts are > 25 x 10^9/l it is recommended to administer prednisone/prednisolone 100 mg intravenous shortly before infusion with **BLITZIMA** to decrease the rate and severity of acute infusion reactions and/or cytokine release syndrome.

The recommended dosage of **BLITZIMA** in combination with chemotherapy for previously untreated and relapsed/refractory patients is 375 mg/m² body surface area administered on day 0 of the first treatment cycle followed by 500 mg/m² body surface area administered on day 1 of each subsequent cycle for 6 cycles in total. The chemotherapy should be given after **BLITZIMA** infusion.

Granulomatosis with polyangiitis and microscopic polyangiitis
Patients treated with **BLITZIMA** must be given the patient alert card with each infusion.

The recommended dosage of **BLITZIMA** for induction of remission therapy of granulomatosis with polyangiitis and microscopic polyangiitis is 375 mg/m² body surface area, administered as an intravenous infusion once weekly for 4 weeks (four infusions in total).

Pneumocystis jiroveci pneumonia (PCP) prophylaxis is recommended for patients with granulomatosis with polyangiitis or microscopic polyangiitis during and following **BLITZIMA** treatment, as appropriate.

Special populations
Elderly
No dose adjustment is required in elderly patients (aged >65 years).
Paediatric population
The safety and efficacy of **BLITZIMA** in children below 18 years has not been established. No data are available.

Method of administration
The prepared **BLITZIMA** solution should be administered as an IV infusion through a dedicated line. It should not be administered as an IV injection or bolus.
Patients should be closely monitored for the onset of cytokine release syndrome (see **WARNINGS AND SPECIAL PRECAUTIONS**). Patients who develop evidence of severe reactions, especially severe dyspnoea, bronchospasm or hypoxia should have the infusion interrupted immediately. Patients with non-Hodgkin's lymphoma should then be evaluated for evidence of tumour lysis syndrome including appropriate laboratory tests and, for pulmonary infiltration, with a chest X-ray. In all patients, the infusion should not be restarted until complete resolution of all symptoms, and normalisation of laboratory values and chest X-ray findings. At this time, the infusion can be initially resumed at not more than one-half the previous rate. If the same severe adverse reactions occur for a second time, the decision to stop the treatment should be seriously considered on a case by case basis.
Mild or moderate infusion-related reactions (IRRs) (see **SIDE EFFECTS**) usually respond to a reduction in the rate of infusion. The infusion rate may be increased upon improvement of symptoms.

First infusion
The recommended initial rate for infusion is 50 mg/h; after the first 30 minutes, it can be escalated in 50 mg/h increments every 30 minutes, to a maximum of 400 mg/h.

Subsequent infusions
All indications
Subsequent doses of **BLITZIMA** can be infused at an initial rate of 100 mg/h, and increased by 100 mg/h increments at 30 minute intervals, to a maximum of 400 mg/h.

Special precautions for disposal and other handling
BLITZIMA is provided in sterile, preservative-free, non-pyrogenic, single use vials.
Aseptically withdraw the necessary amount of **BLITZIMA**, and dilute to a calculated concentration of 1 to 4 mg/ml rituximab into an infusion bag containing sterile, pyrogen-free sodium chloride 9 mg/ml (0,9 %) solution for injection or 5 % dextrose in water. For mixing the solution, gently invert the bag in order to avoid foaming. Care must be taken to ensure the sterility of prepared solutions. Since **BLITZIMA** does not contain any anti-microbial preservative or bacteriostatic agents, aseptic technique must be observed. Parenteral medicines should be inspected visually for particulate matter and discolouration prior to administration.

Compatibility:
No incompatibilities between rituximab and polyvinyl chloride or polyethylene bags or infusion sets have been observed.
Rituximab is compatible with 0,9 % sodium chloride and 5 % dextrose solutions.

SIDE EFFECTS
Summary of the safety profile (non-Hodgkin's lymphoma and chronic lymphocytic leukaemia)
The overall safety profile of rituximab in non-Hodgkin's lymphoma and CLL is based on data from patients from clinical trials and from post-marketing surveillance. These patients were treated either with rituximab monotherapy (as induction treatment or maintenance treatment following induction treatment) or in combination with chemotherapy.
The most frequently observed adverse drug reactions (ADRs) in patients receiving rituximab were IRRs which occurred in the majority of patients during the first infusion. The incidence of infusion related symptoms decreases substantially with subsequent infusions and is less than 1 % after eight doses of rituximab.
Infectious events (predominantly bacterial and viral) occurred in approximately 30 – 55 % of patients during clinical trials in patients with NHL and in 30 – 50 % of patients during clinical trials in patients with CLL.
The most frequent reported or observed serious adverse drug reactions were:
- IRRs (including cytokine-release syndrome, tumour-lysis syndrome)
- Infections
- Cardiovascular events

Other serious ADRs reported include hepatitis B reactivation and progressive multifocal leukoencephalopathy (PML). See **WARNINGS AND SPECIAL PRECAUTIONS**.

ADRs reported in clinical trials or during post-marketing surveillance in patients with NHL and CLL disease treated with rituximab monotherapy/maintenance or in combination with chemotherapy
The frequencies of ADRs reported with rituximab alone or in combination with chemotherapy are summarised below. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000), very rare (< 1/10 000) and not known (cannot be estimated from the available data).
The ADRs identified only during post marketing surveillance, and for which a frequency could not be estimated, are listed under "not known".

Infections and infestations:
Very common: bacterial infection, viral infections, +bronchitis
Common: sepsis, +pneumonia, +febrile infection, +herpes zoster, +respiratory tract infection, fungal infections, infections of unknown aetiology, +acute bronchitis, +sinusitis, hepatitis B[1]
Very rare: progressive multifocal leukoencephalopathy (PML)

Blood and the lymphatic system disorders:
Very common: neutropenia, leucopenia, +febrile neutropenia, +thrombocytopenia
Common: anaemia, +pancytopenia, +granulocytopenia
Uncommon: coagulation disorders, aplastic anaemia, haemolytic anaemia, lymphadenopathy
Very rare: transient increase in serum IgM levels[3]
Not known: late neutropenia[3]

Immune system disorders:
Very common: infusion related reactions[4], angioedema
Common: hypersensitivity
Rare: anaphylaxis
Very rare: tumour lysis syndrome, cytokine release syndrome[4], serum sickness
Not known: infusion related acute reversible thrombocytopenia[4]

Metabolism and nutrition disorders:
Common: hyperglycaemia, weight decrease, peripheral oedema, face oedema, increased LDH, hypocalcaemia

Psychiatric disorders:
Uncommon: depression, nervousness

Nervous system disorders:
Common: paraesthesia, hypoaesthesia, agitation, insomnia, vasodilatation, dizziness, anxiety
Uncommon: dysgeusia
Very rare: peripheral neuropathy, facial nerve palsy[5]
Not known: cranial neuropathy, loss of other senses[5]

Eye disorders:
Common: lacrimation disorder, conjunctivitis
Very rare: severe vision loss[5]

Ear and labyrinth disorders:
Common: tinnitus, ear pain
Not known: hearing loss[5]

Cardiac disorders:
Common: +myocardial infarction[4 and 6], arrhythmia, +atrial fibrillation, tachycardia, +cardiac disorder
Uncommon: +left ventricular failure, +supraventricular tachycardia, +ventricular tachycardia, +angina, +myocardial ischaemia, bradycardia
Rare: severe cardiac disoders[4 and 6]
Very rare: heart failure[4 and 6]

Vascular disorders:
Common: hypertension, orthostatic hypotension, hypotension
Very rare: vasculitis (predominately cutaneous), leukocytoclastic vasculitis

Respiratory, thoracic and mediastinal disorders:
Common: bronchospasm[4], respiratory disease, chest pain, dyspnoea, increased cough, rhinitis
Uncommon: asthma, bronchiolitis obliterans, lung disorder, hypoxia
Rare: interstitial lung disease[7]
Very rare: respiratory failure[4]
Not known: lung infiltration

Gastrointestinal disorders:
Very common nausea
Common: vomiting, diarrhoea, abdominal pain, dysphagia, stomatitis, constipation, dyspepsia, anorexia, throat irritation
Uncommon: abdominal enlargement
Very rare: gastrointestinal perforation[7]

Skin and subcutaneous tissue disorders:
Very common: pruritus, rash, +alopecia
Common: urticaria, sweating, night sweats, +skin disorder
Very rare: severe bullous skin reactions, Stevens-Johnson Syndrome, toxic epidermal necrolysis (Lyell's Syndrome)[7]

Musculoskeletal, connective tissue and bone disorders:
Common: hypertonia, myalgia, arthralgia, back pain, neck pain, pain

Renal and urinary disorders:
Very rare: renal failure[4]

General disorders and administration site conditions:
Very common: fever, chills, asthenia, headache
Common: tumour pain, flushing, malaise, cold syndrome, +fatigue, +shivering, +multi organ failure[4]
Uncommon: infusion site pain

Investigations:
Very common: decreased IgG levels

For each term, the frequency count was based on reactions of all grades (from mild to severe), except for terms marked with "+" where the frequency count was based only on severe (≥ grade 3 NCI common toxicity criteria) reactions. Only the highest frequency observed in the trials is reported
1 includes reactivation and primary infections; frequency based on R-FC regimen in relapsed/refractory CLL
2 see also section infection below
see also section haematologic adverse reactions below
see also section infusion-related reactions below. Rarely fatal cases reported
signs and symptoms of cranial neuropathy. Occurred at various times up to several months after completion of rituximab therapy
6 observed mainly in patients with prior cardiac condition and/or cardiotoxic chemotherapy and were mostly associated with infusion related reactions
7 Includes fatal cases

The following terms have been reported as adverse events during clinical trials, however, were reported at a similar or lower incidence in the rituximab-arms compared to control arms: haematotoxicity, neutropenic infection, urinary tract infection, sensory disturbance, pyrexia.

Description of selected adverse reactions
Signs and symptoms suggestive of an infusion-related reaction were reported in more than 50 % of patients in clinical trials, and were predominantly seen during the first infusion, usually in the first one to two hours.
These symptoms mainly comprised fever, chills and rigors. Other symptoms included flushing, angioedema, bronchospasm, vomiting, nausea, urticaria/rash, fatigue, headache, throat irritation, rhinitis, pruritus, pain, tachycardia, hypertension, hypotension, dyspnoea, dyspepsia, asthenia and features of tumour lysis syndrome. Severe infusion-related reactions (such as bronchospasm, hypotension) occurred in up to 12 % of the cases.
Additional reactions reported in some cases were myocardial infarction, atrial fibrillation, pulmonary oedema and acute reversible thrombocytopenia. Exacerbations of pre-existing cardiac conditions such as angina pectoris or congestive heart failure or severe cardiac disorders (heart failure, myocardial infarction, atrial fibrillation), pulmonary oedema, multi-organ failure, tumour lysis syndrome, cytokine release syndrome, renal failure, and respiratory failure were reported at lower or unknown frequencies. The incidence of infusion-related symptoms decreased substantially with subsequent infusions and is < 1 % of patients by the eighth cycle of treatment.

Infections
Rituximab induces B-cell depletion in about 70-80 % of patients, but was associated with decreased serum immunoglobulins only in a minority of patients.
Localised candida infections as well as *Herpes zoster* were reported at a higher incidence in the rituximab-containing arm of randomised studies. Severe infections were reported in about 4 % of patients treated with rituximab monotherapy. Higher frequencies of infections overall, including grade 3 or 4 infections, were observed during rituximab maintenance treatment up to 2 years when compared to observation. There was no cumulative toxicity in terms of infections reported over a 2 year treatment period. In addition, other serious viral infections either new, reactivated or exacerbated, some of which were fatal, have been reported with rituximab treatment. The majority of patients had received rituximab in combination with chemotherapy or as part of a haematopoetic stem cell transplant. Examples of these serious viral infections are infections caused by the herpes viruses (Cytomegalovirus, Varicella Zoster Virus and Herpes Simplex Virus), JC virus (progressive multifocal leukoencephalopathy (PML)) and hepatitis C virus. Cases of fatal PML that occurred after disease progression and retreatment have also been reported in clinical trials. Cases of hepatitis B reactivation, have been reported, the majority of which were in patients receiving rituximab in combination with cytotoxic chemotherapy. In patients with relapsed/refractory CLL, the incidence of grade 3/4 hepatitis B infection (reactivation and primary infection) was 2 % in R-FC vs 0 % FC. Progression of Kaposi's sarcoma has been observed in rituximab-exposed patients with pre-existing Kaposi's sarcoma. These cases occurred in non-approved indications and the majority of patients were HIV positive.

Haematologic adverse reactions
In clinical trials with rituximab monotherapy 4 weeks, haematological abnormalities occurred in a minority of patients and were usually mild and reversible. , neutropenia was reported in 4,2 %, anaemia in 1,1 % and thrombocytopenia in 1,7 % of the patients. D ntenance treatment for up to 2 years, leucopenia (5 % vs. 2 %, grade 3/4) and neutropenia (10% vs. were reported at a higher incidence when compared to observation. The incidence of thrombocytopenia was low (< 1 , grade /4) and was not different between treatment arms.
During the treatment course in studies with rituximab in combination with chemotherapy, grade 3/4 leucopenia (R-CHOP 88 % vs. CHOP 79 %, R-FC 23 % vs. FC 12%), neutropenia (R-CVP 24 % vs. CVP 14 %; R-CHOP 97 % vs. CHOP 88 %, R-FC 30 % vs. FC 19 % in previously untreated CLL), pancytopenia (R-FC 3 % vs. FC 1 % in previously untreated CLL) were usually reported with higher frequencies when compared to chemotherapy alone. However, the higher incidence of neutropenia in patients treated with rituximab and chemotherapy was not associated with a higher incidence of infections and infestations compared to patients treated with chemotherapy alone. Studies in previously untreated and relapsed/refractory CLL have established that in up to 25 % of patients treated with R-FC neutropenia was prolonged (defined as neutrophil count remaining below 1x10^9/l between day 24 and 42 after the last dose) or occurred with a late onset (defined as neutrophil count below 1x10^9/l later than 42 days after last dose in patients with no previous prolonged neutropenia or who recovered prior to day 42) following treatment with rituximab plus FC. There were no differences reported for the incidence of anaemia. Some cases of late neutropenia occurring more than four weeks after the last infusion of rituximab were reported. In the CLL first-line study, Binet stage C patients experienced more adverse events in the R-FC arm compared to the FC arm (R-FC 83 % vs. FC 71 %). In the relapsed/refractory CLL study grade 3/4 thrombocytopenia was reported in 11 % of patients in the R-FC group compared to 9 % of patients in the FC group.
In studies of rituximab in patients with Waldenstrom's macroglobulinaemia, transient increases in serum IgM levels have been observed following treatment initiation, which may be associated with hyperviscosity and related symptoms. The transient IgM increase usually returned to at least baseline level within 4 months.

Cardiovascular adverse reactions
Cardiovascular reactions during clinical trials with rituximab monotherapy were reported in 18,8 % of patients with the most frequently reported events being hypotension and hypertension. Cases of grade 3 or 4 arrhythmia (including ventricular and supraventricular tachycardia) and angina pectoris during infusion were reported. During maintenance treatment, the incidence of grade 3/4 cardiac disorders was comparable between patients treated with rituximab and observation. Cardiac events were reported as serious adverse events (including atrial fibrillation, myocardial infarction, left ventricular failure, myocardial ischaemia) in 3 % of patients treated with rituximab compared to < 1 % on observation. In studies evaluating rituximab in combination with chemotherapy, the incidence of grade 3 and 4 cardiac arrhythmias, predominantly supraventricular arrhythmias such as tachycardia and atrial flutter/fibrillation, was higher in the R-CHOP group (14 patients, 6,9 %) as compared to the CHOP group (3 patients, 1,5 %). All of these arrhythmias either occurred in the context of a rituximab infusion or were associated with predisposing conditions such as fever, infection, acute myocardial infarction or pre-existing respiratory and cardiovascular disease. No difference between the R-CHOP and CHOP group was observed in the incidence of other grade 3 and 4 cardiac events including heart failure, myocardial disease and manifestations of coronary artery disease. In CLL, the overall incidence of grade 3 or 4 cardiac disorders was low both in the first-line study (4 % R-FC, 3 % FC) and in the relapsed/refractory study (4 % R-FC, 4 % FC).

Respiratory system
Cases of interstitial lung disease, some with fatal outcome, have been reported.

Neurologic disorders
During the treatment period (induction treatment phase comprising of R-CHOP for at most eight cycles), four patients (2 %) treated with R-CHOP, all with cardiovascular risk factors, experienced thromboembolic cerebrovascular accidents during the first treatment cycle. There was no difference between the treatment groups in the incidence of other thromboembolic events. In contrast, three patients (1,5 %) had cerebrovascular events in the CHOP group, all of which occurred during the follow-up period. In CLL, the overall incidence of grade 3 or 4 nervous system disorders was low both in the first-line study (4 % R-FC, 4 % FC) and in the relapsed/refractory study (3 % R-FC, 3 % FC).
Cases of posterior reversible encephalopathy syndrome (PRES) / reversible posterior leukoencephalopathy syndrome (RPLS) have been reported. Signs and symptoms included visual disturbance, headache, seizures and altered mental status, with or without associated hypertension. A diagnosis of PRES/RPLS requires confirmation by brain imaging. The reported cases had recognised risk factors for PRES/RPLS, including the patients' underlying disease, hypertension, immunosuppressive therapy and/or chemotherapy.

Gastrointestinal disorders
Gastrointestinal perforation in some cases leading to death has been observed in patients receiving rituximab for treatment of non-Hodgkin's lymphoma. In the majority of these cases, rituximab was administered with chemotherapy.

IgG levels
In the clinical trial evaluating rituximab maintenance treatment in relapsed/refractory follicular lymphoma, median IgG levels were below the lower limit of normal (LLN) (< 7 g/l) after induction treatment in both the observation and the rituximab groups. In the observation group, the median IgG level subsequently increased to above the LLN, but remained constant in the rituximab group. The proportion of patients with IgG levels below the LLN was about 60 % in the rituximab group throughout the 2 year treatment period, while it decreased in the observation group (36 % after 2 years).
A small number of spontaneous and literature cases of hypogammaglobulinaemia have been observed in paediatric patients treated with rituximab, in some cases severe and requiring long-term immunoglobulin substitution therapy. The consequences of long term B cell depletion in paediatric patients are unknown.

Skin and subcutaneous tissue disorders
Toxic Epidermal Necrolysis (Lyell Syndrome) and Stevens Johnson Syndrome, some with fatal outcome, have been reported very rarely.

Patient subpopulations - rituximab monotherapy
Elderly patients (≥ 65 years):
The incidence of ADRs of all grades and grade 3 /4 ADR was similar in elderly patients compared to younger patients (< 65 years).

Bulky disease
There was a higher incidence of grade 3/4 ADRs in patients with bulky disease than in patients without bulky disease (25,6 % vs. 15,4 %). The incidence of ADRs of any grade was similar in these two groups.

Re-treatment
The percentage of patients reporting ADRs upon re-treatment with further courses of rituximab was similar to the percentage of patients reporting ADRs upon initial exposure (any grade and grade 3/4 ADRs).

Patient subpopulations - rituximab combination therapy
Elderly patients (≥ 65 years)
The incidence of grade 3/4 blood and lymphatic adverse events was higher in elderly patients compared to younger patients (< 65 years), with previously untreated or relapsed/refractory CLL.

Summary of the safety profile (granulomatosis with polyangiitis and microscopic polyangiitis)
In the clinical trial in granulomatosis with polyangiitis and microscopic polyangiitis, 99 patients were treated with rituximab (375 mg/m², once weekly for 4 weeks) and glucocorticoids (see **Pharmacodynamic properties**).

The ADRs listed in Table 1 were all adverse events which occurred at an incidence of ≥ 5 % in the rituximab group.

Table 1: ADRs occurring at 6-months in ≥ 5 % of patients receiving rituximab, and at a higher frequency than the comparator group, in the pivotal clinical study

Body system Adverse reaction	Rituximab (n=99)
Infections and infestations	
Urinary tract infection	7 %
Bronchitis	5 %
Herpes zoster	5 %
Nasopharyngitis	5 %
Blood and lymphatic system disorders	
Thrombocytopenia	7 %
Immune system disorders	
Cytokine release syndrome	5 %
Metabolism and nutrition disorders	
Hyperkalaemia	5 %
Psychiatric disorders	
Insomnia	14 %
Nervous system disorders	
Dizziness	10 %
Tremor	10 %
Vascular disorders	
Hypertension	12 %
Flushing	5 %
Respiratory, thoracic and mediastinal disorders	
Cough	12 %
Dyspnoea	11 %
Epistaxis	11 %
Nasal congestion	6 %
Gastrointestinal disorders	
Diarrhoea	18 %
Dyspepsia	6 %
Constipation	5 %
Skin and subcutaneous tissue disorders	
Acne	7 %
Musculoskeletal and connective tissue disorders	
Muscle spasms	18 %
Arthralgia	15 %
Back pain	10 %
Muscle weakness	5 %
Musculoskeletal pain	5 %
Pain in extremities	5 %
General disorders and administration sita conditions	
Peripheral oedema	16 %
Investigations	
Decreased haemoglobin	6 %

Description of selected adverse drug reactions
Infusion related reactions
IRRs in the GPA and MPA clinical trial were defined as any adverse event occurring within 24 hours of an infusion and considered to be infusion-related by investigators in the safety population. Ninety-nine patients were treated with rituximab and 12 % experienced at least one IRR. All IRRs were CTC Grade 1 or 2. The most common IRRs included cytokine release syndrome, flushing, throat irritation, and tremor. Rituximab was given in combination with intravenous glucocorticoids which may reduce the incidence and severity of these events.

Infections
In the 99 rituximab patients, the overall rate of infection was approximately 237 per 100 patient years (95 % CI 197-285) at the 6-month primary endpoint. Infections were predominately mild to moderate and consisted mostly of upper respiratory tract infections, herpes zoster and urinary tract infections.
The rate of serious infections was approximately 25 per 100 patient years. The most frequently reported serious infection in the rituximab group was pneumonia at a frequency of 4 %.

Malignancies
The incidence of malignancy in rituximab treated patients in the granulomatosis with polyangiitis and microscopic polyangiitis clinical study was 2,00 per 100 patient years at the study common closing date (when the final patient had completed the follow-up period).
On the basis of standardised incidence ratios, the incidence of malignancies appears to be similar to that previously reported in patients with ANCA-associated vasculitis.

Cardiovascular adverse reactions
Cardiac events occurred at a rate of approximately 273 per 100 patient years (95 % CI 149-470) at the 6 month primary endpoint. The rate of serious cardiac events was 2,1 per 100 patient years (95 % CI 3-15). The most frequently reported events were tachycardia (4 %) and atrial fibrillation (3 %) (see **WARNINGS AND SPECIAL PRECAUTIONS**).

Neurologic events
Cases of posterior reversible encephalopathy syndrome (PRES) reversible posterior leukoencephalopathy syndrome (RPLS) have been reported in autoimmune conditions Signs and symptoms included visual disturbance, headache, seizures and altered mental status, with or without associated hypertension A diagnosis of PRES/RPLS requires confirmation by brain imaging. The reported cases had recognised risk factors for PRES/RPLS, including the patients' underlying disease, hypertension, immunosuppressive therapy and/or chemotherapy.

Hepatitis B reactivation
A small number of cases of hepatitis B reactivation, some with fatal outcome, have been reported in granulomatosis with polyangiitis and microscopic polyangiitis patients receiving rituximab in the post-marketing setting.

Hypogammaglobulinaemia
Hypogammaglobulinaemia (IgA, IgG or IgM below the lower limit of normal) has been observed in granulomatosis with polyangiitis and microscopic polyangiitis patients treated with rituximab. At 6 months, in the active-controlled, randomised, double-blind, multicentre, non-inferiority trial, in the rituximab group, 27 %, 58 % and 51 % of patients with normal immunoglobulin levels at baseline, had low IgA, IgG and IgM levels, respectively compared to 25 %, 50 % and 46 % in the cyclophosphamide group. There was no increased rate in overall infections or serious infections in patients with low IgA, IgG or IgM.

Neutropenia
In the active controlled, randomised, double-blind, multicentre, non-inferiority trial of rituximab in granulomatosis with polyangiitis and microscopic polyangiitis, 24 % of patients in the rituximab group (single course) and 23 % of patients in the cyclophosphamide group developed CTC grade 3 or greater neutropenia. Neutropenia was not associated with an observed increase in serious infection in rituximab treated patients. The effect of multiple rituximab courses on the development of neutropenia in granulomatosis with polyangiitis and microscopic polyangiitis patients has not been studied in clinical trials.

Skin and subcutaneous tissue disorders
Toxic epidermal necrolysis (Lyell's Syndrome) and Stevens Johnson Syndrome, some with fatal outcome, have been reported very rarely.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT
Limited experience with doses higher than the approved dose of intravenous rituximab formulation is available from clinical trials in humans. The highest intravenous dose of rituximab tested in humans to date is 5 000 mg (2 250 mg/m²), tested in a dose escalation study in patients with CLL. No additional safety signals were identified.
Patients who experience overdose should have immediate interruption of their infusion and be closely monitored.
In the post marketing setting five cases of rituximab overdose have been reported. Three cases had no reported adverse event. The two adverse events that were reported were flu-like symptoms, with a dose of 1,8 g of rituximab and fatal respiratory failure, with a dose of 2 g of rituximab.

IDENTIFICATION
A clear, colourless solution.

PRESENTATION
BLITZIMA 100 mg: Clear, colourless, type I glass vial with a chlorobutyl rubber stopper and an aluminium seal with a yellow flip-off cap. Pack of 2 vials.
BLITZIMA 500 mg: Clear, colourless, type I glass vial with a chlorobutyl rubber stopper and an aluminium seal with a dark grey flip-off cap. Pack of 1 vial.

STORAGE INSTRUCTIONS
Store at 2 °C to 8 °C.
Keep the container in the outer carton in order to protect from light.
Diluted product
The prepared infusion solution of rituximab is physically and chemically stable for 24 hours at 2 °C to 8 °C and subsequently 12 hours at room temperature (not more than 30 °C).
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 to 8 °C, unless dilution has taken place in controlled and validated aseptic conditions.
KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS
BLITZIMA 100 mg: 53/26/0506
BLITZIMA 500 mg: 53/26/0507

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION
Adcock Ingram Limited,
1 New Road,
Erand Gardens,
Midrand, 1685,
South Africa

DATE OF PUBLICATION OF THE PACKAGE INSERT
25 August 2020

adcock ingram

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