PATIENT INFORMATION LEAFLET

SCHEDULING STATUS

S4

PROPRIETARY NAME, STRENGTH AND PHARMACEUTICAL FORM

MabThera® 100 Infusion

MabThera® 500 Infusion

Read all of this leaflet carefully before you start receiving MabThera

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or pharmacist.
- MabThera 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.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

WHAT MABTHERA CONTAINS

Single dose vials containing 100 mg (in 10 mℓ) or 500 mg (in 50 mℓ) of rituximab concentrate solution for infusion.

The other ingredients are polysorbate 80, sodium chloride, sodium citrate dihydrate, water for injection, and hydrochloric acid.

WHAT MABTHERA IS USED FOR

Rituximab is an antibody which is a type of protein. Rituximab binds to the surface of a type of white blood cell, the B lymphocytes. When rituximab binds to the surface of this cell it causes the cell to die.

MabThera may be used for the treatment of several different conditions. Your doctor may prescribe MabThera for the treatment of:

a) Non-Hodgkin's Lymphoma (NHL)

Non-Hodgkin's Lymphoma is a disease of the lymphatic system, and B lymphocytes are involved in the cause of some of the symptoms you may have. MabThera can be used alone or with other medicines your doctor may prescribe to induce remission of your disease. MabThera may be used as a continuous (maintenance) treatment for 2 years in patients who have responded to induction treatment.

b) Chronic Lymphocytic Leukaemia (CLL)

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

c) Rheumatoid Arthritis (RA)

MabThera is used for the treatment of rheumatoid arthritis. Rheumatoid arthritis is a disease of the joints. B lymphocytes are involved in the cause of some of the symptoms you have. MabThera is used to treat rheumatoid arthritis in people who have already tried some other medicines which have either stopped working or have not worked well enough. MabThera is usually taken together with another medicine called methotrexate.

MabThera slows down the damage to your joints caused by rheumatoid arthritis and improves your ability to do normal daily activities.

d) Granulomatosis with polyangiitis (Wegener's) (GPA) and Microscopic polyangiitis (MPA):

MabThera is used for inducing remission in granulomatosis with polyangiitis (formerly called Wegener's granulomatosis) (GPA) or microscopic polyangiitis (MPA), taken in combination with corticosteroids. GPA and MPA are two forms of inflammation of blood vessels which mainly affects the lungs and kidneys, but may affect other organs as well B lymphocytes are involved in the cause of these conditions.

BEFORE TAKING MABTHERA

Do not use MabThera:

- if you are allergic to rituximab, to other similar proteins, or to any of the other ingredients in the solution.
- if you have an active, severe infection or have a severely decreased immune system function.
- if you have severe heart failure or severe uncontrolled heart disease and have RA, GPA or MPA.

If you are not sure about this, you should ask your doctor who will inform you accordingly.

Take special care with MabThera:

- if you think you have hepatitis infection now or have had it in the past. Patients who have had hepatitis B might have a repeat attack of hepatitis. Patients with a history of hepatitis B infection will be carefully checked by their doctor for signs of active hepatitis B.
- if you are taking treatment for high blood pressure. You may be asked not to take your medicines 12 hours before your infusion of MabThera. Some people have a fall in their blood pressure during the infusion.
- if you have ever had heart disease (i.e. angina, palpitations, or heart failure) or a history of breathing problems. Your doctor will take special care of you during your treatment with MabThera (in any of the above cases).
- tell your doctor if you are taking or have previously taken medicines which may affect your immune system, such as chemotherapy or immune-suppressive agents.

If you have RA, GPA or MPA 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 MabThera help to fight infection and you should wait until the infection has passed before you are given MabThera. Also please tell your doctor if you had a lot of infections in the past or suffer from severe infections.
- if you think you may need any vaccinations in the near future, including vaccinations needed to travel to other countries. Some vaccines should not be given at the same time as MabThera or in the months after you receive MabThera. Your doctor will check if you should have any vaccines before you receive MabThera.

Use in children:

At present, there is not much information about MabThera treatment in children and adolescents; if you are under 18 years of age, you or your parent should ask your doctor if MabThera is right for you.

Pregnancy and Breastfeeding

If you are pregnant or breastfeeding your baby, please consult your doctor, pharmacist or other healthcare professional for advice before receiving MabThera.

Pregnancy: You must tell your doctor if you are pregnant, if you think you are pregnant or if you intend to become pregnant. This is because MabThera is an antibody and can cross the placenta and affect your baby. You should not receive MabThera when you are pregnant.

If you can get pregnant, you must use an effective method of birth control during therapy with MabThera and for 12 months after your last treatment with MabThera.

Breastfeeding: MabThera can also get into breast milk. You should not breastfeed your baby during treatment with MabThera and for 12 months after your last treatment with MabThera.

Driving and using machinery:

It is not known whether MabThera has an effect on your ability to drive a car or operate machinery. You should first note how MabThera affects you before you drive or use machines.

Taking other medicines with MabThera:

Before starting treatment, make sure your doctor knows if you are taking other medicines (including those not prescribed by your doctor). This is extremely important, as using more than one medicine at the same time can strengthen or weaken their effect. MabThera should not be used with other medicines without your doctor's consent.

Always tell your healthcare professional if you are taking any other medicine. (This includes complementary or traditional medicines.)

HOW TO USE MABTHERA

MabThera is administered by a healthcare professional after dilution as an intravenous infusion ("drip"). Your doctor will give you a medicine to prevent or reduce pain and/or fever and allergy before each infusion of MabThera.

You will be observed by a healthcare professional while you are being given MabThera in case you have any side effects during the infusion.

Before the infusion is given you will be given medicines to prevent or reduce possible reactions to MabThera.

a) If you are being treated for non-Hodgkin's lymphoma

If you are treated with MabThera alone you will receive infusions at weekly intervals for a total of four infusions (days 1, 8, 15 and 22), so that a course of treatment usually lasts for 22 days. Repeated treatment courses with MabThera are possible. If you are treated with MabThera in combination with other medicines, you will receive an infusion of MabThera on the same day as the other medicines, which are usually given 8 times at 3-week intervals. If you have responded to treatment and are further treated with MabThera as continuous (maintenance) treatment, you will receive one infusion of MabThera every 2 or 3 months (as directed by your doctor) for two years. Your doctor may change the number of infusions depending on your disease.

b) If you are being treated for chronic lymphocytic leukemia

When you are treated with MabThera in combination with chemotherapy, you will receive MabThera infusions on day 0 (the day before chemotherapy), cycle 1 then day 1 of each cycle for 6 cycles in total. Each cycle has a duration of 28 days. The chemotherapy should be given after the MabThera infusion. Your doctor will decide if you should receive supportive therapy at that time.

c) If you are being treated for rheumatoid arthritis

Each course of treatment is made up of two separate infusions which are given 2 weeks apart. Repeated courses of treatment with MabThera are possible. Depending on the signs and symptoms of your disease, your doctor will decide when you should receive more MabThera. This may be months from now.

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

Treatment with MabThera uses four separate infusions given at weekly intervals. Corticosteroids will usually be given by injection before the start of MabThera treatment. Corticosteroids given by mouth may be started at any time by your doctor to treat your condition. If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

Do not share medicines prescribed for you with another person.

In the event of over dosage, consult your doctor or pharmacist. If neither is available, contact the nearest hospital or poison centre.

If you have missed a dose or taken more than you should:

You will be receiving doses according to your treatment plan and therefore you should go to the oncology clinic according to your scheduled appointments.

POSSIBLE SIDE EFFECTS

MabThera can cause side effects. Side effects are mild to moderate but some may be serious and may be fatal.

Infusion reactions

During or within the first 2 hours of the first infusion you may develop fever, chills and shivering. Less frequently, some patients may experience blisters, itching, sickness, tiredness, headache, breathing difficulties, tongue or throat swelling, itchy, runny nose, vomiting, flushing or palpitations, heart attack or low number of platelets. If you have heart disease or angina, these 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 for a while. 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 not to continue with MabThera treatment if you have a serious infusion-related reaction.

Infections

Tell your doctor after your MabThera treatment if you get any symptoms of an infection, for example fever, cough, sore throat, burning pain when passing urine, or you start to feel weak or generally unwell. You might get infections more easily following MabThera therapy. Often these are colds, but there have been cases of pneumonia or urinary infections.

There have been patients being treated with MabThera who had experienced a serious brain infection, which was fatal. **Tell your doctor immediately** if you have memory loss, trouble thinking, difficulty with walking or loss of vision.

Skin Reactions

Severe blistering skin conditions that can be life-threatening have occurred, including Stevens-Johnson Syndrome. Redness, often associated with blisters, may appear on the skin or on mucous membranes, such as inside the mouth, the genital areas or the eyelids, and fever may be present. **Tell your doctor immediately if you experience any of these symptoms.**

Advanced Multiple Brain Disease

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).

Other reactions

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

The most commonly reported side effects due to MabThera are:

- infections such as pneumonia (bacterial) and herpes (viral) or bronchial tube inflammation (bronchitis)
- low number of white blood cells, with or without fever, low number of platelets in the blood
- allergic reactions after infusion
- nausea
- skin rashes, itching, bald spots on the scalp, fever, chills, physical weakness, headache
- infections such as sepsis and pneumonia (bacterial), herpes and hepatitis B (viral) or candidal (fungal) bronchial tube and sinuses inflammation, or other general infections of unknown origin
- low number of red blood cells, low number of red and white blood cells and platelets
- allergic reactions (hypersensitivity)
- high sugar level in the blood, weight loss, excess fluid in the face and the body, increased blood levels of the enzyme (LDH), low blood level of calcium
- abnormal sensations of the skin, such as numbness, tingling, pricking, burning, a creeping skin sensation, decreased sense of touch. Feeling restless, difficulty falling asleep, becoming

red in the face and bruising of the skin as a consequence of dilation of the blood vessels, dizziness, anxiety

- an increased production of tears, secretion and shedding disorders, inflammation of the eye (conjunctivitis)
- ringing sound in the ears, ear pain
- heart disorders (heart attack, irregular heart rate, abnormally fast heart rate)
- high or low blood pressure, a decrease in blood pressure upon assuming an upright posture
- inflammation, irritation and/or tightness of the lungs, throat and/or sinuses, shortness of breath, too little oxygen reaching the body organs, coughing
- vomiting, diarrhoea, pain in the abdomen, irritation and/or ulceration of the throat and the mouth, difficulties in swallowing, constipation, indigestion. Eating disorders: decrease in the amount of food eaten with a consequential dangerous loss in weight
- skin disorders, burning sensation of the skin, itching, increased perspiration, night sweats
- musculoskeletal disorders**,** abnormal increase in tightness of muscle tone, pain, joint pain, muscle pain, back and neck pain
- general disorders, tumour pain, becoming markedly red in the face and other areas of the skin, general discomfort or uneasiness, flu syndrome, fatigue, shaking, multi-organ dysfunction.

Less frequent side effects of MabThera include:

- abnormal clotting, decrease of blood cells production, auto-immune decrease of red blood cells, swollen/enlarged lymph nodes

- low mood and loss of interest or pleasure in usual activities, nervousness
- taste changes
- heart disorder (heart attack, abnormally fast heart rate, reduced heart rate, irregular heart rate, chest pain) inflammation, irritation and/or tightness of the lungs, asthma, shortness of breath
- enlargement of the abdomen
- pain at the infusion site.
- temporary increased immunoglobulins, chemical disturbances in blood caused by the breakdown of dying cancer cells, which can also lead to kidney failure
- nerve damage in arms and legs, paralysis of the face
- heart failure
- inflammation of blood vessels including those leading to skin symptoms
- perforation of the bowel wall
- kidney failure
- 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.
- Infection caused by a fungus called *Pneumocystis jirovecii*

Events occurring at a frequency not known:

- delayed reduction of white blood cells
- infusion-related immediate reduction of platelets (reversible), can be fatal in rare cases
- hearing loss, loss of other senses.

b) If you are being treated for rheumatoid arthritis

The most frequent side effects due to MabThera are:

- infections such as pneumonia (bacterial)
- pain on passing water (urinary tract infection)
- allergic reactions that are most likely to occur during an infusion, but can occur up to 24-hours after infusion

- changes in blood pressure, nausea, rash, fever, feeling itchy, runny or block nose and sneezing, shaking, rapid heart beat, and tiredness
- headache
- changes in laboratory tests carried out by your doctor. These include a decrease in the amount of some specific proteins in the blood (immunoglobulins) which help protect against infection.
- infections such as bronchial tube inflammation (bronchitis)
- a feeling of fullness or a throbbing pain behind the nose, cheeks and eyes (sinusitis), pain in the abdomen, vomiting and diarrhoea, breathing problems
- fungal foot infection (athlete's foot)
- high cholesterol levels in the blood
- abnormal sensations of the skin, such as numbness, tingling, pricking or burning, sciatica, migraine, dizziness
- loss of hair
- anxiety, depression
- indigestion, diarrhoea, acid reflux, irritation and /or ulceration of the throat and the mouth
- pain in the tummy, back, muscles and/or joints.

Less frequent side effects due to MabThera include:

- Excess fluid retention in the face and body
- Inflammation, irritation and / or tightness of the lungs, and throat, coughing
- Skin reactions including hives, itching and rash
- Allergic reactions including wheezing or shortness of breath, swelling of the face and tongue, collapse
- A complex of symptoms occurring within a few weeks of an infusion of MabThera including allergic like reactions such as rash, itching, joint pain, swollen lymph glands and fever.
- Severe blistering skin conditions that can be life-threatening. Redness, often associated with blisters, may appear on the skin or on mucous membranes, such as inside the mouth, the genital areas or the eyelids, and fever may be present.

Other reported side effects due to MabThera include a decreased number of white cells in the blood (neutrophils) that help to fight against infection. Some infections may be severe (please see information on *Infections* within this section).

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

Frequent side effects due to MabThera are:

- 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 side effects due to MabThera include:

- 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

MabThera may also cause changes in laboratory tests carried out by your doctor. These include a decreased number of white cells in the blood (neutrophils) that help to fight against infection and a decrease in the amount of some specific proteins in the blood (immunoglobulins) which help protect against infection.

If you are receiving MabThera in combination with other medicines, some of the side effects you may experience may be due to the other medicine.

If any of the side effects gets serious, or, if you notice any side effects not listed in this leaflet, please inform your doctor, nurse or pharmacist immediately.

STORAGE AND DISPOSAL INFORMATION OF MABTHERA

Store all medicines out of the reach of children.

Always store the vials in the closed original pack at 2 – 8 °C (in the refrigerator). Keep the container in the outer carton in order to protect from light.

Do not use after the expiry date dated on the outer pack and on the vial label.

PRESENTATION OF MABTHERA

MabThera 100: Packs of 2 vials. Colourless 10 ml glass vial with a laminated grey butyl stopper. The two piece crimp closure for the vial consists of a metal cap sealed with a red plastic flip-off disc.

MabThera 500: Pack of 1 vial. Colourless 50 ml glass vial with a laminated grey butyl stopper. The two piece crimp closure for the vial consists of a metal cap sealed with a grey plastic flip-off disc.

IDENTIFICATION OF MABTHERA

MabThera is a clear to opalescent, colourless to pale yellow liquid provided in sterile, preservative-free, non-pyrogenic, single dose vials.

REGISTRATION NUMBERS

MabThera 100: 32/26/0578

MabThera 500: 32/26/0579

NAME AND ADDRESS OF REGISTRATION HOLDER

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