

Mabixen®

Rituximab

Read all of this leaflet carefully before you are given this medicine, it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If you get any side effects talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.
- Mabixen® 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.

WHAT IS IN THIS LEAFLET:

1. What Mabixen® is and what it is used for.
2. What you need to know before you use Mabixen®.
3. How to use Mabixen®.
4. Possible side effects.
5. How to store Mabixen®.
6. Contents of the pack and other information.

1. WHAT MABIXEN® IS AND WHAT IT IS USED FOR

Mabixen® contains the active substance rituximab. This is a type of protein called a "monoclonal antibody". It sticks to the surface of a type of white blood cell called "B-Lymphocyte". When rituximab sticks to the surface of this cell, the cell dies. Mabixen® may be used for the treatment of several different conditions in adults. Your doctor may prescribe Mabixen® for the treatment of:

a) Non-Hodgkin's Lymphoma

This is a disease of the lymph tissue (part of the immune system) that affects a type of white blood cell called B-Lymphocytes.

Mabixen® can be given alone or with other medicines called "chemotherapy".

In patients where the treatment is working, Mabixen® may be used as a maintenance treatment for 2 years after completing the initial treatment.

b) Chronic lymphocytic leukemia

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

c) Rheumatoid arthritis

Mabixen® 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. Mabixen® is used to treat rheumatoid arthritis in people who have already tried some other medicines which have either stopped working, have not worked well enough, or have caused side effects. Mabixen® is usually taken together with another medicine called methotrexate. Mabixen® slows down the damage to your joints caused by rheumatoid arthritis and improves your ability to do normal daily activities.

The best responses to Mabixen® are seen in those who have a positive blood test to rheumatoid factor (RF) and/or anti-Cyclic Citrullinated Peptide (anti-CCP). Both tests are commonly positive in rheumatoid arthritis and aid in confirming the diagnosis.

d) Granulomatosis with polyangiitis or microscopic polyangiitis

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

2. WHAT YOU NEED TO KNOW BEFORE YOU USE MABIXEN®

Do not take Mabixen® if:

- you are allergic to rituximab, other proteins which are like rituximab, or any of the other ingredients of this medicine (listed in section 6);
 - you have a severe active infection at the moment;
 - you have a weak immune system;
 - you have severe heart failure or severe uncontrolled heart disease and have rheumatoid arthritis, granulomatosis with polyangiitis, or microscopic polyangiitis.
- Do not have Mabixen® if any of the above apply to you. If you are not sure, talk to your doctor, pharmacist, or nurse before you are given Mabixen®.

Warnings and precautions

Talk to your doctor, pharmacist, or nurse before you are given Mabixen® if:

- you have ever had or might now have a hepatitis infection. This is because in a few cases Mabixen® 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 doctors for signs of this infection;
- you have ever had heart problems (such as angina, palpitations, or heart failure) or breathing problems.

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

If you have rheumatoid arthritis, 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 Mabixen® help to fight infection and you should wait until the infection has passed before you are given Mabixen®. 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 Mabixen® or in the four weeks after you receive Mabixen®. Your doctor will check if you should have any vaccines before you receive Mabixen®.

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 Mabixen® in children and young people.

Other medicines and Mabixen®

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

In particular, tell your doctor:

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

If any of the above apply to you (or you are not sure), talk to your doctor, pharmacist or nurse before you are given Mabixen®.

Pregnancy and breast-feeding

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

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

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

Driving and using machines

It is not known whether Mabixen® has an effect on you being able to drive or use any tools or

machines.

MABIXEN® contains sodium

This medicine contains 32.6 mg sodium in each 10 mL vial and 263.2 mg in each 50 mL vial. This is equivalent to 2.6% (for 10ml vial) and 13.2% (for 50 ml vial) of the recommended maximum daily dietary intake of sodium for an adult.

3. HOW MABIXEN® IS GIVEN

Mabixen® 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 Mabixen® as a drip (intra-venous infusion).

Medicines given before each Mabixen® administration

Before you are given Mabixen®, 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 Mabixen® alone

Mabixen® will be given to you once a week for 4 weeks. Repeated treatment courses with Mabixen® are possible.

• If you are having Mabixen® with chemotherapy

Mabixen® 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 Mabixen® as a maintenance treatment every 2 or 3 months for two years. Your doctor may change this, depending on how you respond to the medicine.

b) If you are being treated for chronic lymphocytic leukemia

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

c) If you are being treated for rheumatoid arthritis

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

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

Treatment with Mabixen® uses four separate infusions given at weekly intervals. Corticosteroids will usually be given by injection before the start of Mabixen® treatment. Corticosteroids given by mouth may be started at any time by your doctor to treat your condition.

If you are responding well to treatment, you may be given Mabixen® as a maintenance treatment. This will be administered as 2 separate infusions which are given 2 weeks apart, followed by 1 infusion every 6 months for at least 2 years. Your doctor may decide to treat you longer with Mabixen® (up to 5 years), depending on how respond to the medicine.

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

4. POSSIBLE SIDE EFFECTS

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

Infusion reactions

During or within the first 24 hours of the first infusion you may develop fever, chills, and shivering. Less frequently, some patients may experience pain at the infusion site, blisters, itching, sickness (nausea), tiredness, headache, breathing difficulties, blood pressure raised, wheezing, throat discomfort, tongue or throat swelling, itchy or runny nose, vomiting, flushing or palpitations, heart attack or a low number of platelets. If you have heart disease or angina, these reactions might get worse. **Tell the person giving you the infusion immediately** if you develop any of these symptoms, as the infusion may need to be slowed down or stopped. You may require additional treatment such as an antihistamine or paracetamol. When these symptoms go away or improve, the infusion can be continued. These reactions are less likely to happen after the second infusion. Your doctor may decide to stop your Mabixen® 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 Mabixen®.

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

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

Skin reactions

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

Other side effects include:

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

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

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

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

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

- general discomfort or feeling uneasy or tired, shaking, signs of flu;
- multiple-organ failure.

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

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

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

- short term increase in the amount of some types of 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, paralyzed face;
- heart failure;
- inflammation of blood vessels including those leading to skin symptoms;
- respiratory failure;
- damage to the intestinal wall (perforation);
- severe skin problems causing blisters that can be life-threatening. Redness, often associated with blisters, may appear on the skin or on mucous membranes, such as inside the mouth, the genital areas, or the eyelids, and fever may be present;
- kidney failure;
- severe vision loss.

Not known (it is not known how often these side effects happen):

- a reduction in white blood cells which does not happen straight away;
- reduced platelets number just after the infusion – this can be reversed, but can be fatal in rare cases;
- hearing loss, loss of other senses.

b) If you are being treated for rheumatoid arthritis

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

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

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

- infections such as bronchial tube inflammation (bronchitis);
- a feeling of fullness or throbbing pain behind the nose, cheeks, and eyes (sinusitis), pain in the abdomen, vomiting, and diarrhea, 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, diarrhea, acid reflux, irritation and /or ulceration of the throat and the mouth;
- pain in the tummy, back, muscles and/or joints.

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

- excess fluid retention in the face and body;
- inflammation, irritation and / or tightness of the lungs, and throat, coughing;
- skin reactions including hives, itching, and rash;
- allergic reactions including wheezing or shortness of breath, swelling of the face and tongue, collapse.

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

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

Other rarely-reported side-effects due to Mabixen® 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

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

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

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

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

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

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

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

If you are having Mabixen® with other medicines, some of the side effects you may get may be due to the other medicines.

Reporting of side effects

If you get any side effects talk to your doctor, pharmacist, or nurse. This includes any side effects not listed in this leaflet.

By reporting side effects, you can help provide more information on the safety of this medicine.

5. HOW TO STORE MABIXEN®

Keep all medicines out of the reach and sight of children.

Do not use Mabixen® after the expiry date stated on the label.

Store in a refrigerator (2 °C – 8 °C).

Keep the container in the outer carton in order to protect it from light.

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

6. CONTENTS OF THE PACK AND OTHER INFORMATION

What Mabixen® contains

The active ingredient in Mabixen® is called rituximab.

The 10 mL vial contains 100 mg of rituximab (10 mg/ml).

The 50 mL vial contains 500 mg of rituximab (10 mg/ml).

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

What MABIXEN® looks like and the content of the pack

Mabixen® is a clear, colorless to light yellow solution, supplied as a concentrate for solution for infusion.

Vials of 10 mL are available as a pack of 2 vials.

Vials of 50 mL are available as a pack of 2 vials.

Marketing Authorization Holder and Manufacturer:

Manufactured by JSC BIOCAD, Russia

For

Benta S.A.L.

Dbayeh – Lebanon

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