PATIENT PACKAGE INSERT IN ACCORDANCE WITH THE
PHARMACISTS' REGULATIONS (PREPARATIONS) - 1986

The medicine is dispensed according to a physician's prescription only

Benlysta I.V. 120 mg

Powder for concentrate for solution for infusion

Each vial contains:

120 mg of belimumab (80 mg/ml after reconstitution)

Benlysta I.V. 400 mg

Powder for concentrate for solution for infusion

Each vial contains:

400 mg of belimumab (80 mg/ml after reconstitution)

For the list of the inactive and allergenic ingredients in the medicine, see section 2 – "Important information about some of the ingredients in the medicine" and section 6 – "Additional information".

Read the leaflet carefully in its entirety before using the medicine. This leaflet contains concise information about the medicine. If you have further questions, refer to the physician or pharmacist.

This medicine has been prescribed for you. Do not pass it on to others. It may harm them even if it seems to you that their medical condition is similar.

1. WHAT IS THE MEDICINE INTENDED FOR?

Benlysta is indicated as an add-on therapy in patients from the age of 5 years and up with active, autoantibody-positive systemic lupus erythematosus (SLE) with a high degree of disease activity (e.g., positive anti-dsDNA and low complement) despite standard therapy.

Benlysta, in combination with immunosuppressive therapies, is intended for the treatment of adult patients with active lupus nephritis.

Therapeutic group: selective immunosuppressant.

Lupus is a disease in which the immune system (the system that fights infection) attacks your own cells and tissues, causing inflammation and organ damage. The disease can affect almost any organ in the body, and is thought to involve a type of white blood cells called B cells.

Benlysta contains belimumab (a human monoclonal antibody). It reduces the number of B cells in your blood by blocking the action of BLyS, a protein that helps B cells to live longer and is found in high levels in people with lupus.

You will be given Benlysta in addition to your usual treatment for lupus.

2. BEFORE USING THE MEDICINE

Do not use the medicine if:

- you are sensitive (allergic) to belimumab or to any of the additional ingredients contained in this medicine (listed in section 6).

→ Tell your physician **if you think any of these may apply to you.**

Special warnings regarding use of the medicine

Before the treatment with Benlysta, tell the physician if:

- you have a current or long-term **infection** or if you often get infections (see section 4). Your physician will decide if you can be given Benlysta.
- you are **planning to get vaccinated or were vaccinated** within the last 30 days. Some vaccines should not be given just before or during treatment with Benlysta.
- your lupus **affects your nervous system.**
- you are an HIV (human immunodeficiency virus) carrier or have low immunoglobulin levels.
- you have, or have had, hepatitis B or C.
- you have had an organ transplant or a bone marrow or stem cell transplant.
- you have had cancer.

→ **Tell your physician** if any of these may apply to you.

Depression and suicide

There have been reports of depression, suicidal thoughts, and suicide attempts including suicide during treatment with Benlysta. Tell your physician if you have a history of these conditions. If you experience new or worsening symptoms at any time:

→ **Contact your physician or go to a hospital straight away.**

If you feel depressed or have thoughts of harming yourself or committing suicide, you may find it helpful to tell a relative or close friend and ask them to read this leaflet. You might ask them to tell you if they are worried about changes in your mood or behavior.

Look out for important symptoms

Patients taking medicines that affect their immune system may be more at risk of contracting infections, including a rare but serious brain infection called progressive multifocal leukoencephalopathy (PML).

→ **For further information, read "Increased risk of brain infection" in section 4 of this leaflet.**

Children and adolescents

This medicine is not intended for use:

- in children under 5 years of age with SLE (lupus).
- in children and adolescents (under 18 years of age) with active lupus nephritis.

Drug interactions

If you are taking, or have recently taken, other medicines, including non-prescription medicines and nutritional supplements, tell the physician or pharmacist. Especially if you are taking medicines that affect the immune system, including any medicine that affects your B cells (to treat cancer or inflammatory diseases).

→ Using such medicines in combination with Benlysta may make your immune system less effective. This could increase your risk of contracting a serious infection.

Pregnancy and breast-feeding

Contraceptives in women of child-bearing potential

Use an effective method of contraception during treatment with Benlysta and for at least 4 months after the last dose.

Pregnancy

Benlysta is not usually recommended if you are pregnant.

- **Tell your physician if you are pregnant,** think you may be pregnant, or are planning to become pregnant. Your physician will decide if you can be given Benlysta.
- **If you become pregnant while being treated with Benlysta,** tell your physician.

Breast-feeding

Tell your physician if you are breast-feeding. It is likely that Benlysta can pass into breast milk. Your physician will discuss with you whether you should stop treatment with Benlysta while you are breast-feeding, or if you should stop breast-feeding.

Driving and using machines

Benlysta can cause side effects that may impair your ability to drive or operate machinery.

Important information about some of the ingredients in the medicine

Important information about the contents of Benlysta:

Benlysta contains less than 1 mmol sodium (23 mg) per dose, so it is essentially sodium-free.

3. HOW SHOULD YOU USE THE MEDICINE?

Always use the preparation according to the physician's instructions.

Check with the physician or pharmacist if you are uncertain about the dosage and treatment regimen of the medicine.

The dosage and treatment regimen will be determined by the physician only.

A nurse or physician will give you Benlysta through a drip in your vein (intravenous infusion) over one hour.

Instructions in English for preparation for healthcare professionals are in section "Instructions for use and handling" at the end of this leaflet.

Adults and children (from 5 years of age and up)

Your physician will determine the correct dose according to your body weight. The usual dosage is generally 10 mg for each kilogram (kg) of your body weight.

You will usually receive Benlysta on the first day of treatment then again 14 and 28 days later. After this, Benlysta is usually given once every four weeks.

Medicines given before the infusion

Your physician may decide to give you medicines which help reduce any infusion reactions before you are given Benlysta. These may include a type of medicine called an anti-histamine and a medicine to prevent a high temperature. You will be closely monitored and if you do have any reactions, they will be treated.

Stopping treatment with Benlysta

Even if there is an improvement in your health, do not stop treatment with the medicine without consulting the physician.

Your physician will decide if you need to stop using Benlysta.

Do not exceed the recommended dose.

If you took an overdose, or if a child has accidentally swallowed the medicine, refer immediately to a physician or proceed to a hospital emergency room, and bring the package of the medicine with you.

Adhere to the treatment regimen recommended by your physician.

Do not take medicines in the dark! Check the label and the dose each time you take a medicine. Wear glasses if you need them.

If you have further questions regarding use of the medicine, consult the physician or pharmacist.

4. SIDE EFFECTS

As with any medicine, use of Benlysta may cause side effects in some users. Do not be alarmed by reading the list of side effects. You may not suffer from any of them.

Allergic reactions – refer for medical help immediately

Benlysta can cause an infusion reaction or an allergic (hypersensitivity) reaction. These side effects are common (may affect in up to 1 in 10 people).

These effects can occasionally be severe (uncommon side effects, may occur in up to 1 in 100 people), and could be life-threatening. These severe effects are more likely to happen on the day of your first or second treatment, but they can be delayed and occur

a few days later.

Tell your physician or nurse immediately, or proceed to the emergency room of the nearest hospital, if you experience any of the following symptoms of an allergic or infusion reaction:

• swelling of the face, lips, mouth or tongue
• wheezing, difficulty in breathing or shortness of breath
• rash
• itchy bumps on the skin or hives

Rarely, less severe delayed reactions to Benlysta can also occur, usually 5 to 10 days after the infusion. They include symptoms such as rash, nausea, tiredness, muscle aches, headaches, or facial swelling.

If you experience these symptoms, particularly if you experience two or more symptoms together:

→ **tell the physician or nurse.**

Infections

Benlysta can make you more likely to get infections, including infections of the urinary tract and airways. Younger children may be at increased risk. These side effects are very common and may affect more than 1 in 10 people. Some infections can be severe and can uncommonly cause death.

If you experience any of the following symptoms of an infection:

• fever and/or chills
• cough, breathing problems
• diarrhea, vomiting
• burning sensation while passing urine; urinating often
• warm, red or painful skin or sores on your body.

→ **Refer to your physician or nurse immediately.**

Depression and suicide

There have been reports of depression, suicidal thoughts, and suicide attempts during treatment with Benlysta. Depression can affect in up to 1 in 10 people, suicidal thoughts and suicide attempts can affect in up to 1 in 100 people. If you feel depressed, have

thoughts about harming yourself or other distressing thoughts, or if you are depressed and notice that you feel worse or develop new symptoms:

→ **Contact your physician or go to a hospital straight away.**

Increased risk of brain infection:

Medicines that weaken your immune system, such as Benlysta, may put you at higher risk of getting a rare but serious and life-threatening brain infection called progressive multifocal leukoencephalopathy (PML).

Symptoms of PML include:

• memory loss
• trouble thinking
• difficulty talking or walking
• loss of vision

→ **Tell your physician** immediately if you experience any of these symptoms, or similar problems that lasted more than several days.

If you already had these symptoms before you started treatment with Benlysta:

→ **Tell your physician immediately** if you notice any changes in these symptoms.

Additional side effects:

Very common side effects

These may affect **more than 1 in 10** people:

• bacterial infections (see “Infections” section above)
• nausea, diarrhea.

Common side effects

These may affect **up to 1 in 10** people:

• high temperature
• low white blood cell count (can be identified in a blood test)
• nose, throat, or stomach infection
• pain in hands or feet
• migraine

Uncommon side effects

These may affect **up to 1 in 100** people:

• itchy, bumpy rash (hives), skin rash.

If a side effect occurs, if one of the side effects worsens, or if you suffer from a side effect not mentioned in this leaflet, consult with the physician.

Reporting side effects

Side effects can be reported to the Ministry of Health by clicking on the link "Report Side Effects of Drug Treatment" found on the Ministry of Health homepage (www.health.gov.il) that directs you to the online form for reporting side effects, or by entering the link:

https://sideeffects.health.gov.il/

5. HOW TO STORE THE MEDICINE?

• Avoid poisoning! This medicine and any other medicine should be kept in a closed place out of the reach and sight of children and/or infants in order to avoid poisoning. Do not induce vomiting unless explicitly instructed to do so by the physician.

• Do not use the medicine after the expiry date (exp. date) that appears on the package. The expiry date refers to the last day of that month.

• Store in a refrigerator (between 2°C to 8°C).

• Do not freeze.

• For single use only.

• Store in the original package in order to protect from light.

• Do not discard medicines in the wastewater or household waste bin. Ask the pharmacist how to dispose of medicines that are no longer in use. These measures will help protect the environment.

6. ADDITIONAL INFORMATION

• In addition to the active ingredient, the medicine also contains:
sucrose, sodium citrate dihydrate, polysorbate and citric acid monohydrate.
For further information, see section 2 **"Important information about some of the ingredients in the medicine"**.

• What the medicine looks like and the contents of the package:

Benlysta is supplied as a white to off-white powder for preparation of an infusion solution, in a glass vial, sealed with aluminum and a silicon cap.

Each package contains one vial.

- License Holder: GlaxoSmithKline (Israel) Ltd., 25 Basel St., Petach Tikva.
- Manufacturer: Glaxo Group Ltd., Brentford, UK.
- Registration number of the medicine in the National Drug Registry of the Ministry of Health:

  Benlysta I.V. 120 mg: 147-37-33499

  Benlysta I.V. 400 mg: 147-38-33510

Revised in December 2022 according to MoH guidelines.

Ben PT v7C

The following information is intended for healthcare professionals only:

Instructions for use and handling –

reconstitution, dilution and administration

1) How to reconstitute Benlysta

Reconstitution and dilution needs to be carried out under aseptic conditions.

Allow 10 to 15 minutes for the vial to warm to room temperature (15°C to 25°C).

It is recommended that a 21-25 gauge needle be used when piercing the vial stopper for reconstitution and dilution.

WARNING: The 5 mL and 20 mL vials are reconstituted with different volumes of diluent, see below:

120 mg vial

The 120 mg single-use vial of Benlysta is reconstituted with 1.5 mL of water for injections to yield a final concentration of 80 mg/mL belimumab.

400 mg vial

The 400 mg single-use vial of Benlysta is reconstituted with 4.8 mL of water for injections to yield a final concentration of 80 mg/mL belimumab.

Amount of Benlysta	Vial size	Volume of diluent	Final concentration
120 mg	5 mL	1.5 mL	80 mg/mL
400 mg	20 mL	4.8 mL	80 mg/mL

The stream of water for injections should be directed toward the side of the vial to minimize foaming. Gently swirl the vial for 60 seconds. Allow the vial to sit at room temperature (15°C to 25°C) during reconstitution, gently swirling the vial for 60 seconds every 5 minutes until the powder is dissolved. Do not shake. Reconstitution is typically complete within 10 to 15 minutes after the water has been added, but it may take up to 30 minutes. Protect the reconstituted solution from sunlight.

If a mechanical reconstitution device is used to reconstitute Benlysta it should not exceed 500 rpm and the vial should be swirled for no longer than 30 minutes.

2) Before diluting Benlysta

Once reconstitution is complete, the solution should be opalescent and colorless to pale

yellow, and without particles. Small air bubbles, however, are expected and acceptable.

120 mg vial

After reconstitution, a volume of 1.5 mL (corresponding to 120 mg belimumab) can be withdrawn from each 5 mL vial.

400 mg vial

After reconstitution, a volume of 5 mL (corresponding to 400 mg belimumab) can be withdrawn from each 20 mL vial.

3) How to dilute the solution for infusion

The reconstituted medicinal product is diluted to 250 mL with sodium chloride 9 mg/mL (0.9%), sodium chloride 4.5 mg/mL (0.45%), or Lactated Ringer's solution for injection. For patients whose body weight is less than or equal to 40 kg, infusion bags with 100 mL of these diluents may be considered providing that the resulting belimumab concentration in the infusion bag does not exceed 4 mg/mL.

5% glucose intravenous solutions are incompatible with Benlysta and must not be used.

From a 250 mL (or 100 mL) infusion bag or bottle of sodium chloride 9 mg/mL (0.9%), sodium chloride 4.5 mg/mL (0.45%), or Lactated Ringer's solution for injection, withdraw and discard a volume equal to the volume of the reconstituted Benlysta solution required for the patient's dose. Then add the required volume of the reconstituted Benlysta solution into the infusion bag or bottle. Gently invert the bag or bottle to mix the solution. Any unused solution in the vials must be discarded.

Inspect the Benlysta solution visually for particulate matter and discoloration prior to administration. Discard the solution if any particulate matter or discoloration is observed.

The reconstituted solution, if not used immediately, should be protected from direct sunlight and stored refrigerated at 2°C to 8°C. Solutions diluted in sodium chloride 9 mg/mL (0.9%), sodium chloride 4.5 mg/mL (0.45%), or Lactated Ringer's solution for injection may be stored at 2°C to 8°C or room temperature (15°C to 25°C).

The total time from reconstitution of Benlysta to completion of infusion should not exceed 8 hours.

4) How to administer the diluted solution

Benlysta is infused over a 1 hour period.

Benlysta should not be infused concomitantly in the same intravenous line with other agents.

No incompatibilities between Benlysta and polyvinylchloride or polyolefin bags have been observed.