Patient leaflet in accordance with the Pharmacists' Regulation (Preparations) - 1986

This medicine is dispensed with a doctor's prescription only.

BLINCYTO®

38.5 mcg powder for concentrate for solution for infusion

Active Ingredient
The active substance is blinatumomab. Each vial of powder contains 38.5 mcg of blinatumomab.

For Inactive ingredients and allergens in the medicine – see section 6 ''Additional information''.
Read this leaflet carefully and until the end before using this medicine. This leaflet contains concise information about the medicine. If you have additional questions, contact your doctor or pharmacist.

This medicine is prescribed for treating your illness. Do not pass it on to others. It may cause them harm even if it appears to you that their medical condition is similar.

In addition to the patient leaflet, **BLINCYTO** has Patient Card and Educational Brochure for Patients and Caregivers. The Card and Brochure include important safety information that you should be aware of before and during treatment with **BLINCYTO** and act accordingly. The patient card, brochure and the patient leaflet should be read prior treatment initiation with this product. The card and brochure should be kept for additional reading as needed.

1. What is this Medicine Intended for?

- BLINCYTO is indicated as monotherapy for the treatment of adults with CD19 positive relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL). Patients with Philadelphia chromosome-positive B-cell precursor ALL should have failed treatment with at least 2 tyrosine kinase inhibitors (TKIs) and have no alternative treatment options.
- BLINCYTO is indicated as monotherapy for the treatment of adults with Philadelphia chromosome-negative CD19 positive B-cell precursor ALL in first or second complete remission with minimal residual disease (MRD) greater than or equal to 0.1%.
- BLINCYTO is indicated as monotherapy for the treatment of pediatric patients aged 1 year or older with Philadelphia chromosome-negative CD19 positive B-cell precursor ALL which is refractory or in relapse after receiving at least two prior therapies or in relapse after receiving prior allogeneic hematopoietic stem cell transplantation.
- BLINCYTO is indicated as monotherapy for the treatment of pediatric patients aged 1 year or older with high-risk first relapsed Philadelphia

chromosome-negative CD19 positive B-cell precursor ALL as part of the consolidation therapy.

Limitations of use:
After failure of two previous treatments and with no CNS involvement.

Therapeutic group: BLINCYTO belongs to a group of medicines called antineoplastic agents which target cancer cells.

2. Before Using this Medicine

X Don't use this medicine if:

- you are allergic to blinatumomab or any of the other ingredients of this medicine (refer to the listed ingredients in section 6).
- you are breast-feeding.

Special warnings regarding the usage of the medicine
Talk to your doctor, pharmacist or nurse before using BLINCYTO if any of these apply to you. BLINCYTO may not be suitable for you:

- if you have ever had neurological problems, for example, shaking (or tremor), abnormal sensations, seizures, memory loss, confusion, disorientation, loss of balance, or difficulty speaking. If you are still suffering from active neurological problems or conditions, tell your doctor. If your leukemia has spread to your brain and/or spinal cord, your doctor may have to treat this first before you can start treatment with BLINCYTO. Your doctor will assess your nervous system and conduct tests before deciding if you should receive BLINCYTO. Your doctor may need to take special care of you during your treatment with BLINCYTO.
- if you have an active infection.
- if you have ever had an infusion reaction after previously using BLINCYTO. Symptoms may include wheezing, flushing, face swelling, difficulty breathing, low or high blood pressure.
- if you think you may need any vaccinations in the near future, including those needed to travel to other countries. Some vaccines must not be given within two weeks before, at the same time as or in the months after you receive treatment with BLINCYTO. Your doctor will check if you should have the vaccination.

Tell your doctor, pharmacist or nurse immediately if you experience any new symptoms, including but not limited to the following symptoms whilst receiving BLINCYTO as these may need to be treated and your dose adjusted:

- effects on your nervous system. Symptoms include feeling confused, feeling less alert, or having difficulty speaking and/or writing. Some of these may be signs of a serious immune reaction called 'immune effector cell-associated neurotoxicity syndrome' (ICANS).
- if you develop chills or shivering, or you feel warm; you should take your temperature as you may have a fever - these may be symptoms of an infection.
- if you develop a reaction at any time during your infusion, which may include dizziness, feeling faint, nauseated, face swelling, difficulty breathing, wheezing, or rash.

- if you have severe and persistent stomach pain, with or without nausea and vomiting, as these may be symptoms of a serious and potentially fatal condition known as pancreatitis (inflammation of the pancreas).

Your doctor or nurse will monitor you for signs and symptoms of these reactions.

Tell your doctor, pharmacist or nurse immediately if you became pregnant whilst receiving BLINCYTO. Your doctor will talk to you about precautions in using vaccinations for your baby.

Before each infusion cycle of BLINCYTO, you will be given medicines which help reduce a potentially life-threatening complication known as tumor lysis syndrome, which is caused by chemical disturbances in the blood due to the breakdown of dying cancer cells. You may also be given medicines to reduce fever.

During treatment, especially in the first few days after treatment start, you may experience a severe low white blood cell count (neutropenia), severe low white blood cell count with a fever (febrile neutropenia), elevated liver enzymes, or elevated uric acid. Your doctor will take regular blood tests to monitor your blood counts during treatment with BLINCYTO.

Children and adolescents
BLINCYTO should not be used in children below 1 year of age.

Other medicines and BLINCYTO
If you are taking or have lately taken other medicines, including non-prescription medicines and food supplements, tell your doctor or pharmacist.

Pregnancy, breast-feeding and fertility
If you are pregnant, think you may be pregnant or trying to get pregnant consult with your doctor, pharmacist or nurse before use.

Contraception

Women who are able to become pregnant have to use effective contraception during treatment and for at least 48 hours after your last treatment. Talk to your doctor or nurse about suitable methods of contraception.

Pregnancy

The effects of BLINCYTO in pregnant women are not known but based on its mechanism of action, BLINCYTO may harm your unborn baby. You should not use BLINCYTO during pregnancy, unless your doctor thinks that it is the best medicine for you.

If you become pregnant during BLINCYTO treatment, please inform your doctor or nurse. Your doctor will talk to you about precautions in using vaccinations for your baby.

Breast-feeding

You must not breast-feed during and for at least 48 hours after your last treatment. It is not known whether BLINCYTO is excreted in breast milk but a risk for suckling baby cannot be excluded.

Driving and using machines
Do not drive, use heavy machines, or engage in hazardous activities while you are being given BLINCYTO. BLINCYTO can cause neurological problems such as dizziness, seizures, confusion, coordination and balance disorders.

Important information on part of the medicine ingredients
This medicine contains less than 1 mmol sodium (23 mg) over a 24-hour infusion, that is to say essentially 'sodium-free'.

3. How to use this Medicine?

Always use this medicine exactly as your doctor has told you. Check with your doctor or a pharmacist if you are not sure.

The dosage and treatment regimen will be determined by the attending doctor only.
Do not exceed the recommended dose.

BLINCYTO will be given to you through a vein (intravenous) continuously for 4 weeks using an infusion pump (this is 1 treatment cycle). You will then have a 2-week break where you will not be given the infusion. Your infusion catheter will be attached to you at all times during each cycle of your treatment.

BLINCYTO is usually given for 2 treatment cycles if you have relapsed/refractory acute lymphoblastic leukemia, or for 1 treatment cycle if you have minimal residual acute lymphoblastic leukemia. If you respond to this treatment, your doctor may decide to give you up to 3 additional cycles of treatment. The number of treatment cycles and the dose which you will be given will depend on how you tolerate and respond to BLINCYTO. Your doctor will discuss with you how long your treatment will last. In pediatric patients with high-risk first relapse of acute lymphoblastic leukemia, BLINCYTO will be given for 1 treatment cycle. Your treatment may also be interrupted depending on how you tolerate BLINCYTO.

If you have relapsed/refractory acute lymphoblastic leukemia it is recommended that the first 9 days of treatment and the first 2 days of the second cycle will be given to you in a hospital or clinic under the supervision of a doctor or nurse experienced in the use of anti-cancer medicines.

If you have minimal residual acute lymphoblastic leukemia, it is recommended that the first 3 days of treatment and the first 2 days of subsequent cycles will be given to you in a hospital or clinic under the supervision of a doctor or nurse experienced in the use of anti-cancer medicines.

For pediatric patients with high-risk first relapse of acute lymphoblastic leukemia it is recommended that the first 3 days of the treatment cycle with BLINCYTO be given to

you in a hospital or clinic under the supervision of a doctor or nurse experienced in the use of anti-cancer medicines.

If you have or had neurological problems, it is recommended that the first 14 days of treatment will be given to you in a hospital or clinic. Your doctor will discuss with you if you can continue treatment at home after your initial hospital stay. Treatment may include a bag change by a nurse.

Your doctor will determine when your BLINCYTO infusion bag will be changed, which may range from every day to every 4 days. The infusion rate may be faster or slower depending on how often the bag is changed.

Your first treatment cycle

If you have relapsed/refractory acute lymphoblastic leukemia and your body weight is greater than or equal to 45 kilograms, the recommended initial dose in your first cycle is 9 micrograms per day for 1 week. Your doctor may decide to then increase your dose to 28 micrograms per day for weeks 2, 3, and 4 of your treatment.

If your body weight is less than 45 kilograms, the recommended initial dose in your first cycle will be based on your weight and height. Your doctor may decide to then increase your dose for weeks 2, 3, and 4 of your treatment.

If you have minimal residual acute lymphoblastic leukemia, your dose of BLINCYTO will be 28 micrograms per day throughout the first cycle.

If you are a pediatric patient with high-risk first relapse of acute lymphoblastic leukemia and your body weight is less than 45 kilograms, the recommended dose for 1 treatment cycle will be based on your weight and height. If your body weight is greater than or equal to 45 kilograms, your dose of BLINCYTO will be 28 micrograms per day throughout 1 treatment cycle.

Your next treatment cycles

If your doctor determines that you should be given more treatment cycles of BLINCYTO and if your body weight is greater than or equal to 45 kilograms, your pump will be set to infuse a dose of 28 micrograms per day.

If your doctor determines that you should be given more cycles of BLINCYTO and if your body weight is less than 45 kilograms, your pump will be set to infuse a dose based on your weight and height.

Medicines given before each cycle of BLINCYTO

Before your treatment with BLINCYTO, you will be given other medicines (premedication) to help reduce infusion reactions and other possible side effects. These may include corticosteroids (e.g. dexamethasone).

Infusion catheter

If you have a catheter for infusion, it is very important to keep the area around the catheter clean; otherwise you could get an infection. Your doctor or nurse will show you how to care for your catheter site.

Infusion pump and intravenous tubing

Do not adjust the settings on the pump, even if there is a problem or the pump alarm sounds. Any changes to the pump settings may result in a dose that is too high or too low.

Contact your doctor or nurse immediately if:
- there is a problem with the pump or the pump alarm sounds
- the infusion bag empties before the scheduled bag change
- if the infusion pump stops unexpectedly. Do not try to restart your pump.

Your doctor or nurse will advise you on how to manage your daily activities around your infusion pump. Contact your doctor or nurse if you have questions.

If you accidentally took a higher dose
Contact your doctor or pharmacist immediately.

If you forgot to take the medicine
Take BLINCYTO as soon as you can after the missed dose. Then, contact your doctor who will tell you when you should schedule your next dose, and follow the new schedule exactly as your doctor has told you.

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

Do not take medicines in the dark! Check the label and the dose <u>each time</u> you take medicine. Wear glasses if needed.

If you have any additional questions on the use of this medicine, consult a doctor or a pharmacist.

4. <u>Side Effects</u>

Like any medicine, using BLINCYTO may cause side effects in some of the users. Do not be alarmed by reading the list of side effects. It is possible that you will not suffer from any one of them.

Tell your doctor immediately if you get any of the following or combination of the following side effects:
- chills, shivering, fever, rapid heart rate, decreased blood pressure, aching muscles, feeling tired, coughing, difficulty breathing, confusion, redness, swelling or discharge in the affected area or at the site of the infusion line - these may be signs of an infection.

- neurologic events: shaking (or tremor), confusion, disturbances of brain function (encephalopathy), difficulty in communicating (aphasia), seizure (convulsion).
- fever, swelling, chills, decreased or increased blood pressure and fluid in the lungs, which may become severe - these may be signs of a so-called cytokine release syndrome.
- if you have severe and persistent stomach pain, with or without nausea and vomiting, as these may be symptoms of a serious and potentially fatal condition known as pancreatitis (inflammation of the pancreas).

Treatment with BLINCYTO can cause a decrease in the levels of certain white blood cells with or without fever (febrile neutropenia or neutropenia) or can lead to increased blood levels of potassium, uric acid, and phosphate and decreased blood levels of calcium (tumor lysis syndrome). Your doctor will take regular blood tests during treatment with BLINCYTO.

Other side effects include:

Very common side effects (may affect more than 1 in 10 patients):
- infections in the blood including bacteria, viruses, or other types of infection
- decreased levels of certain white blood cells with or without fever ((febrile) neutropenia, leukopenia), decreased levels of red blood cells, decreased levels of platelets
- fever, swelling, chills, decreased or increased blood pressure and fluid in the lungs, which may become severe (cytokine release syndrome)
- not being able to sleep, headache, shaking (or tremor). These may be symptoms of neurological problems associated with a condition called immune effector cell-associated neurotoxicity syndrome (ICANS).
- rapid heart rate (tachycardia)
- low blood pressure
- high blood pressure (hypertension)
- cough
- nausea, diarrhea, vomiting, constipation, abdominal pain
- rash
- back pain, pain in extremity
- fever (pyrexia), swelling of the face, lips, mouth, tongue or throat which may cause difficulty in swallowing or breathing (edema), chills
- low levels of antibodies called “immunoglobulins” which help the immune system fight infection (decreased immunoglobulins)
- increased levels of liver enzymes (ALT, AST, GGT)
- reactions related to infusion may include, wheezing, flushing, face swelling, difficulty breathing, low blood pressure, high blood pressure

Common side effects (may affect up to 1 in 10 patients):
- serious infection which can result in organ failure, shock or can be fatal (sepsis)
- lung infection (pneumonia)
- fungal infection
- increased levels of white blood cell count (leukocytosis), decreased levels of certain white blood cells (lymphopenia)

- allergic reaction
- complications occurring after cancer treatment leading to increased blood levels of potassium, uric acid, and phosphate and decreased blood levels of calcium (tumor lysis syndrome)
- confusion, disorientation, disturbances of brain function (encephalopathy) such as difficulty in communicating (aphasia), tingling of skin (paresthesia), seizure, difficulty thinking or processing thoughts, difficulty remembering, difficulty in controlling movement (ataxia), feeling sleepy (somnolence), numbness, dizziness. These may be symptoms of neurological problems associated with a condition called immune effector cell-associated neurotoxicity syndrome (ICANS).
- nerve problems affecting the head and neck such as visual disturbances, drooping eyelid and/or sagging muscles on one side of the face, difficulty hearing or trouble swallowing (cranial nerve disorders)
- wheezing or difficulty in breathing (dyspnea), breathlessness (respiratory failure)
- flushing
- coughing with phlegm
- increased bilirubin in the blood
- bone pain
- chest pain or other pain
- high levels of some enzymes including blood enzymes
- increase in your weight

Uncommon side effects (may affect up to 1 in 100 patients):
- excessive activation of white blood cells associated with inflammation (hemophagocytic histiocytosis)
- swollen lymph nodes (lymphadenopathy)
- fever, swelling, chills, decreased or increased blood pressure and fluid in the lungs, which may be severe and can be fatal (cytokine storm)
- a condition which causes fluid to leak from the small blood vessels into your body (capillary leak syndrome)
- difficulty speaking and/or writing. These may be symptoms of neurological problems associated with a condition called immune effector cell-associated neurotoxicity syndrome (ICANS).

Additionally, the side effects that happened more often in adolescents and children include:
- decreased levels of red blood cells (anemia), decreased levels of platelets (thrombocytopenia), decreased levels of certain white blood cells (leukopenia)
- fever (pyrexia)
- reactions related to infusion may include face swelling, low blood pressure, high blood pressure (infusion-related reaction)
- increase in your weight
- high blood pressure (hypertension)

If a side effect occurs, if any of the side effects gets worse or if you suffer from a side effect not mentioned in the leaflet, you should consult with the doctor.

Reporting of side effects

You can report adverse reactions to the Ministry of Health by clicking on the link "report on adverse reactions following medication treatment" located on the homepage of the Ministry of Health website (www.health.gov.il) which directs you to the online form for reporting adverse reactions or by using the link: https://sideeffects.health.gov.il/

5. How to Store the Medicine?

Avoid poisoning! This medicine and any other medicine must be stored in a safe place out of the reach and sight of children and/or infants to avoid poisoning. Do not induce vomiting without an explicit instruction from the doctor.
Do not use this medicine after the expiry date (exp. Date) which is stated on the label and carton. The expiry date refers to the last day of that month.

Unopened vials:
- Store and transport refrigerated (2°C - 8°C).
- Do not freeze.
- Store in the original carton in order to protect from light.

Reconstituted solution (BLINCYTO solution):
- When refrigerated, the reconstituted solution must be used within 24 hours. Alternatively, the vials can be stored at room temperature (up to 27°C) for up to 4 hours.

Diluted solution (prepared infusion bag):
If your infusion bag is changed at home:
- Infusion bags containing BLINCYTO solution for infusion will arrive in special packaging containing cooling packs.
  - Do not open the package.
  - Store the package at room temperature (up to 27°C).
  - Do not refrigerate or freeze the package.
- The package will be opened by your nurse and the infusion bags will be stored in a refrigerator until infusion.
- When refrigerated, the infusion bags must be used within 10 days of preparation.
- Once at room temperature (up to 27°C) the solution will be infused within 96 hours.

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

6. Additional Information

In addition to the active ingredient, this medicine also contains:

Excipients of powder:
- Citric acid monohydrate,
- Trehalose Dihydrate,
- Lysine Hydrochloride,
- Polysorbate 80,
- Sodium Hydroxide.

Excipients of stabilizer solution:
- Citric acid monohydrate,
- Lysine Hydrochloride,
- Polysorbate 80,
- Sodium Hydroxide,
- Water for injections.

What does the medicine look like and what are the contents of the package?
BLINCYTO is a powder and stabilizer solution for infusion.
Each pack of BLINCYTO contains:
- 1 glass vial containing a white to off-white powder.
- 1 glass vial containing a colorless-to-slightly yellow, clear solution.

Registration Holder's name and address:
Amgen Europe B.V.
P.O. BOX 53313, Tel - Aviv, Israel.

Manufacturer's name and address:
Amgen Europe B.V.
Minervum 7061, Breda, The Netherlands.

Revised in May 2025.

Registration number of the medicine in the National Drugs Registry at the Ministry of Health: 156 76 34580