Package leaflet: Information for the patient

BLINCYTO 38.5 micrograms powder for concentrate and solution for solution for infusion
blinatumomab

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because 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.

What is in this leaflet

1. What BLINCYTO is and what it is used for

The active ingredient in BLINCYTO is blinatumomab. This belongs to a group of medicines called antineoplastic agents which target cancer cells.

BLINCYTO is used to treat adults with acute lymphoblastic leukaemia. Acute lymphoblastic leukaemia is a cancer of the blood in which a particular kind of white blood cell called "B-lymphocyte" is growing out of control. This medicine works by enabling your immune system to attack and destroy these abnormal white blood cancer cells. BLINCYTO is used when acute lymphoblastic leukaemia has come back or has not responded to previous treatment (referred to as relapsed/refractory acute lymphoblastic leukaemia).

It is also used in patients with acute lymphoblastic leukaemia who still have a small number of cancer cells remaining after previous treatment (referred to as minimal residual disease).

BLINCYTO is used to treat children (≥ 1 year old), teenagers and young adults with acute lymphoblastic leukaemia (ALL) when previous treatments have not worked or have stopped working.

2. What you need to know before you use BLINCYTO

Do not use BLINCYTO:
- if you are allergic to blinatumomab or any of the other ingredients of this medicine (listed in section 6).
- if you are breast-feeding.

Warnings and precautions

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 in speaking. If you are still suffering from active neurological problems or conditions, tell your doctor. If your leukaemia 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 of the following reactions whilst receiving BLINCYTO as these may need to be treated and your dose adjusted:

- if you experience seizures, difficulty in speaking or slurred speech, confusion and disorientation, or loss of balance.
- if you develop chills or shivering, or 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 tumour 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

Tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take any other medicines.

Pregnancy and breast-feeding

If you are pregnant, are breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or nurse for advice before taking this medicine.

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.

BLINCYTO contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per dose, i.e. it is essentially ‘sodium-free’.

3. How to use BLINCYTO

Always use this medicine exactly as your doctor, pharmacist or nurse have told you. Check with your doctor, pharmacist or nurse if you are not sure.

How BLINCYTO is given

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 leukaemia, or for 1 treatment cycle if you have minimal residual disease acute lymphoblastic leukaemia. 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. Your treatment may also be interrupted depending on how you tolerate BLINCYTO.

If you have relapsed/refractory acute lymphoblastic leukaemia it is recommended that the first 9 days of treatment and the first two 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 disease acute lymphoblastic leukaemia, 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.

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 cycle

If you have relapsed/refractory acute lymphoblastic leukaemia 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 disease acute lymphoblastic leukaemia, your dose of BLINCYTO will be 28 micrograms per day throughout the first cycle.

Your next cycles

If your doctor determines that you should be given more 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 (pre-medication) 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.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Some of these side effects may be serious.

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 (tumour 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 people):
- infections in the blood including bacteria, fungi, 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)
- rapid heart rate (tachycardia)
- low blood pressure
- cough
- nausea, diarrhoea, 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 (oedema), 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 people):
- serious infection which can result in organ failure, shock or can be fatal (sepsis)
- lung infection (pneumonia)
- increased levels of white blood cell count (leucocytosis), 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 (tumour lysis syndrome)
- confusion, disorientation
- disturbances of brain function (encephalopathy) such as difficulty in communicating (aphasia), tingling of skin (paraesthesia), seizure, difficulty thinking or processing thoughts, difficulty remembering, difficulty in controlling movement (ataxia)
- feeling sleepy (somnolence), numbness, dizziness
- 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 (dyspnoea), breathlessness (respiratory failure)
- high blood pressure (hypertension)
- 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 people):
- 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 in speaking

Additionally, the side effects that happened more often in adolescents and children include:
- decreased levels of red blood cells (anaemia), 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)

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly (see details below). By reporting side effects you can help provide more information on the safety of this medicine.

United Kingdom
Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store

Ireland
HPRA Pharmacovigilance
Earlsfort Terrace
IRL - Dublin 2
Tel: +353 1 6764971
Fax: +353 1 6762517
Website: www.hpra.ie
e-mail: medsafety@hpra.ie

Malta
ADR Reporting
Website: www.medicinesauthority.gov.mt/adrportal
The Medicines Authority
Post-Licensing Directorate
203 Level 3, Rue D'Argens
GŻR-1368 Gżira
Website: www.medicinesauthority.gov.mt
e-mail: postlicensing.medicinesauthority@gov.mt

5. How to store BLINCYTO

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label and carton after EXP. 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. Contents of the pack and other information

What BLINCYTO contains

- The active substance is blinatumomab. Each vial of powder contains 38.5 micrograms of blinatumomab. Reconstitution with water for injections results in a final blinatumomab concentration of 12.5 micrograms/mL.
- The other ingredients in the powder are citric acid monohydrate (E330), trehalose dihydrate, lysine hydrochloride, polysorbate 80, and sodium hydroxide.
- The solution (stabiliser) contains citric acid monohydrate (E330), lysine hydrochloride, polysorbate 80, sodium hydroxide and water for injections.

What BLINCYTO looks like and contents of the pack

BLINCYTO is a powder for concentrate and solution for solution for infusion.
Each pack of BLINCYTO contains:

- 1 glass vial containing a white to off-white powder.
- 1 glass vial containing a colourless-to-slightly yellow, clear solution.

Marketing Authorisation Holder and Manufacturer
Amgen Europe B.V.
Minervum 7061
4817 ZK Breda
The Netherlands

Marketing Authorisation Holder
Amgen Europe B.V.
Minervum 7061
4817 ZK Breda
The Netherlands

Manufacturer
Amgen NV
Telecomlaan 5-7
1831 Diegem
Belgium

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

United Kingdom
Amgen Limited
Tel: +44 (0)1223 420305

Ireland
Amgen Ireland Limited
Tel: +353 1 8527400

Malta
Amgen B.V.
The Netherlands
Tel: +31 (0)76 5732500

This leaflet was last revised in January 2019.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

The following information is intended for healthcare professionals only:

BLINCYTO solution for infusion is administered as a continuous intravenous infusion delivered at a constant flow rate using an infusion pump, over a period of up to 96 hours.

Philadelphia chromosome negative relapsed or refractory B-precursor ALL

Recommended daily dose by patient weight. Patients greater than or equal to 45 kg receive a fixed-dose and for patients less than 45 kg, the dose is calculated using the patient's body surface area (BSA).

Patient weight	Cycle 1			Subsequent cycles	
	Days 1-7	Days 8-28	Days 29-42	Days 1-28	Days 29-42
Greater than or equal to 45 kg *(fixed-dose)*	9 mcg/day via continuous infusion	28 mcg/day via continuous infusion	14 day treatment free interval	28 mcg/day via continuous infusion	14 day treatment free interval
Less than 45 kg *(BSA-based dose)*	5 mcg/m^2/day via continuous infusion *(not to exceed 9 mcg/day)*	15 mcg/m^2/day via continuous infusion *(not to exceed 28 mcg/day)*		15 mcg/m^2/day via continuous infusion *(not to exceed 28 mcg/day)*	

MRD positive B-precursor ALL

The recommended dose of BLINCYTO throughout each 4-week treatment cycle is 28 mcg/day.

The starting volume (270 mL) is more than the volume administered to the patient (240 mL) to account for the priming of the intravenous tubing and to ensure that the patient will receive the full dose of BLINCYTO.

Infuse BLINCYTO solution according to the instructions on the pharmacy label on the prepared bag at one of the following constant infusion rates:

- Infusion rate of 10 mL/h for a duration of 24 hours
- Infusion rate of 5 mL/h for a duration of 48 hours
- Infusion rate of 3.3 mL/h for a duration of 72 hours
- Infusion rate of 2.5 mL/h for a duration of 96 hours

The choice of the infusion duration should be made by the treating physician considering the frequency of the infusion bag changes. The target therapeutic dose of BLINCYTO delivered does not change.

Aseptic preparation

Aseptic handling must be ensured when preparing the infusion. Preparation of BLINCYTO should be:

- performed under aseptic conditions by trained personnel in accordance with good practice rules especially with respect to the aseptic preparation of parenteral products.
- prepared in a laminar flow hood or biological safety cabinet using standard precautions for the safe handling of intravenous agents.

It is very important that the instructions for preparation and administration provided in this section are strictly followed to minimise medication errors (including underdose and overdose).

Special instructions to support accurate preparation

- A solution (stabiliser) is provided inside the BLINCYTO package and is used to coat the pre-filled infusion bag prior to addition of reconstituted BLINCYTO. **Do not use this solution (stabiliser) for reconstitution of BLINCYTO powder for concentrate.**
- The entire volume of the reconstituted and diluted BLINCYTO will be more than the volume to be administered to the patient (240 mL). This is to account for intravenous infusion line loss and to assure that the patient will receive the full dose of BLINCYTO.
- When preparing an infusion bag, remove all air from infusion bag. This is particularly important when using an ambulatory infusion pump.
- Use the specific volumes described in the reconstitution and dilution instructions below to minimise errors in calculation.

Other instructions

- BLINCYTO is compatible with polyolefin, PVC non-di-ethylhexylphthalate (non-DEHP), or ethyl vinyl acetate (EVA) infusion bags/pump cassettes.
- Pump specifications: The infusion pump to administer BLINCYTO solution for infusion should be programmable, lockable and have an alarm. Elastomeric pumps should not be used.
- Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Preparation of the solution for infusion

Specific reconstitution and dilution instructions are provided for each dose and infusion time. Verify the prescribed dose and infusion time of BLINCYTO and identify the appropriate dosing preparation in the relevant table below. Table 1 provides instructions for patients weighing greater than or equal to 45 kg whereas table 2 and table 3 provide instructions for patients weighing less than 45 kg. Follow the steps for reconstituting BLINCYTO and preparing the infusion bag detailed below table 3.

Table 1. For patients weighing greater than or equal to 45 kg: volumes of sodium chloride 9 mg/mL (0.9%) solution for injection, solution (stabiliser), and reconstituted BLINCYTO to add to infusion bag

Pre-filled bag containing sodium chloride 9 mg/mL (0.9%) solution for injection			250 mL (usual overfill volume of 265 to 275 mL)
Solution (stabiliser)			5.5 mL
Dose	**Infusion duration (hours)**	**Infusion rate (mL/hour)**	**Reconstituted BLINCYTO (number of packages)**
9 mcg/day	24	10	0.83 mL (1)
	48	5	1.7 mL (1)
	72	3.3	2.5 mL (1)
	96	2.5	3.3 mL (2)
28 mcg/day	24	10	2.6 mL (1)
	48	5	5.2 mL (2)
	72	3.3	8 mL (3)
	96	2.5	10.7 mL (4)

Table 2. For patients weighing less than 45 kg: volumes of sodium chloride 9 mg/mL (0.9%) solution for injection, solution (stabiliser), and reconstituted BLINCYTO to add to infusion bag for 5 mcg/m^2/day dose

Sodium chloride 9 mg/mL (0.9%) solution for injection (starting volume)				250 mL (usual overfill volume of 265 to 275 mL)
Solution (stabiliser)				5.5 mL
Dose	**Infusion duration**	**Infusion rate**	**BSA (m^2)**	**Reconstituted BLINCYTO (number of packages)**
5 mcg/m^2/day	24 hours	10 mL/hour	1.50 – 1.59	0.70 mL (1)
			1.40 – 1.49	0.66 mL (1)
			1.30 – 1.39	0.61 mL (1)
			1.20 – 1.29	0.56 mL (1)
			1.10 – 1.19	0.52 mL (1)
			1.00 – 1.09	0.47 mL (1)
			0.90 – 0.99	0.43 mL (1)
			0.80 – 0.89	0.38 mL (1)
			0.70 – 0.79	0.33 mL (1)
			0.60 – 0.69	0.29 mL (1)
			0.50 – 0.59	0.24 mL (1)
			0.40 – 0.49	0.20 mL (1)
	48 hours	5 mL/hour	1.50 – 1.59	1.4 mL (1)
			1.40 – 1.49	1.3 mL (1)
			1.30 – 1.39	1.2 mL (1)
			1.20 – 1.29	1.1 mL (1)
			1.10 – 1.19	1.0 mL (1)
			1.00 – 1.09	0.94 mL (1)
			0.90 – 0.99	0.85 mL (1)
			0.80 – 0.89	0.76 mL (1)
			0.70 – 0.79	0.67 mL (1)
			0.60 – 0.69	0.57 mL (1)
			0.50 – 0.59	0.48 mL (1)
			0.40 – 0.49	0.39 mL (1)
	72 hours	3.3 mL/hour	1.50 – 1.59	2.1 mL (1)
			1.40 – 1.49	2.0 mL (1)
			1.30 – 1.39	1.8 mL (1)
			1.20 – 1.29	1.7 mL (1)
			1.10 – 1.19	1.6 mL (1)
			1.00 – 1.09	1.4 mL (1)
			0.90 – 0.99	1.3 mL (1)
			0.80 – 0.89	1.1 mL (1)
			0.70 – 0.79	1 mL (1)
			0.60 – 0.69	0.86 mL (1)
			0.50 – 0.59	0.72 mL (1)
			0.40 – 0.49	0.59 mL (1)
	96 hours	2.5 mL/hour	1.50 – 1.59	2.8 mL (1)
			1.40 – 1.49	2.6 mL (1)
			1.30 – 1.39	2.4 mL (1)
			1.20 – 1.29	2.3 mL (1)
			1.10 – 1.19	2.1 mL (1)
			1.00 – 1.09	1.9 mL (1)
			0.90 – 0.99	1.7 mL (1)
			0.80 – 0.89	1.5 mL (1)
			0.70 – 0.79	1.3 mL (1)
			0.60 – 0.69	1.2 mL (1)
			0.50 – 0.59	0.97 mL (1)
			0.40 – 0.49	0.78 mL (1)

Table 3. For patients weighing less than 45 kg: volumes of sodium chloride 9 mg/mL (0.9%) solution for injection, solution (stabiliser), and reconstituted BLINCYTO to add to infusion bag for 15 mcg/m^2/day dose

Sodium chloride 9 mg/mL (0.9%) solution for injection (starting volume)				250 mL (usual overfill volume of 265 to 275 mL)
Solution (stabiliser)				5.5 mL
Dose	**Infusion duration**	**Infusion rate**	**BSA (m^2)**	**Reconstituted BLINCYTO (number of packages)**
15 mcg/m^2/day	24 hours	10 mL/hour	1.50 – 1.59	2.1 mL (1)
			1.40 – 1.49	2.0 mL (1)
			1.30 – 1.39	1.8 mL (1)
			1.20 – 1.29	1.7 mL (1)
			1.10 – 1.19	1.6 mL (1)
			1.00 – 1.09	1.4 mL (1)
			0.90 – 0.99	1.3 mL (1)
			0.80 – 0.89	1.1 mL (1)
			0.70 – 0.79	1.00 mL (1)
			0.60 – 0.69	0.86 mL (1)
			0.50 – 0.59	0.72 mL (1)
			0.40 – 0.49	0.59 mL (1)
	48 hours	5 mL/hour	1.50 – 1.59	4.2 mL (2)
			1.40 – 1.49	3.9 mL (2)
			1.30 – 1.39	3.7 mL (2)
			1.20 – 1.29	3.4 mL (2)
			1.10 – 1.19	3.1 mL (2)
			1.00 – 1.09	2.8 mL (1)
			0.90 – 0.99	2.6 mL (1)
			0.80 – 0.89	2.3 mL (1)
			0.70 – 0.79	2.0 mL (1)
			0.60 – 0.69	1.7 mL (1)
			0.50 – 0.59	1.4 mL (1)
			0.40 – 0.49	1.2 mL (1)
	72 hours	3.3 mL/hour	1.50 – 1.59	6.3 mL (3)
			1.40 – 1.49	5.9 mL (3)
			1.30 – 1.39	5.5 mL (2)
			1.20 – 1.29	5.1 mL (2)
			1.10 – 1.19	4.7 mL (2)
			1.00 – 1.09	4.2 mL (2)
			0.90 – 0.99	3.8 mL (2)
			0.80 – 0.89	3.4 mL (2)
			0.70 – 0.79	3.0 mL (2)
			0.60 – 0.69	2.6 mL (1)
			0.50 – 0.59	2.2 mL (1)
			0.40 – 0.49	1.8 mL (1)
	96 hours	2.5 mL/hour	1.50 – 1.59	8.4 mL (3)
			1.40 – 1.49	7.9 mL (3)
			1.30 – 1.39	7.3 mL (3)
			1.20 – 1.29	6.8 mL (3)
			1.10 – 1.19	6.2 mL (3)
			1.00 – 1.09	5.7 mL (3)
			0.90 – 0.99	5.1 mL (2)
			0.80 – 0.89	4.6 mL (2)
			0.70 – 0.79	4.0 mL (2)
			0.60 – 0.69	3.4 mL (2)
			0.50 – 0.59	2.9 mL (2)
			0.40 – 0.49	2.3 mL (1)

These supplies are also required, but **not** included in the package

- Sterile single-use disposable syringes
- 21-23 gauge needle(s) (recommended)
- Water for injections
- Infusion bag with 250 mL sodium chloride 9 mg/mL (0.9%) solution for injection;
  - To minimise the number of aseptic transfers, use a 250 mL pre-filled infusion bag. **BLINCYTO dose calculations are based on a usual overfill volume of 265 to 275 mL sodium chloride 9 mg/mL (0.9%) solution for injection.**
  - Use only polyolefin, PVC non-di-ethylhexylphthalate (non-DEHP), or ethyl vinyl acetate (EVA) infusion bags/pump cassettes.
- Polyolefin, PVC non-DEHP, or EVA intravenous tubing with a sterile, non-pyrogenic, low protein-binding 0.2 micrometre in-line filter.
  - Ensure that the tubing is compatible with the infusion pump.

Reconstitution and preparation of BLINCYTO solution for infusion using an infusion bag pre-filled with 250 mL sodium chloride 9 mg/mL (0.9%) solution for injection

1. Use an infusion bag pre-filled with 250 mL sodium chloride 9 mg/mL (0.9%) solution for injection that usually contains a total volume of 265 to 275 mL.
2. To coat the infusion bag, using a syringe, aseptically transfer 5.5 mL of the solution (stabiliser) to the infusion bag. Gently mix the contents of the bag to avoid foaming. Discard the remaining solution (stabiliser) vial.
3. Using a syringe, reconstitute each vial of BLINCYTO powder for concentrate using 3 mL of water for injections. Direct the water for injections toward the side of the vial during reconstitution. Gently swirl contents to avoid excess foaming. Do not shake.
   - **Do not reconstitute BLINCYTO powder for concentrate with the solution (stabiliser).**
   - The addition of water for injections to the powder for concentrate results in a total volume of 3.08 mL for a final BLINCYTO concentration of 12.5 mcg/mL.
4. Visually inspect the reconstituted solution for particulate matter and discolouration during reconstitution and prior to infusion. The resulting solution should be clear to slightly opalescent, colourless-to-slightly yellow. **Do <u>not</u> use if the solution is cloudy or has precipitated.**
5. Using a syringe, aseptically transfer reconstituted BLINCYTO into the infusion bag (refer to table 1 to table 3 for the specific volume of reconstituted BLINCYTO). Gently mix the contents of the bag to avoid foaming. Discard any remaining BLINCYTO reconstituted solution.
6. Under aseptic conditions, attach the intravenous tubing to the infusion bag with the sterile 0.2 micron in-line filter.
7. Remove air from the infusion bag and prime the intravenous infusion line **only** with the prepared solution for infusion. **Do not prime with sodium chloride 9 mg/mL (0.9%) solution for injection.**
8. Store at 2°C – 8°C if not used immediately.

For instructions on administration, see Summary of Product Characteristics section 4.2.

<u>Method of administration</u>

Important Note: Do not flush the BLINCYTO infusion line or intravenous catheter, especially when changing infusion bags. Flushing when changing bags or at completion of infusion can result in excess dosage and complications thereof. When administering via multi-lumen venous catheter, BLINCYTO should be infused through a dedicated lumen.

BLINCYTO solution for infusion is administered as a continuous intravenous infusion delivered at a constant flow rate using an infusion pump over a period of up to 96 hours.

The BLINCYTO solution for infusion must be administered using intravenous tubing that contains a sterile, non-pyrogenic, low protein-binding 0.2 micrometre in-line filter.

The infusion bag must be changed at least every 96 hours by a healthcare professional for sterility reasons.

Storage conditions and shelf life

Unopened vials:

5 years (2°C - 8°C)

Reconstituted solution:

Chemical and physical in-use stability has been demonstrated for 24 hours at 2°C - 8°C or 4 hours at or below 27°C.

From a microbiological point of view, unless the method of reconstituting precludes the risks of microbial contamination, the reconstituted solution should be diluted immediately. If not diluted immediately, in-use storage times and conditions are the responsibility of the user.

Diluted solution (prepared infusion bag)

Chemical and physical in-use stability has been demonstrated for 10 days at 2°C - 8°C or 96 hours at or below 27°C.

From a microbiological point of view, the prepared infusion bags 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 - 8°C, unless dilution has taken place in controlled and validated aseptic conditions.