AUSTRALIAN PI – BLINCYTO® (BLINATUMOMAB)

WARNING

The following have occurred in patients receiving BLINCYTO:

- **Cytokine Release Syndrome, which may be life-threatening or fatal**
- **Neurological toxicities, which may be severe, life-threatening, or fatal**
- **Reactivation of JC viral infection**

Interrupt or discontinue BLINCYTO as recommended if any of these adverse events occur (See Section 4.4 Special warnings and precautions for use and Section 4.2 Dose and method of administration).

1 NAME OF THE MEDICINE

Blincyto® is the Amgen Inc. trademark for blinatumomab (rch).

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Blinatumomab is a bispecific T cell engager (BiTE®) antibody construct that selectively binds with high affinity to CD19 (expressed on cells of B-lineage origin) and CD3 (expressed on T cells). Using recombinant DNA technology, Blincyto is produced in a well-characterised mammalian cell (Chinese hamster ovary) culture and is purified by a series of steps that include measures to inactivate and remove viruses. It consists of 504 amino acids and has a molecular weight of approximately 54 kilodaltons.

Each single-use vial of Blincyto contains 38.5 micrograms preservative-free blinatumomab.

After reconstitution with 3 mL of preservative-free sterile Water for Injections, the resulting total volume of reconstituted solution is 3.1 mL and each mL contains 12.5 micrograms blinatumomab. The extractable amount of blinatumomab per vial is 35 micrograms in a volume of 2.8 mL reconstituted solution.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Blincyto is supplied as a sterile, preservative-free, white to off-white lyophilised powder (38.5 micrograms/vial)

IV solution stabiliser is supplied as a sterile, preservative-free, colourless to slightly yellow, clear solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Blincyto is indicated for the treatment of relapsed or refractory B-cell precursor acute lymphoblastic leukaemia (ALL).

Blincyto is indicated for the treatment of minimal residual disease (MRD) positive B-cell precursor acute lymphoblastic leukaemia (ALL) in patients in complete haematological remission.

Note to indication: the indications in Philadelphia positive, MRD positive and paediatric patients were approved based on phase II, non-randomised evidence. An improvement in clinical outcomes by direct prospective comparison in a randomised setting relative to other standard-of-care salvage therapies has not been established.

4.2 Dose and method of administration

Dosage (dose and interval)

Use of Blincyto should be restricted to physicians experienced in the treatment of haematological malignancies.

For the treatment of relapsed or refractory B-cell precursor ALL, hospitalisation is recommended at a minimum for the first 9 days of the first cycle and the first 2 days of the second cycle.

For the treatment of MRD positive B-cell precursor ALL, hospitalisation is recommended at a minimum for the first 3 days of the first cycle and the first 2 days of the second cycle.

For all subsequent cycle starts and reinitiation (e.g., if treatment is interrupted for 4 or more hours), supervision by a healthcare professional or hospitalisation is recommended.

Blincyto infusion bags should be admixed to infuse over 24 hours, 48 hours, 72 hours or 96 hours (see Section 4.2 Dose and method of administration, Preparation and administration).

Treatment of Relapsed or Refractory B-cell Precursor ALL

Blincyto is administered as a continuous intravenous infusion delivered at a constant flow rate using an infusion pump. A single cycle of treatment is 28 days (4 weeks) of continuous infusion followed by a 14 day (2-week) treatment-free interval. Patients may receive 2 cycles of induction treatment followed by 3 additional cycles of Blincyto consolidation treatment.

See Table 1 for the 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).

Table 1. Blincyto Recommended Dosage for Relapsed or Refractory B-cell Precursor ALL

<table>
<tr><th rowspan="2">Patient Weight</th><th colspan="3">Treatment Cycle 1</th><th colspan="2">Subsequent Treatment Cycles</th></tr>
<tr><th>Days 1-7</th><th>Days 8-28</th><th>Days 29-42</th><th>Days 1-28</th><th>Days 29-42</th></tr>
<tr><td>Greater than or Equal to 45 kg (fixed-dose)</td><td>9 micrograms /day</td><td>28 micrograms /day</td><td rowspan="2">14-day treatment-free interval</td><td>28 micrograms /day</td><td rowspan="2">14-day treatment-free interval</td></tr>
<tr><td>Less than 45 kg (BSA-based dose)</td><td>5 micrograms/ m^2/day (not to exceed 9 micrograms/ day)</td><td>15 micrograms/ m^2/day (not to exceed 28 micrograms/ day)</td><td>15 micrograms/ m^2/day (not to exceed 28 micrograms/ day)</td></tr>
</table>

*For maintenance therapy, a cycle of treatment of Blincyto consists of 28 days of continuous intravenous infusion followed by a 56-day treatment-free interval.

Premedication and Additional Medication Recommendations

Additional premedication recommendations are as follows:

Patient Group	Premedication
Adults	Premedicate with dexamethasone 20 mg intravenously 1 hour prior to the first dose of Blincyto of each cycle.
Paediatrics	Premedicate with dexamethasone 10 mg/m^2 (not to exceed 20 mg) orally or intravenously 6 to 12 hours prior to the start of Blincyto (Cycle 1 day 1), followed by premedication with dexamethasone 5 mg/m^2 orally or intravenously within 30 minutes of the start of Blincyto (Cycle 1 day 1).

Intrathecal chemotherapy prophylaxis is recommended before and during Blincyto therapy to prevent central nervous system ALL relapse.

Pre-phase Treatment for Patients with High Tumour Burden

- 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.

1. IV solution stabiliser is provided with the Blincyto package and is used to coat the prefilled IV bag or cassette prior to addition of reconstituted Blincyto to prevent adhesion of Blincyto to IV bags or cassettes and IV lines. **Do not use IV solution stabiliser for reconstitution of Blincyto**.
2. The entire volume of the reconstituted and diluted Blincyto will be more than the volume administered to the patient (240 mL) to account for the priming of the IV line and to ensure that the patient will receive the full dose of Blincyto.
3. When preparing an IV bag, remove air from IV bag. This is particularly important for use with an ambulatory infusion pump.
4. Use the specific volumes described in the reconstitution and dilution instructions.

- Blincyto is compatible with polyolefin, PVC non-di-ethylhexylphthalate (non-DEHP), or ethyl vinyl acetate (EVA) infusion bags/pump cassettes.

Specific reconstitution and dilution instructions are provided below for each dose and infusion time. Verify the prescribed dose and infusion time of Blincyto and identify the appropriate dosing preparation section listed below. Follow the steps for reconstituting Blincyto and preparing either an IV bag or a cassette.

Before preparation, ensure you have the following supplies ready.

1. A sufficient number of packages of Blincyto (each package includes 1 vial of Blincyto and 1 vial of IV solution stabiliser).
   - Refer to Tables 3 to 7 for the number of packages of Blincyto required for a given dose/duration/rate of infusion. Only one package is required unless indicated otherwise.
   - The extractable amount of blinatumomab per vial is 35 micrograms in a volume of 2.8 mL reconstituted solution.
   - The IV solution stabiliser is to be added to the IV bag containing 0.9% sodium chloride prior to addition of reconstituted Blincyto to prevent adhesion of Blincyto to IV bags and IV lines.
2. The following supplies which are also required, but not included in the package:
   - Sterile single-use disposable syringes
   - 21 to 23 gauge needle(s) (recommended)
   - Preservative-free sterile Water for Injections
   - 250 mL 0.9% sodium chloride IV bag OR a 250 mL cassette
     - If using IV bags, to minimise the number of aseptic transfers, it is recommended to use a 250 mL-prefilled IV bag. 250 mL prefilled IV bags typically contain overfill with a total volume of 265 to 275 mL. Blincyto dose

calculations are based on a starting volume of 265 mL to 275 mL 0.9% sodium chloride.
  - Use only polyolefin, PVC non-di-ethylhexylphthalate (non-DEHP), or ethyl vinyl acetate (EVA) infusion bags/pump cassettes.
- Polyolefin, PVC non-DEHP, or EVA IV tubing with a sterile, non-pyrogenic, low protein-binding 0.2 micron in-line filter
- Ensure that the IV tubing is compatible with the infusion pump

Clearly label the prepared IV infusion bag or cassette with the dose, infusion rate and duration of infusion.

Reconstitution of Blincyto and Preparation of Blincyto Solution for Infusion Using a Prefilled 250 mL 0.9% Sodium Chloride IV Infusion Bag

The IV bag must be changed at least every 24 to 96 hours by a healthcare professional for sterility reasons.

- Administer Blincyto as a continuous intravenous infusion at a constant flow rate using an infusion pump. The pump should be programmable, lockable, non-elastomeric, and have an alarm.
- Prepared Blincyto infusion bags should be infused over 24 hours, 48 hours, 72 hours, or 96 hours. The choice of the infusion duration should be made by the treating physician considering the frequency of the infusion bag changes.
- The starting volume (265-275 mL) is more than the volume administered to the patient (240 mL) to account for the priming of the IV 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 Blincyto solution for infusion must be administered using IV tubing that contains a sterile, non-pyrogenic, low protein-binding 0.2 micron in-line filter.

Important Note: Do not flush the Blincyto IV catheter, especially when changing infusion bags. Flushing when changing bags or at completion of infusion can result in excess dosage and complications thereof. Blincyto should be infused through a dedicated lumen.

1. Add 3 mL of preservative-free sterile Water for Injections by directing the water along the walls of the Blincyto vial and not directly on the lyophilised powder (resulting in a final Blincyto concentration of 12.5 micrograms/mL)
   - Do not reconstitute Blincyto with IV solution stabiliser.

2. Gently swirl contents to avoid excess foaming. **Do not shake.**
3. 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 not use if solution is cloudy or has precipitated**.

Verify the prescribed dose and infusion duration for each Blincyto infusion bag. To minimise errors, **use the specific volumes described in Tables 3 to 5 to prepare the Blincyto infusion bag.**

- Table 3 for patients weighing greater than or equal to 45 kg
- Tables 4 and 5 for patients weighing less than 45 kg

1. Use a prefilled 250 mL 0.9% sodium chloride IV bag. 250 mL-prefilled bags typically contain overfill to a total volume of 265 to 275 mL. If necessary adjust the IV bag volume by adding or removing 0.9% sodium chloride to achieve a starting volume between 265 and 275 mL.
   - Use only polyolefin, PVC DEHP-free, or EVA IV bags
2. **Aseptically transfer 5.5 mL IV solution stabiliser to the IV bag containing 0.9% sodium chloride**. Gently mix the contents of the bag to avoid foaming. Discard the vial containing the unused IV solution stabiliser.
3. **Aseptically transfer the specified volume of reconstituted Blincyto (see Tables 3 to 5 for the specific volume to be added)** into the IV bag containing 0.9% sodium chloride and IV solution stabiliser. Gently mix the contents of the bag to avoid foaming.
4. Under aseptic conditions, attach the IV tubing to the IV bag with the sterile 0.2 micron in-line filter.
   - Use only polyolefin, PVC DEHP-free, or EVA IV lines with a sterile, non-pyrogenic, low protein-binding 0.2 micron in-line filter
   - Ensure that the IV tubing is compatible with the infusion pump
5. Remove air from the IV bag. This is particularly important for use with an ambulatory infusion pump. **Prime the IV tubing only with the prepared solution for infusion. Do not prime with 0.9% sodium chloride.**
6. Store at 2°C to 8°C if not used immediately (see Section 6.4 Special Precautions for Storage).

Table 3. For Patients Weighing Greater Than or Equal to 45 kg: Volumes of Reconstituted Blincyto to Add to IV Bag

Dose	Infusion Duration	Infusion Rate	Reconstituted Blincyto
9 micrograms/day	24 hours	10 mL/hour	0.83 mL
	48 hours	5 mL/hour	1.7 mL
	72 hours	3.3 mL/hour	2.5 mL
	96 hours	2.5 mL/hour	3.3 mL[a]
28 micrograms/day	24 hours	10 mL/hour	2.6 mL
	48 hours	5 mL/hour	5.2 mL[a]
	72 hours	3.3 mL/hour	8 mL[b]
	96 hours	2.5 mL/hour	10.7 mL[c]

a. 2 packages of Blincyto are needed for preparation of 9 micrograms/day dose infused over 96 hours at a rate of 2.5 mL/hour and 28 micrograms/day dose infused over 48 hours at a rate of 5 mL/hour
b. 3 packages of Blincyto are needed for preparation of 28 micrograms/day dose infused over 72 hours at a rate of 3.3 mL/hour
c. 4 packages of Blincyto are needed for preparation of 28 micrograms/day dose infused over 96 hours at a rate of 2.5 mL/hour

Table 4. For Patients Weighing Less Than 45 kg: Volumes of Reconstituted Blincyto to Add to IV Bag for 5 micrograms/m²/day Dose

Dose	Infusion Duration	Infusion Rate	BSA (m^2)	Reconstituted Blincyto
5 micrograms/m^2/day	24 hours	10 mL/hour	1.5 – 1.59	0.7 mL
			1.4 – 1.49	0.65 mL
			1.3 – 1.39	0.61 mL
			1.2 – 1.29	0.56 mL
			1.1 – 1.19	0.52 mL
			1 – 1.09	0.47 mL
			0.9 – 0.99	0.43 mL
			0.8 – 0.89	0.38 mL
			0.7 – 0.79	0.34 mL
			0.6 – 0.69	0.29 mL
			0.5 – 0.59	0.25 mL
			0.4 – 0.49	0.2 mL
	48 hours	5 mL/hour	1.5 – 1.59	1.4 mL
			1.4 – 1.49	1.3 mL
			1.3 – 1.39	1.2 mL
			1.2 – 1.29	1.1 mL
			1.1 – 1.19	1 mL
			1 – 1.09	0.94 mL
			0.9 – 0.99	0.85 mL
			0.8 – 0.89	0.76 mL
			0.7 – 0.79	0.67 mL
			0.6 – 0.69	0.58 mL
			0.5 – 0.59	0.49 mL
			0.4 – 0.49	0.40 mL

Dose	Infusion Duration	Infusion Rate	BSA (m^2)	Reconstituted Blincyto
5 micrograms/m^2/day	72 hours	3.3 mL/hour	1.5 – 1.59	2.1 mL
			1.4 – 1.49	2 mL
			1.3 – 1.39	1.8 mL
			1.2 – 1.29	1.7 mL
			1.1 – 1.19	1.5 mL
			1 – 1.09	1.4 mL
			0.9 – 0.99	1.3 mL
			0.8 – 0.89	1.1 mL
			0.7 – 0.79	1.01 mL
			0.6 – 0.69	0.87 mL
			0.5 – 0.59	0.74 mL
			0.4 – 0.49	0.60 mL
	96 hours	2.5 mL/hour	1.5 – 1.59	2.8 mL
			1.4 – 1.49	2.6 mL
			1.3 – 1.39	2.4 mL
			1.2 – 1.29	2.2 mL
			1.1 – 1.19	2.1 mL
			1 – 1.09	1.9 mL
			0.9 – 0.99	1.7 mL
			0.8 – 0.89	1.5 mL
			0.7 – 0.79	1.3 mL
			0.6 – 0.69	1.2 mL
			0.5 – 0.59	0.98 mL
			0.4 – 0.49	0.80 mL

Table 5. For Patients Weighing Less Than 45 kg: Volumes of Reconstituted Blincyto to Add to IV Bag for 15 micrograms/m²/day Dose

Dose	Infusion Duration	Infusion Rate	BSA (m^2)	Reconstituted Blincyto
15 micrograms/m^2 /day	24 hours	10 mL/hour	1.5 – 1.59	2.1 mL
			1.4 – 1.49	2 mL
			1.3 – 1.39	1.8 mL
			1.2 – 1.29	1.7 mL
			1.1 – 1.19	1.5 mL
			1 – 1.09	1.4 mL
			0.9 – 0.99	1.3 mL
			0.8 – 0.89	1.1 mL
			0.7 – 0.79	1.01 mL
			0.6 – 0.69	0.87 mL
			0.5 – 0.59	0.74 mL
			0.4 – 0.49	0.6 mL
	48 hours	5 mL/hour	1.5 – 1.59	4.2 mL[a]
			1.4 – 1.49	3.9 mL[a]
			1.3 – 1.39	3.6 mL[a]
			1.2 – 1.29	3.4 mL[a]
			1.1 – 1.19	3.1 mL[a]
			1 – 1.09	2.8 mL
			0.9 – 0.99	2.6 mL
			0.8 – 0.89	2.3 mL
			0.7 – 0.79	2 mL
			0.6 – 0.69	1.7 mL
			0.5 – 0.59	1.5 mL
			0.4 – 0.49	1.2 mL

Dose	Infusion Duration	Infusion Rate	BSA (m^2)	Reconstituted Blincyto
15 micrograms/m^2/day	72 hours	3.3 mL/hour	1.5 – 1.59	6.3 mL[b]
			1.4 – 1.49	5.9 mL[b]
			1.3 – 1.39	5.4 mL[c]
			1.2 – 1.29	5.0 mL[c]
			1.1 – 1.19	4.6 mL[c]
			1 – 1.09	4.2 mL[c]
			0.9 – 0.99	3.8 mL[c]
			0.8 – 0.89	3.4 mL[c]
			0.7 – 0.79	3 mL[c]
			0.6 – 0.69	2.6 mL
			0.5 – 0.59	2.2 mL
			0.4 – 0.49	1.8 mL
	96 hours	2.5 mL/hour	1.5 – 1.59	8.3 mL[d]
			1.4 – 1.49	7.8 mL[d]
			1.3 – 1.39	7.3 mL[d]
			1.2 – 1.29	6.7 mL[d]
			1.1 – 1.19	6.2 mL[d]
			1 – 1.09	5.6 mL[d]
			0.9 – 0.99	5.1 mL[e]
			0.8 – 0.89	4.6 mL[e]
			0.7 – 0.79	4 mL[e]
			0.6 – 0.69	3.5 mL[e]
			0.5 – 0.59	2.9 mL[e]
			0.4 – 0.49	2.4 mL

a. 2 packages of Blincyto are needed for preparation of 15 micrograms/m^2/day dose infused over 48 hours at a rate of 5 mL/hour for patients with a BSA greater than 1.09 m^2
b. 3 packages of Blincyto are needed for preparation of 15 micrograms/m^2/day dose infused over 72 hours at a rate of 3.3 mL/hour for patients with a BSA greater than 1.39 m^2
c. 2 packages of Blincyto are needed for preparation of 15 micrograms/m^2/day dose infused over 72 hours at a rate of 3.3 mL/hour for patients with a BSA of 0.70 m^2 to 1.39 m^2
d. 3 packages of Blincyto are needed for preparation of 15 micrograms/m^2/day dose infused over 96 hours at a rate of 2.5 mL/hour for patients with a BSA greater than 0.99 m^2
e. 2 packages of Blincyto are needed for preparation of 15 micrograms/m^2/day dose infused over 96 hours at a rate of 2.5 mL/hour for patients with a BSA of 0.50 m^2 to 0.99 m^2

Preparation of Blincyto Solution for Infusion Using a 250 mL Cassette

Verify the prescribed dose and infusion duration for each Blincyto cassette. To minimise errors, **use the specific volumes described in Tables 6 to 8 to prepare the Blincyto cassette.**

- Table 6 for patients weighing greater than or equal to 45 kg
- Tables 7 and 8 for patients weighing less than 45 kg

1. Aseptically transfer sterile 0.9% sodium chloride into the cassette. The volume to transfer should be 250 mL **minus 5 mL IV solution stabiliser and reconstituted Blincyto to be added**. For example, for a cassette that will deliver 9 micrograms/day over 96 hours, load 242 mL 0.9% sodium chloride into the cassette (250 mL minus 5 mL IV solution stabiliser minus 3 mL reconstituted Blincyto for a total volume of 242 mL). **The final solution volume should equal 250 mL**.
2. Aseptically transfer 5 mL of IV solution stabiliser to the cassette. Gently mix the contents of the cassette to avoid foaming. Discard the vial containing the unused IV solution stabiliser.
3. Refer to Tables 6 to 8 for the expected number of Blincyto vials needed to prepare the required dose of Blincyto for the infusion duration. Reconstitute each vial of Blincyto using 3 mL of preservative-free sterile Water for Injections. Direct preservative-free Sterile 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 with IV solution stabiliser.
   - The addition of preservative-free sterile Water for Injections to the lyophilised powder results in a total volume of 3.1 mL for a final Blincyto concentration of 12.5 micrograms/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 not use if solution is cloudy or has precipitated**.
5. Using an appropriate sized syringe, aseptically transfer the required volume (Tables 6 to 8) of reconstituted Blincyto into the cassette. Gently mix the contents of the cassette to avoid foaming.
6. Redraw approximately 10 mL of fluid from the cassette and inject back to ensure no Blincyto remains in the cassette line. Gently mix again.
7. Remove air from the cassette using a syringe. Under aseptic conditions, attach the IV tubing with the sterile 0.2 micron in-line filter to the cassette.
8. Prime the IV line **only** with the prepared solution for infusion. **Do not prime with 0.9% sodium chloride.**
   Store at 2°C to 8°C if not used immediately.

Table 6. For Patients Weighing Greater Than or Equal to 45 kg: Volume of Blincyto Required for 250 mL Cassette

Dose	Cassette Duration	Expected Number of Blincyto vials required*	Reconstituted Blincyto
9 microgram/ day	24 hours	1	0.75 mL
	48 hours	1	1.5 mL
	72 hours	1	2.25 mL
	96 hours	2	3 mL
28 microgram/ day	24 hours	1	2.3 mL
	48 hours	2	4.7 mL
	72 hours	3	7 mL
	96 hours	4	9.3 mL

*Extractable amount per vial is 35 micrograms in a volume of 2.8 mL reconstituted solution.

Table 7. For Patients Weighing Less Than 45 kg: Volume of Blincyto Required for 250 mL Cassette for 5 microgram/m²/day Dose

Dose	Cassette Duration	Expected Number of Blincyto vials required*	BSA (m^2)	Volume of Reconstituted Blincyto
5 mcg/m²/day	24 hours	1	1.5 – 1.59	0.65
		1	1.4 – 1.49	0.6
		1	1.3 – 1.39	0.56
		1	1.2 – 1.29	0.52
		1	1.1 – 1.19	0.48
		1	1 – 1.09	0.44
		1	0.9 – 0.99	0.39
		1	0.8 – 0.89	0.35
		1	0.7 – 0.79	0.31
		1	0.6 – 0.69	0.27
		1	0.5 – 0.59	0.23
		1	0.4 – 0.49	0.19
	48 hours	1	1.5 – 1.59	1.3
		1	1.4 – 1.49	1.2
		1	1.3 – 1.39	1.1
		1	1.2 – 1.29	1
		1	1.1 – 1.19	0.95
		1	1 – 1.09	0.87
		1	0.9 – 0.99	0.79
		1	0.8 – 0.89	0.7
		1	0.7 – 0.79	0.62
		1	0.6 – 0.69	0.54
		1	0.5 – 0.59	0.45
		1	0.4 – 0.49	0.37

Dose	Cassette Duration	Expected Number of Blincyto vials required*	BSA (m^2)	Volume of Reconstituted Blincyto
5 mcg/m^2/day	72 hours	1	1.5 – 1.59	1.9
		1	1.4 – 1.49	1.8
		1	1.3 – 1.39	1.7
		1	1.2 – 1.29	1.6
		1	1.1 – 1.19	1.4
		1	1 – 1.09	1.3
		1	0.9 – 0.99	1.2
		1	0.8 – 0.89	1.1
		1	0.7 – 0.79	0.93
		1	0.6 – 0.69	0.81
		1	0.5 – 0.59	0.68
		1	0.4 – 0.49	0.56
	96 hours	1	1.5 – 1.59	2.6
		1	1.4 – 1.49	2.4
		1	1.3 – 1.39	2.2
		1	1.2 – 1.29	2.1
		1	1.1 – 1.19	1.9
		1	1 – 1.09	1.7
		1	0.9 – 0.99	1.6
		1	0.8 – 0.89	1.4
		1	0.7 – 0.79	1.2
		1	0.6 – 0.69	1.1
		1	0.5 – 0.59	0.91
		1	0.4 – 0.49	0.74

Table 8. For Patients Weighing Less Than 45 kg: Volume of Blincyto Required for 250 mL Cassette for 15 microgram/m^2/day Dose

Dose	Cassette Duration	Expected Number of Blincyto vials required*	BSA (m^2)	Volume of Reconstituted Blincyto
15 mcg/m^2/day	24 hours	1	1.5 – 1.59	1.9
		1	1.4 – 1.49	1.8
		1	1.3 – 1.39	1.7
		1	1.2 – 1.29	1.6
		1	1.1 – 1.19	1.4
		1	1 – 1.09	1.3
		1	0.9 – 0.99	1.2
		1	0.8 – 0.89	1.1
		1	0.7 – 0.79	0.93
		1	0.6 – 0.69	0.81
		1	0.5 – 0.59	0.68
		1	0.4 – 0.49	0.56
	48 hours	2	1.5 – 1.59	3.9
		2	1.4 – 1.49	3.6
		2	1.3 – 1.39	3.4
		2	1.2 – 1.29	3.1
		2	1.1 – 1.19	2.9
		1	1 – 1.09	2.6
		1	0.9 – 0.99	2.4
		1	0.8 – 0.89	2.1
		1	0.7 – 0.79	1.9
		1	0.6 – 0.69	1.6
		1	0.5 – 0.59	1.4
		1	0.4 – 0.49	1.1

Dose	Cassette Duration	Expected Number of Blincyto vials required*	BSA (m^2)	Volume of Reconstituted Blincyto
15 mcg/m^2/day	72 hours	3	1.5 – 1.59	5.8
		2	1.4 – 1.49	5.4
		2	1.3 – 1.39	5
		2	1.2 – 1.29	4.7
		2	1.1 – 1.19	4.3
		2	1 – 1.09	3.9
		2	0.9 – 0.99	3.5
		2	0.8 – 0.89	3.2
		1	0.7 – 0.79	2.8
		1	0.6 – 0.69	2.4
		1	0.5 – 0.59	2
		1	0.4 – 0.49	1.7
	96 hours	3	1.5 – 1.59	7.7
		3	1.4 – 1.49	7.2
		3	1.3 – 1.39	6.7
		3	1.2 – 1.29	6.2
		3	1.1 – 1.19	5.7
		2	1 – 1.09	5.2
		2	0.9 – 0.99	4.7
		2	0.8 – 0.89	4.2
		2	0.7 – 0.79	3.7
		2	0.6 – 0.69	3.2
		1	0.5 – 0.59	2.7
		1	0.4 – 0.49	2.2

Dosage adjustment

If the interruption after an adverse event is no longer than 7 days, continue the same cycle to a total of 28 days of infusion inclusive of days before and after the interruption in that cycle.

If an interruption due to an adverse event is longer than 7 days, start a new cycle.

Toxicity	Grade*	Patients Greater Than or Equal to 45 kg	Patients Less Than 45 kg
Cytokine Release Syndrome (CRS)	Grade 3	Interrupt Blincyto until resolved, then restart Blincyto at 9 micrograms/day. Escalate to 28 micrograms/day after 7 days if the toxicity does not recur.	Interrupt Blincyto until resolved, then restart Blincyto at 5 micrograms/m^2/day. Escalate to 15 micrograms/m^2/day after 7 days if the toxicity does not recur.
	Grade 4	Discontinue Blincyto permanently.	
Neurologic Events	Seizure	Discontinue Blincyto permanently if more than one seizure occurs.	
	Grade 3	Interrupt Blincyto until no more than Grade 1 (mild) and for at least 3 days, then restart Blincyto at 9 micrograms/day. Escalate to 28 micrograms/day after 7 days if the toxicity does not recur. For reinitiation, premedicate with 24 mg dexamethasone with a 4-day taper. As secondary prophylaxis, consider appropriate anticonvulsant medication. If the toxicity occurred at 9 micrograms/day, or if the toxicity takes more than 7 days to resolve, discontinue Blincyto permanently.	Interrupt Blincyto until no more than Grade 1 (mild) and for at least 3 days, then restart Blincyto at 5 micrograms/m^2/day. Escalate to 15 micrograms/m^2/day after 7 days if the toxicity does not recur. Consider appropriate anticonvulsant medication. If the toxicity occurred at 5 micrograms/m^2/day, or if the toxicity takes more than 7 days to resolve, discontinue Blincyto permanently.
	Grade 4	Discontinue Blincyto permanently.	
Other Clinically Relevant Adverse Reactions	Grade 3	Interrupt Blincyto until no more than Grade 1 (mild), then restart Blincyto at 9 micrograms/day. Escalate to 28 micrograms/day after 7 days if the toxicity does not recur.	Interrupt Blincyto until no more than Grade 1 (mild), then restart Blincyto at 5 micrograms/m^2/day. Escalate to 15 micrograms/m^2/day after 7 days if the toxicity does not recur.
	Grade 4	Consider discontinuing Blincyto permanently.	

*Based on the Common Terminology Criteria for Adverse Events (CTCAE). Grade 3 is severe, and Grade 4 is life-threatening.

Special populations

No formal pharmacokinetic studies using Blincyto have been conducted in patients with renal impairment. Based on pharmacokinetic analyses, dose adjustment is not necessary in patients with mild to moderate renal dysfunction (see Section 5.2 Pharmacokinetic properties).

No formal pharmacokinetic studies using Blincyto have been conducted in patients with hepatic impairment. Since Blincyto is a protein and not metabolised via the hepatic pathway, the effect of liver dysfunction on drug exposure is not expected and dose adjustment is not necessary (see Section 5.2 Pharmacokinetic properties).

4.3 Contraindications

Blincyto is contraindicated in patients with known hypersensitivity to CHO-cell derived proteins, blinatumomab or any of the excipients (see Section 6.1 List of excipients).

4.4 Special warnings and precautions for use

Neurologic events

Neurologic events have been observed in patients receiving Blincyto. Among patients that experienced a neurologic event, the median time to the first event was within the first 2 weeks of Blincyto treatment and the majority of events resolved. Infrequently, a neurologic event led to treatment discontinuation. Grade 3 or higher (severe or life-threatening) neurologic events following initiation of Blincyto administration included encephalopathy, seizures, speech disorders, disturbances in consciousness, confusion and disorientation, and coordination and balance disorders. Some events were reported with a fatal outcome.

There is limited experience with Blincyto in patients with active ALL in the central nervous system (CNS) or a history of neurologic events. Patients with a history or presence of clinically relevant CNS pathology were excluded from clinical trials. Patients receiving Blincyto should be clinically monitored for signs and symptoms of neurologic events. Management of these signs and symptoms may require either temporary interruption or discontinuation of Blincyto (see Section 4.2 Dose and method of administration, Dosage adjustment).

Infections

Patients with ALL are immunocompromised and consequently at increased risk for serious infections. In patients receiving Blincyto, serious infections, including sepsis, pneumonia, bacteraemia, opportunistic infections, and catheter site infections have been observed, some of which were life-threatening or fatal. There is limited experience with Blincyto in patients with an active uncontrolled infection.

Monitor patients for signs and symptoms of infection and treat appropriately. Management of infections may require either temporary interruption or discontinuation of Blincyto (see Section 4.2 Dose and method of administration, Dosage adjustment).

Blincyto should be prepared by personnel appropriately trained in aseptic preparation of oncology drugs. Aseptic technique must be strictly observed when preparing the solution for infusion and when performing routine catheter care (see Section 4.2 Dose and method of administration, Reconstitution and preparation of solution for infusion).

Cytokine release syndrome

Cytokine Release Syndrome (CRS) which may be life-threatening or fatal has been reported in patients receiving Blincyto (see Section 4.8 Adverse effects (Undesirable effects)).

Serious adverse events that may be associated with CRS included pyrexia, asthenia, headache, hypotension, total bilirubin increased, and nausea; these events infrequently led to Blincyto discontinuation. In some cases, disseminated intravascular coagulation, capillary leak syndrome, and haemophagocytic histiocytosis/macrophage activation syndrome have been reported in the setting of CRS. Patients should be closely monitored for signs or symptoms of these events.

To mitigate the risk of CRS, it is important to initiate Blincyto (Cycle 1, Days 1-7) at the recommended starting dose in Table 1 and Table 2. Management of CRS events may require either temporary interruption or discontinuation of Blincyto (see Section 4.2 Dose and method of administration, Dosage adjustment).

Infusion reactions

Infusion reactions may be clinically indistinguishable from manifestations of CRS.

Patients should be observed closely for infusion reactions, especially during the first infusion of the first cycle and treated appropriately. Management of infusion reactions may require

either temporary interruption or discontinuation of Blincyto (see Section 4.2 Dose and method of administration, Dosage adjustment).

Tumour lysis syndrome

Tumour Lysis Syndrome (TLS), which may be life-threatening or fatal has been observed in patients receiving Blincyto.

Appropriate prophylactic measures including hydration should be used for the prevention of TLS during Blincyto treatment. Patients should be closely monitored for signs or symptoms of TLS. Management of these events may require either temporary interruption or discontinuation of Blincyto (see Section 4.2 Dose and method of administration, Dosage adjustment).

Neutropenia and febrile neutropenia

Neutropenia and febrile neutropenia, including life threatening cases, have been observed in patients receiving Blincyto. Monitor laboratory parameters (including, but not limited to white blood cell count and absolute neutrophil count) during Blincyto infusion and treat appropriately.

Medication errors

Medication errors have been observed with Blincyto treatment. It is very important that the instructions for preparation (including reconstitution and dilution) and administration are strictly followed to minimise medication errors (including underdose and overdose) (see Section 4.2 Dose and method of administration, Preparation and administration, and Reconstitution and preparation of solution for infusion).

Elevated liver enzymes

Treatment with Blincyto was associated with transient elevations in liver enzymes. The majority of the events were observed within the first week of Blincyto initiation and did not require interruption or discontinuation of Blincyto.

Monitor alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), and total blood bilirubin prior to the start of and during Blincyto treatment.

Pancreatitis

Pancreatitis, life-threatening or fatal, has been reported in patients receiving Blincyto in clinical trials and the post marketing setting. High-dose steroid therapy may have contributed, in some cases, to the pancreatitis.

Evaluate patients who develop signs and symptoms of pancreatitis. Management of pancreatitis may require either temporary interruption or discontinuation of Blincyto (see Section 4.2 Dose and method of administration, Dosage adjustment).

Leukoencephalopathy

Cranial magnetic resonance imaging (MRI) changes showing leukoencephalopathy have been observed in patients receiving Blincyto, especially in patients with prior treatment with cranial irradiation and anti-leukaemic chemotherapy (including systemic high dose methotrexate or intrathecal cytarabine). The clinical significance of these imaging changes is unknown.

Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The immunogenicity of Blincyto has been evaluated using an electrochemiluminescence detection technology (ECL) screening immunoassay for the detection of binding anti-blinatumomab antibodies. For patients whose sera tested positive in the screening immunoassay, an in vitro biological assay was performed to detect neutralising antibodies.

In clinical studies of adult patients treated with Blincyto, less than 2% tested positive for anti-blinatumomab antibodies. Of patients who developed anti-blinatumomab antibodies, the majority had *in vitro* neutralising activity. Anti-blinatumomab antibody formation might affect pharmacokinetics of Blincyto.

No anti-blinatumomab antibodies (0 out of 70) were detected in clinical studies of paediatric patients with relapsed or refractory ALL treated with Blincyto. Given the low patient numbers in clinical trials, the possibility of anti-blinatumomab antibody formation cannot be excluded.

If formation of anti-blinatumomab antibodies with a clinically significant effect is suspected, contact Amgen's Medical Information line on 1800 803 638 (freecall within Australia) to discuss antibody testing.

The detection of anti-blinatumomab antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including

neutralising antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to blinatumomab with the incidence of antibodies to other products may be misleading.

Use in the elderly

65 years of age) and patients less than 65 years of age treated with Blincyto. However, elderly patients may be more susceptible to serious neurologic events such as cognitive disorder, encephalopathy, and confusion.

Paediatric use

The safety and effectiveness of Blincyto are supported by an open-label, single arm study of 93 paediatric patients with relapsed or refractory B-cell precursor ALL. No data exists for the treatment of ALL in patients aged less than 28 days.

For each cycle of treatment, Blincyto was administered as a continuous intravenous infusion for 28 days (4 weeks) followed by a 14-day (2-week) treatment-free interval. In total, 70 patients (aged 7 months to 17 years) received Blincyto at the recommended dose: 5 micrograms/m^2/day on Days 1-7 (week 1) and 15 micrograms/m^2/day on Days 8-28 (weeks 2 through 4) of cycle 1; then 15 micrograms/m^2/day on Days 1-28 of subsequent cycles.

In the dose evaluation phase of the study, one patient experienced a fatal cardiac failure event in the setting of life-threatening cytokine release syndrome (CRS) and tumour lysis syndrome (TLS) at a dose of 30 micrograms/m^2/day (higher than the maximum recommended dose). A fatal case of respiratory failure with hypotonia, muscle weakness and cardiac arrest with ascending neuropathy was also seen in one patient treated with a dose of 15 micrograms/m^2/day in the first week of treatment, which is higher than the recommended dose of 5 micrograms/m^2/day for the first week of treatment. In this case, febrile neutropenia and a serious viral illness with positive viral blood cultures preceded Blincyto treatment, suggesting a differential diagnosis of Guillain-Barre Syndrome (see Section 4.4 Special warnings and precautions for use and Section 4.8 Adverse effects (Undesirable effects)).

Effects on laboratory tests

No interactions with laboratory and diagnostic tests have been identified.

4.5 Interactions with other medicines and other forms of interactions

No formal drug interaction studies have been conducted with Blincyto. Blincyto is not expected to affect CYP450 enzyme activities.

Transient elevation of cytokines may affect CYP450 enzyme activities. Based on physiologically based pharmacokinetic modelling, the effect of transient cytokine elevation on activities of CYP450 enzymes is less than 30%, lasting for less than a week; the effect on exposures to sensitive CYP450 substrates are less than 2-fold. Hence, Blincyto-mediated cytokine elevation appears to have a low potential of clinically meaningful drug interaction.

Immunisation

The safety of immunisation with live viral vaccines during or following Blincyto therapy has not been studied. Vaccination with live virus vaccines is not recommended for at least 2 weeks prior to the start of Blincyto treatment, during treatment, and until recovery of B lymphocytes to normal range following last cycle of Blincyto.

4.6 Fertility, pregnancy and lactation

Effects on fertility

No studies have been conducted to evaluate the effects of Blincyto on fertility. There were no effects on male or female mouse reproductive organs in 13-week toxicity studies with the murine surrogate molecule.

Use in pregnancy

Pregnancy Category: C

The safety and efficacy of blinatumomab in pregnant women has not been established. In a developmental toxicity study conducted in mice using a murine surrogate molecule, there was no indication of maternal toxicity, embryofetal toxicity, or teratogenicity. The expected depletions of B and T cells were observed in the pregnant mice but haematological effects were not assessed in foetuses.

Treatment of pregnant women with blinatumomab may compromise the immunity of the fetus. Blincyto should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

Women of childbearing potential should use contraception during and for at least 48 hours after treatment with Blincyto.

Due to the potential for depletion of B lymphocytes in infants following exposure to Blincyto during pregnancy, the infant's B lymphocytes should be monitored before the initiation of live virus vaccination. Live virus vaccines can be administered when the B lymphocytes are within the normal range.

Use in lactation

It is unknown whether blinatumomab or metabolites are excreted in human milk.

A risk to newborns or infants cannot be excluded. Because of the potential for Blincyto to cause adverse effects in infants, nursing should be discontinued during and for at least 48 hours after treatment with Blincyto.

4.7 Effects on ability to drive and use machines

No studies on effects of Blincyto on the ability to drive and use machines have been performed. However, due to the potential for neurologic events, patients receiving Blincyto should refrain from driving, engaging in hazardous occupations or activities such as driving or operating heavy or potentially dangerous machinery while Blincyto is being administered. Patients should be advised that they may experience neurologic events.

4.8 Adverse effects (Undesirable effects)

Acute Lymphoblastic Leukaemia in Adult Patients

The adverse reactions described in this section were identified in the randomised phase III clinical study (N = 267) of adult patients with Philadelphia chromosome-negative relapsed or refractory B-cell precursor ALL.

The most serious adverse reactions that may occur during Blincyto treatment include:

infections (28.1%), neutropenia/febrile neutropenia (10.5%), neurologic events (6.7%), cytokine release syndrome (3.7%), and tumour lysis syndrome (1.1%).

The most common adverse reactions were: infections (64.0%), pyrexia (60.3%), infusion-related reactions (34.1%), headache (28.8%), anaemia (27.3%), febrile neutropenia (24.0%), thrombocytopenia (24.0%), neutropenia (23.2%), oedema (17.2%), and increased liver enzymes (16.9%).

Adverse reactions are presented below by system organ class and frequency category. Frequency categories were determined from the crude incidence rate reported for each adverse reaction in the phase III clinical study (N = 267). Within each system organ class, adverse reactions are:

MedDRA system organ class	**Very common 1/10)**	**Common 1/100 to < 1/10)**	**Uncommon 1/1000 to < 1/100)**
Infections and infestations	Fungal infections[a,b] Bacterial infections[a,b] Viral infections[a,b] Infections – pathogen unspecified[b]		
Blood and lymphatic system disorders	Febrile neutropenia[12] Neutropenia Thrombocytopenia[17] Anaemia[1]	Haemophagocytic histiocytosis Leukopenia[10] Leukocytosis[2] Lymphopenia[11] Lymphadenopathy	
Immune system disorders	Cytokine release syndrome[a]	Hypersensitivity	Cytokine storm
Metabolism and nutrition disorders		Tumour lysis syndrome	
Psychiatric disorders	Insomnia	Confusional state[a] Disorientation	
Nervous system disorders	Headache	Encephalopathy[a] Seizure Aphasia Paraesthesia Memory impairment Cognitive disorder Tremor[a] Somnolence Hypoaesthesia Dizziness	Speech disorder

MedDRA system organ class	Very common 1/10)	Common 1/100 to < 1/10)	Uncommon 1/1000 to < 1/100)
Cardiac disorders	Tachycardia[16]		
Vascular disorders	Hypotension[8]	Hypertension[7] Flushing	
Respiratory, thoracic and mediastinal disorders	Cough	Dyspnoea[4] Productive cough	
Gastrointestinal disorders			Pancreatitis[a]
Hepatobiliary disorders		Increased blood bilirubin[6]	
Skin and subcutaneous tissue disorders	Rash[15]		
Musculoskeletal and connective tissue disorders	Back pain Bone pain	Pain in extremity	
General disorders and administration site conditions	Pyrexia[14] Oedema[13]	Chest pain[2] Chills Pain	
Investigations	Hepatic enzyme increased[a, 5]	Decreased immunoglobulins[3] Blood alkaline phosphatase increased Weight increased	
Injury, poisoning and procedural complications	Infusion-related reactions[18]	Overdose Accidental overdose	

[a] Additional information is provided in "Description of selected adverse reactions".
[b] MedDRA high level group terms (MedDRA version 18.1).
Event terms that represent the same medical concept or condition were grouped together and reported as a single adverse reaction in the table above. The terms contributing to the relevant adverse reaction are indicated below:

[1] Anaemia includes anaemia and haemoglobin decreased.
[2] Chest pain includes chest discomfort, chest pain, musculoskeletal chest pain and non-cardiac chest pain
[3] Decreased immunoglobulins includes blood immunoglobulin G decreased, globulins decreased, hypogammaglobulinaemia, hypoglobulinaemia and immunoglobulins decreased.
[4] Dyspnoea includes acute respiratory failure, dyspnoea, dyspnoea exertional, respiratory failure and wheezing.
[5] Hepatic enzyme increased includes alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyltransferase increased, hepatic enzyme increased and transaminases increased.
[6] Hyperbilirubinaemia includes blood bilirubin increased and hyperbilirubinaemia.
[7] Hypertension includes blood pressure increased and hypertension.
[8] Hypotension includes blood pressure decreased and hypotension.
[9] Leukocytosis includes leukocytosis and white blood cell count increased.
[10] Leukopenia includes leukopenia and white blood cell count decreased.

[11] Lymphopenia includes lymphocyte count decreased and lymphopenia.
[12] Neutropenia includes neutropenia and neutrophil count decreased.
[13] Oedema includes face oedema, generalised oedema, oedema and oedema peripheral.
[14] Pyrexia includes body temperature increased and pyrexia.
[15] Rash includes erythema, rash, rash erythematous, rash generalised, rash macular, rash maculo-papular and rash pruritic.
[16] Tachycardia includes sinus tachycardia, supraventricular tachycardia and tachycardia.
[17] Thrombocytopenia includes platelet count decreased and thrombocytopenia.
[18] Infusion-related reactions is a composite term that includes the term infusion-related reaction and the following events occurring with the first 48 hours of infusion and event lasted <=2 days: pyrexia, cytokine release syndrome, hypotension, myalgia, acute kidney injury, hypertension, and rash erythematous.

The adverse reaction profile in Blincyto-treated patients in this study was similar in type to those seen in the phase I/II single-arm studies; Capillary Leak Syndrome was observed in one patient in the phase II single-arm study (Study 2).

Acute Lymphoblastic Leukaemia in Paediatric Patients

The adverse reactions in Blincyto-treated paediatric patients were similar in type to those seen in adult patients.
difference) in the paediatric population compared to the adult population (Study 1) were:

MedDRA system organ class	Very common 1/10)	Common 1/100 to < 1/10)	Uncommon 1/1000 to < 1/100)
Blood and lymphatic system disorders	Anaemia Thrombocytopenia Leukopenia		
General disorders and administration site conditions	Pyrexia		
Injury, poisoning and procedural complications	Infusion-related reaction		
Vascular disorders	Hypertension		
Investigations	Weight increased		

Relapsed or Refractory Philadelphia Chromosome-positive B-cell Precursor ALL and MRD-positive B-cell Precursor ALL in Adult Patients

The adverse reaction profile in Blincyto-treated Philadelphia chromosome-positive relapsed or refractory B-cell precursor ALL patients and MRD positive B-precursor ALL adult patients was similar in type to those seen in the randomised phase III clinical study in Philadelphia chromosome-negative relapsed or refractory B-precursor ALL.

The most common adverse reactions among adult patients were pyrexia (90.5%), headache (39.4%), tremor (29.2%), chills (28.5%), fatigue (26.3%), nausea (23.4%), vomiting (21.2%), hypokalaemia (20.4%), and diarrhoea (20.4%).

The most common serious adverse reaction during blinatumomab treatment among adult patients was pyrexia (12.4%).

Description of selected adverse reactions

Neurologic events

In the phase III clinical study with Blincyto (N = 267), 61.0% of patients experienced one or more neurologic adverse reactions (including psychiatric disorders), primarily involving the central nervous system. Serious 3 neurologic adverse reactions were observed in 6.7% and 9.4% of patients respectively, of which the most common were encephalopathy, aphasia, confusional state, and somnolence. The majority of neurologic events (80.7%) were clinically reversible. The median time to the first event was within the first two weeks of treatment. One case of fatal encephalopathy has been reported in an earlier phase II clinical single-arm study.

Neurologic events were reported for 71.5% of adult patients with MRD positive B-precursor ALL of which 3 and grade 4 events, respectively, were reported for 16.1% and 2.2% of adult patients with MRD positive B-cell precursor ALL.

For clinical management of neurologic events, see Section 4.4 Special warnings and precautions for use, Neurological events and Section 4.2 Dose and method of administration, Dosage adjustment.

Infections

Life-threatening or fatal viral, bacterial, and fungal infections have been reported in patients treated with Blincyto. In addition, reactivation of JC and BK viral infections has been observed in the phase II clinical study in adults with Philadelphia chromosome-negative relapsed or refractory B-precursor ALL. 2 experienced a higher incidence of serious infections compared to patients with ECOG performance status of < 2. For clinical management of infections, see Section 4.4 Special warnings and precautions for use, Infections. In paediatric clinical trials, the incidence of herpes simplex virus in patients receiving the recommended dose of Blincyto was 4.3%.

Cytokine release syndrome (CRS)

In the phase III clinical study (N = 267) with Blincyto, CRS was reported in 16.1% of patients with a median time to onset of 2 days. Serious CRS reactions were reported in 3.7% of patients with a median time to onset of 4 days. Capillary leak syndrome was observed in 1 patient in the phase II clinical study.

Cytokine release syndrome was reported in 2.9% of adult patients with MRD positive B-precursor ALL. Grade 3 events were reported for 1.5% of adult patients with MRD positive B- 4 events were reported.

For clinical management of CRS, see Section 4.4 Special warnings and precautions for use, Cytokine release syndrome.

Elevated liver enzymes

In the pivotal clinical study with Blincyto, (N = 267), 21.7% of patients reported elevated liver enzymes. 3 adverse reactions such as ALT increased, AST increased, and blood bilirubin increased were observed in 1.1% and 12.7% of patients respectively. The median time to onset to the first event was 3 days from the start of Blincyto treatment initiation and did not require interruption or discontinuation of Blincyto.

Elevated liver enzyme events were reported for 12.4% of adult patients with MRD positive B- 4 events, respectively, were reported for 8.0% and 4.4% of adult patients with MRD positive B-precursor ALL.

The duration of hepatic adverse reactions has generally been brief and with rapid resolution, often when continuing uninterrupted treatment with Blincyto.

For clinical management of elevated liver enzymes, see Section 4.4 Special warnings and precautions for use, Elevated liver enzymes.

Post-marketing experience

Pancreatitis, life threatening or fatal, has been reported in patients receiving Blincyto (see Section 4.4 Special warnings and precautions for use).

Serious events of cranial nerve disorder have been reported.

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal

product. Healthcare professionals are asked to report any suspected adverse reactions at http://www.tga.gov.au/reporting-problems.

4.9 Overdose

Overdoses have been observed including one patient who received 133-fold the recommended therapeutic dose of Blincyto delivered over a short duration. Overdoses resulted in adverse reactions that were consistent with the reactions observed at the recommended therapeutic dose and included fever, tremors, and headache. In the event of overdose, the infusion should be temporarily interrupted and patients should be monitored. Consider re-initiation of Blincyto at the correct therapeutic dose (see Section 4.2 Dose and method of administration).

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Blinatumomab is a bispecific T cell engager (BiTE®) antibody construct that binds specifically to CD19 expressed on the surface of cells of B-lineage origin and CD3 expressed on the surface of T cells. It activates endogenous T cells by connecting CD3 in the T cell receptor (TCR) complex with CD19 on benign and malignant B cells. The anti-tumour activity of blinatumomab immunotherapy is not dependent on T cells bearing a specific TCR or on peptide antigens presented by cancer cells, but is polyclonal in nature and independent of human leukocyte antigen (HLA) molecules on target cells. Blinatumomab mediates the formation of a cytolytic synapse between the T cell and the B cell, releasing proteolytic enzymes to kill both proliferating and resting target cells. Blinatumomab is associated with transient upregulation of cell adhesion molecules, production of cytolytic proteins, release of inflammatory cytokines, and proliferation of T cells, and results in elimination of CD19+ cells.

Pharmacodynamics

Consistent immune-pharmacodynamic responses were observed in the patients studied. During the continuous intravenous infusion over 4 weeks, the pharmacodynamic response was characterised by T cell activation and initial redistribution, rapid peripheral B cell depletion, and transient cytokine elevation.

Peripheral T cell redistribution (i.e., T cell adhesion to blood vessel endothelium and/or transmigration into tissue) occurred after the start of Blincyto infusion or dose escalation. T cell counts initially declined within 1 to 2 days and then returned to baseline levels within 7 to 14 days in the majority of patients. An increase of T cell counts above baseline (T cell expansion) was observed in few patients.

Peripheral B cell counts decreased rapidly to an undetectable level during treatment at 5 micrograms/m^2 9 micrograms/day in the majority of patients. No recovery of peripheral B cell counts was observed during the 2-week Blincyto-free period between treatment cycles. Incomplete depletion of B cells occurred at doses of 0.5 micrograms/m^2/day and 1.5 micrograms/m^2/day and in a few non-responders at higher doses.

Cytokines including IL-2, IL-4, IL-6, IL-8, IL-10, IL-12, TNF- - IL-6, IL-10, and IFN- Transient elevation of cytokines was observed in the first 2 days following the start of Blincyto infusion. The elevated cytokine levels returned to baseline within 24 to 48 hours during the infusion. In subsequent treatment cycles, cytokine elevation occurred in fewer patients with lesser intensity compared to the initial 48 hours of the first treatment cycle.

Clinical trials

Acute Lymphoblastic Leukaemia in Adult Patients

A total of 706 18 years of age with relapsed or refractory B-precursor ALL were exposed to Blincyto during the phase II and phase III clinical studies described below.

In Study 1, the safety and efficacy of Blincyto compared to standard of care (SOC) chemotherapy were evaluated in a randomised, open-label, multicentre study. Eligible patients were 18 years of age with Philadelphia chromosome-negative relapsed or refractory B-cell precursor ALL (had > 5% blasts in the bone marrow and either relapse at any time after allogeneic haematopoietic stem cell transplantation [alloHSCT], untreated first relapse with first remission duration < 12 months, or refractory to last therapy).

Patients were randomised 2:1 to receive Blincyto or 1 of 4 prespecified, investigator-selected, SOC chemotherapy regimens. Randomisation was stratified by age (< 35 years 35 years of age), prior salvage therapy (yes versus no), and prior alloHSCT (yes versus no) as assessed at the time of consent. The demographics and baseline characteristics were well-balanced between the two arms (see Table 9).

Table 9. Demographics and Baseline Characteristics in Phase III Study

Characteristic	Blincyto (N = 271)	SOC Chemotherapy[a] (N = 134)
Age		
Median, years (min, max)	37 (18, 80)	37 (18, 78)
Mean, years (SD)	40.8 (17.1)	41.1 (17.3)
< 35 years, n (%)	123 (45.4)	60 (44.8)
35 years, n (%)	148 (54.6)	74 (55.2)
65 years, n (%)	33 (12.2)	15 (11.2)
75 years, n (%)	10 (3.7)	2 (1.5)
Males, n (%)	162 (59.8)	77 (57.5)
Race, n (%)		
American Indian or Alaska Native	4 (1.5)	1 (0.7)
Asian	19 (7.0)	9 (6.7)
Black (or African American)	5 (1.8)	3 (2.2)
Multiple	2 (0.7)	0
Native Hawaiian or Other Pacific Islander	1 (0.4)	0 (0.0)
Other	12 (4.4)	8 (6.0)
White	228 (84.1)	112 (83.6)
Prior salvage therapy	164 (60.5)	80 (59.7)
Prior alloHSCT[b]	94 (34.7)	46 (34.3)
Eastern Cooperative Group Status - n (%)		
0	96 (35.4)	52 (38.8)
1	134 (49.4)	61 (45.5)
2	41 (15.1)	20 (14.9)
Unknown	0	1 (0.7)
Maximum of central/local bone marrow blasts - n (%)		
Yes	87 (32.1)	34 (25.4)
No	182 (67.2)	99 (73.9)
Unknown	2 (0.7)	1 (0.7)
Maximum of central/local bone marrow blasts - n (%)		
5%	0	0
> 5 to < 10%	9 (3.3)	7 (5.2)
10 to < 50%	60 (22.1)	23 (17.2)
50%	201 (74.2)	104 (77.6)
Unknown	1 (0.4)	0

[a] SOC = standard of care

[b] alloHSCT = allogeneic haematopoietic stem cell transplantation

Blincyto was administered as a continuous intravenous infusion. In the first cycle, the initial dose was 9 micrograms/day for week 1, then 28 micrograms/day for the remaining 3 weeks. The target dose of 28 micrograms/day was administered in cycle 2 and subsequent cycles starting on day 1 of each cycle. Dose adjustment was possible in case of adverse events. Of the 267 patients who received Blincyto, the median number of treatment cycles was two (range: 0 to 9 cycles); of the 109 patients who received SOC chemotherapy, the median number of treatment cycles was one (range: 1 to 4 cycles).

The primary endpoint was overall survival (OS). The study demonstrated statistically significant improvement in OS for patients treated with Blincyto as compared to SOC chemotherapy. In patients with 0 prior salvage therapies the hazard ratio for OS was 0.64 (0.41, 0.99), in patients with one prior salvage therapy the hazard ratio for OS was 0.59 (0.38, 0.91), and in patients with more than two prior salvage therapies the hazard ratio for OS was 1.13 (0.64, 1.99). OS benefit was independent of transplant; consistent results were observed after censoring at the time of HSCT. See Figures 1 and 2 and Table 10 below for efficacy results from Study 1.

Figure 1. Kaplan-Meier Curve of Overall Survival

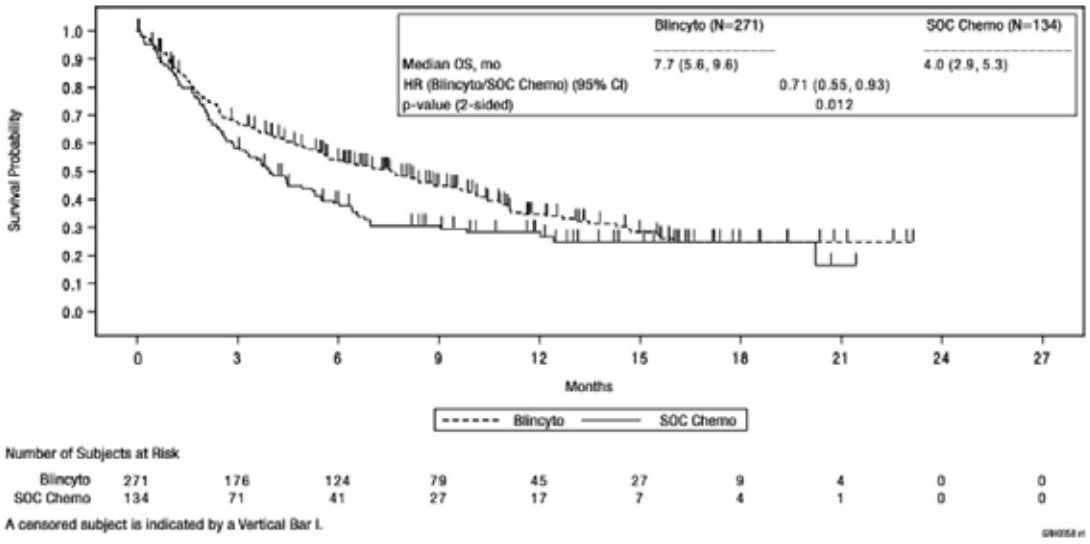
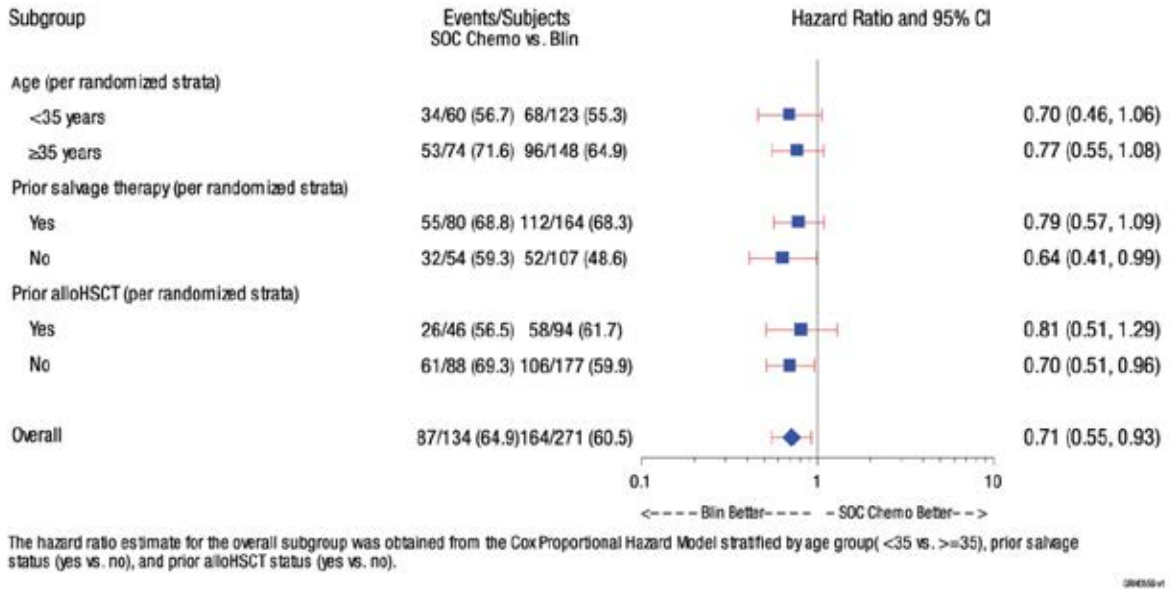


Figure 2. Forest Plot of Overall Survival Across Randomisation Factors



AlloHSCT = allogeneic haematopoietic stem cell transplantation; SOC = standard of care; Blin = blinatumomab

Table 10. Efficacy Results in Patients 18 Years of Age With Philadelphia Chromosome-negative Relapsed or Refractory B-cell Precursor Acute Lymphoblastic Leukaemia (ALL)

	Blincyto (N = 271)	SOC Chemotherapy (N = 134)
Overall Survival		
Median, months [95% CI]	7.7 (5.6, 9.6)	4.0 (2.9, 5.3)
Hazard Ratio [95% CI][a]	0.71 (0.55, 0.93)	
p-value[b]	0.012	
Complete Remission (CR)		
CR[c]/CRh*[d]/CRi[e], n (%) [95% CI]	119 (43.9) (37.9, 50)	33 (24.6) (17.6, 32.8)
Treatment difference [95% CI]	19.3 (9.9, 28.7)	
p-value[b]	< 0.001	
CR, n (%) [95% CI]	91 (33.6) (28.0, 39.5)	21 (15.7) (10, 23)
Treatment difference [95% CI]	17.9 (9.6, 26.2)	
p-value[f]	< 0.001	
Duration of CR/CRh*/CRi[g]		
Median, months [95% CI]	7.3 (5.8, 9.9)	4.6 (1.8, 19)
Event-free Survival[h]		
6-month estimate % [95% CI]	30.7 (25, 36.5)	12.5 (7.2, 19.2)
Hazard Ratio [95% CI]	0.55 (0.43, 0.71)	
MRD Response[i] for CR/CRh*/CRi		
n1/n2 (%)[j] [95% CI]	74/119 (62.2) (52.8, 70.9)	16/33 (48.5) (30.8, 66.5)

[a] Based on stratified Cox's model.
[b] The p-value was derived using stratified log-rank test.
[c] CR was defined as £ 5% blasts in the bone marrow, no evidence of disease, and full recovery of peripheral blood counts (platelets > 100,000/microliter and absolute neutrophil counts [ANC] > 1,000/microliter).
[d] CRh* (complete remission with partial haematologic recovery) was defined as £ 5% blasts in the bone marrow, no evidence of disease, and partial recovery of peripheral blood counts (platelets > 50,000/microliter and ANC > 500/microliter).
[e] CRi (complete remission with incomplete haematologic recovery) was defined as £ 5% blasts in the bone marrow, no evidence of disease, and incomplete recovery of peripheral blood counts (platelets > 100,000/microliter or ANC > 1,000/microliter).
[f] The p-value was derived using Cochran-Mantel-Haenszel test
[g] Duration of CR/CRh*/CRi was defined as time since first response to relapse or death, whichever is earlier. Relapse was defined as haematological relapse (blasts in bone marrow greater than 5% following CR) or an extramedullary relapse.
[h] EFS time was calculated from the time of randomization until the date of disease assessment indicating a relapse after achieving a CR/CRh*/CRi or death, whichever is earlier. Subjects who fail to achieve a CR/CRh*/CRi within 12 weeks of treatment initiation are considered treatment failures and assigned an EFS duration of 1 day.
[i] MRD (minimum residual disease) response was defined as MRD by PCR or flow cytometry < 1×10^{-4}.
[j] n1: number of patients who achieved MRD response and CR/CRh*/CRi; n2: number of patients who achieved CR/CRh*/CRi.

In Study 2, the safety and efficacy of Blincyto were evaluated in an open-label, multicentre, single-arm study. 18 years of age with Philadelphia chromosome-negative relapsed or refractory B-precursor ALL (relapsed with first remission duration of 12 months in first salvage or relapsed or refractory after first salvage therapy or relapsed within 12 months of allogeneic HSCT, and had 10% blasts in bone marrow).

Blincyto was administered as a continuous intravenous infusion. In the first cycle, the initial dose was 9 micrograms/day for week 1, then 28 micrograms/day for the remaining 3 weeks. The target dose of 28 micrograms/day was administered in cycle 2 and subsequent cycles starting on day 1 of each cycle. Dose adjustment was possible in case of adverse events. The treated population included 189 patients who received at least 1 infusion of Blincyto; the median number of treatment cycles was 2 (range: 1 to 5). Patients who responded to Blincyto but later relapsed had the option to be retreated with Blincyto. Among treated patients, the median age was 39 years (range: 18 to 79 years), 64 out of 189 (33.9%) had undergone HSCT prior to receiving Blincyto and 32 out of 189 (16.9%) had received more than 2 prior salvage therapies.

The primary endpoint was the CR/CRh* rate within 2 cycles of treatment with Blincyto. Eighty-one out of 189 (42.9%) patients achieved CR/CRh* within the first 2 treatment cycles with the majority of responses (64 out of 81) occurring within cycle 1 of treatment (see Table 11 and Figure 3 below for efficacy results). Four patients achieved CR during subsequent cycles, resulting in a cumulative CR rate of 35.4% (67 out of 189; 95% CI: 28.6% - 42.7%). Thirty-two out of 189 (16.9%) patients underwent allogeneic HSCT in CR/CRh* induced with Blincyto.

Table 11. 18 Years of Age With Philadelphia Chromosome-Negative Relapsed or Refractory B-Precursor Acute Lymphoblastic Leukaemia (ALL)

	n (%) N = 189	95% CI
Complete remission (CR)[1]/Complete remission with partial haematological recovery (CRh*)[2]	81 (42.9%)	[35.7% - 50.2%]
CR	63 (33.3%)	[26.7% - 40.5%]
CRh*	18 (9.5%)	[5.7% - 14.6%]
Blast free hypoplastic or aplastic bone marrow[3]	17 (9%)	[5.3% - 14.0%]
Partial remission[4]	5 (2.6%)	[0.9% - 6.1%]
Relapse-free[5] survival (RFS) for CR/CRh*	5.9 months	[4.8 to 8.3 months]
Overall survival	6.1 months	[4.2 to 7.5 months]

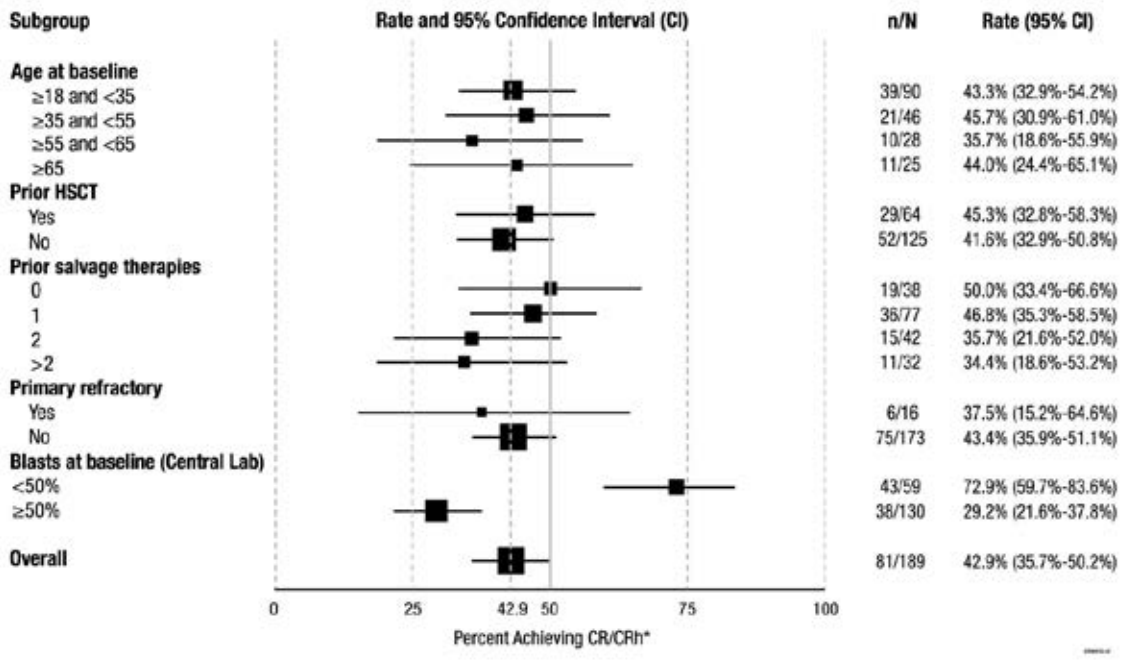
1. CR was defined as £ 5% of blasts in the bone marrow, no evidence of disease, and full recovery of peripheral blood counts (platelets > 100,000/mL and absolute neutrophil counts [ANC] > 1,000/mL).
2. CRh* was defined as £ 5% of blasts in the bone marrow, no evidence of disease, and partial recovery of peripheral blood counts (platelets > 50,000/mL and ANC > 500/mL).
3. Blast free hypoplastic or aplastic bone marrow was defined as bone marrow blasts £ 5%, no evidence of disease, insufficient recovery of peripheral
.
4. Partial remission was defined as bone marrow blasts 6% to 25% with at least a 50% reduction from baseline.
5. Relapse was defined as haematological relapse (blasts in bone marrow greater than 5% following CR) or an extramedullary relapse.

Patients with prior allogeneic HSCT had similar response rates to those without prior HSCT, older patients had similar response rates to younger patients, and no substantial difference was observed in remission rates based on the number of lines of prior salvage treatment (see Figure 3).

To further assess survival, a prespecified landmark analysis comparing responders and non-responders in week 5 of cycles 1 and 2 was conducted. The median overall survival was 11.2 months (95% CI: 7.8 months to not estimable) among patients who achieved CR/CRh* (N = 60) and 3.0 months (95% CI: 2.4 to 4 months) among non-responders (N = 101) in the cycle 1 analysis. The median overall survival was 9.9 months (95% CI: 6.8 months to not estimable) among patients who achieved CR/CRh* (N = 79), and 2.7 months (95% CI: 1.6 to 4.5 months) among non-responders (N = 50) in the cycle 2 analysis.

In a prespecified exploratory analysis, 60 out of 73 MRD evaluable patients with CR/CRh* (82.2%) also had a MRD response (defined as MRD by PCR < 1×10^{-4}).

Figure 3. CR/CRh* Rate During the First Two Cycles by Subgroup



n = number of patients who achieved CR or CRh* in the first two cycles of treatment in the specified group
N = total number of patients in the specified group

In Study 3, the safety and efficacy of Blincyto were evaluated in an open-label, multicentre, dose-escalation study in 36 patients (including 23 patients treated at a dose equivalent to 18 years of age with relapsed and/or refractory B-precursor ALL (first or greater relapse, refractory, or relapse after haematopoietic stem cell transplantation [HSCT]). Fifteen out of 36 (41.7%) patients had undergone allogeneic haematopoietic stem cell transplantation (HSCT) prior to receiving Blincyto. The complete remission/complete remission with partial haematological recovery (CR/CRh*) rate was 69.4% [25 out of 36 patients (95% CI: 51.9% - 83.7%): 15 (41.7%; 95% CI: 25.5% - 59.2%) CR; 10 (27.8%; 95% CI: 14.2% - 45.2%) CRh*]. Twenty-two out of 25 (88%) patients with haematologic CR also had MRD responses (defined as MRD by PCR< 1×10^{-4}). The median duration of remission was 8.9 months, and the median relapse-free survival (RFS) was 7.6 months. The median overall survival (OS) was 9.8 months.

Philadelphia chromosome-positive B-cell precursor ALL

In Study 4, the safety and efficacy of Blincyto were evaluated in an open-label, multicentre, single- 18 years of age with Philadelphia chromosome-positive B-cell precursor ALL, relapsed or refractory to at least 1 second generation or later

tyrosine kinase inhibitor (TKI), or intolerant to second generation TKI, and intolerant or refractory to imatinib mesylate.

Blincyto was administered as a continuous intravenous infusion. In the first cycle, the initial dose was 9 micrograms/day for Week 1, then 28 micrograms/day for the remaining 3 weeks. The dose of 28 micrograms/day was administered in Cycle 2 and subsequent cycles starting on Day 1 of each cycle. Dose adjustment was possible in case of adverse events. The treated population included 45 patients who received at least one infusion of Blincyto; the median number of treatment cycles was 2 (range: 1 to 5). See Table 12 for the demographics and baseline characteristics from Study 4.

Table 12: Demographics and Baseline Characteristics

Characteristic	Blincyto (N = 45)
Age	
Median, years (min, max)	55 (23, 78)
Mean, years (SD)	52.8 (15)
65 Years and < 75 years, n (%)	10 (22.2)
75 Years, n (%)	2 (4.4)
Males, n (%)	24 (53.3)
Race, n (%)	
Asian	1 (2.2)
Black (or African American)	3 (6.7)
Other	2 (4.4)
White	39 (86.7)
Disease History	
Prior TKI treatment[a], n (%)	
1	7 (15.6)
2	21 (46.7)
	17 (37.8)
Prior salvage therapy	31 (61.9)
Prior alloHSCT[b]	20 (44.4)
Bone marrow blasts[c]	
	6 (13.3)
	28 (62.2)

[a] Number of patients that failed ponatinib = 23 (51.1%)
[b] alloHSCT = allogeneic haematopoietic stem cell transplantation
[c] centrally assessed

The primary endpoint was the CR/CRh* rate within two cycles of treatment with Blincyto. Sixteen out of 45 (35.6%) patients achieved CR/CRh* within the first two treatment cycles. Of the 16 patients with CR/CRh* in the first 2 cycles, 12 of 14 (85.7%) patients with a CR and 2 of 2 (100%) patients with a CRh* also achieved an MRD complete response. See Table 13 below for efficacy results from Study 4.

Two patients achieved CR during subsequent cycles, resulting in a cumulative CR rate of 35.6% (16 out of 45; 95% CI: 21.9 – 51.2). Five out of 16 (31.3%) patients underwent allogeneic HSCT in CR/CRh* induced with Blincyto.

Table 13 18 Years of Age With Philadelphia Chromosome-Positive Relapsed or Refractory B-cell Precursor Acute Lymphoblastic Leukaemia (ALL)

Complete remission (CR)[a]/Complete remission with partial haematological recovery (CRh*)[b], n (%) [95% CI]	16 (35.6) [21.9, 51.2]
CR, n (%) [95% CI]	14 (31.1) [18.2, 46.6]
CRh*, n (%) [95% CI]	2 (4.4) [0.5, 15.1]
CRi[c] (without CRh*), n (%) [95% CI]	2 (4.4) [0.5, 15.1]
Blast free hypoplastic or aplastic bone marrow (without CRi)[d], n (%) [95% CI]	3 (6.7) [1.4, 18.3]
Partial remission[e], n (%) [95% CI]	2 (4.4) [0.5, 15.1]
Complete MRD response[f], [95% CI]	18 (40.0) (25.7, 55.7)
Median Relapse[g]-free survival (RFS) for CR/CRh* [95% CI]	6.7 months [4.4 to NE[h]]
Median Overall survival [95% CI]	7.1 months [5.6 to NE[h]]

[a] CR was defined as £ 5% of blasts in the bone marrow, no evidence of disease, and full recovery of peripheral blood counts (platelets > 100,000/microliter and absolute neutrophil counts [ANC] > 1,000/microliter).

[b] CRh* was defined as £ 5% of blasts in the bone marrow, no evidence of disease, and partial recovery of peripheral blood counts (platelets > 50,000/microliter and ANC > 500/microliter).

[c] CRi (complete remission with incomplete haematologic recovery) was defined as £ 5% blasts in the bone marrow, no evidence of disease, and incomplete recovery of peripheral blood counts (platelets > 100,000/microliter or ANC > 1,000/microliter).

[d] Blast free hypoplastic or aplastic bone marrow was defined as bone marrow blasts £ 5%, no evidence of 50,000/microliter and/or ANC 500/microliter.

[e] Partial remission was defined as bone marrow blasts 6% to 25% with at least a 50% reduction from baseline.

[f] Complete MRD response was defined as the absence of detectable MRD confirmed in an assay with minimum sensitivity of 10^{-4}

[g] Relapse was defined as haematological relapse (blasts in bone marrow greater than 5% following CR) or an extramedullary relapse

[h] NE = not estimable

[i]

Treatment effects in evaluable subgroups (e.g., mutation status, number of prior TKIs, prior HSCT status, and relapse without prior HSCT) were in general consistent with the results in the overall population. Patients with T315I mutation, other mutations, or additional cytogenetic abnormalities responded with a similar rate as compared to those that did not have these mutations or abnormalities.

MRD positive B-precursor ALL

In Study 5, the safety and efficacy of Blincyto were evaluated in an open-label, multicentre, single-arm study. Eligible patients were 18 years of age, had received at least 3 blocks of

standard ALL induction therapy, were in complete haematologic remission (defined as < 5% blasts in bone marrow, absolute neutrophil count 1,000/microlitres, platelets 9 g/dL) and had molecular failure or molecular 10^{-3}) (see Table 14).

Blincyto was administered as a continuous intravenous infusion. Patients received Blincyto at a constant dose of 15 microgram/m^2/day (equivalent to the recommended dosage of 28 microgram/day) for all treatment cycles. Patients received up to 4 cycles of treatment. Dose adjustment was possible in case of adverse events. The treated population included who received at least one infusion of Blincyto. Of the 116 patients, 113 patients (97.4%) were included in the primary endpoint full analysis set and 110 patients (94.8%) were included in the key secondary endpoint full analysis set. The median number of treatment cycles was 2 (range: 1 to 4). Please see Table 14 for the demographics and baseline characteristics from Study 5.

Table 14. Demographics and Baseline Characteristics in MRD Study

Characteristic	Blincyto (N = 116)
Age	
Median, years (min, max)	45 (18, 76)
Mean, years (SD)	44.6 (16.4)
65 years, n (%)	15 (12.9)
Males, n (%)	68 (58.6)
Race, n (%)	
Asian	1 (0.9)
Other (mixed)	1 (0.9)
White	102 (87.9)
Unknown	12 (10.3)
Philadelphia chromosome disease status	
Positive	5 (4.3)
Negative	111 (95.7)
Relapse history	
Patients in 1st CR	75 (64.7)
Patients in 2nd CR	39 (33.6)
Patients in 3rd CR	2 (1.7)
MRD level at baseline*	
$^{-1}$ and < 1	9 (7.8)
$^{-2}$ and < 10^{-1}	45 (38.8)
$^{-3}$ and < 10^{-2}	52 (44.8)
< 10^{-3}	3 (2.6)
Below Lower Limit of Quantification	5 (4.3)
Unknown	2 (1.7)

* Centrally assessed in an assay with minimum sensitivity of 10^{-4}

The primary endpoint was the proportion of patients who achieved a complete MRD response within one cycle of Blincyto treatment. Eighty-eight out of 113 (77.9%) patients achieved a complete MRD response after one cycle of treatment. MRD response rates by age and MRD level at baseline subgroups were consistent with the results in the overall population. See Table 15 and Figures 4 to 6 below for efficacy results from Study 5.

Table 15. Efficacy Results in Patients 18 Years of Age With MRD Positive B-Cell Precursor ALL

Complete MRD response[a], n/N (%), [95% CI]	88/113 (77.9) [69.1, 85.1]
65 years, n/N (%), [95% CI]	12/15 (80.0) [51.9, 95.7]
Patients in 1st CR, n/N (%), [95% CI]	60/73 (82.2) [71.5, 90.2]
Patients in 2nd CR, n/N (%), [95% CI]	27/38 (71.1) [54.1, 84.6]
Patients in 3rd CR, n/N (%), [95% CI]	1/2 (50.0) [1.3, 98.7]
Relapse[b]-free survival at 18 months (censored at HSCT or chemotherapy after treatment with Blincyto [95% CI]	54% [33%, 70%]
Median Relapse-free survival by MRD response at cycle 1[c]	
MRD complete responder (N = 85)	23.6 months [17.4, NE[d]]
MRD non-responder (N = 15)	5.7 months [1.6, 13.6]
Median Overall survival[c]	36.5 months [19.2, NE[d]]
MRD complete responder (N = 88)	38.9 months [33.7, NE[d]]
MRD non-responder (N = 24)	10.5 months [3.8, NE[d]]
Duration of complete MRD response	17.3 months [12.6 to 23.3]

a Complete MRD response was defined as the absence of detectable MRD confirmed in an assay with minimum sensitivity of 10^{-4}

b Relapse was defined as haematological relapse (blasts in bone marrow greater than 5% following CR) or an extramedullary relapse

c Landmark analysis from day 45, not censored at HSCT or chemotherapy after treatment with Blincyto

d NE = not estimable

Figure 4. Kaplan-Meier Curve of Haematological Relapse-free Survival

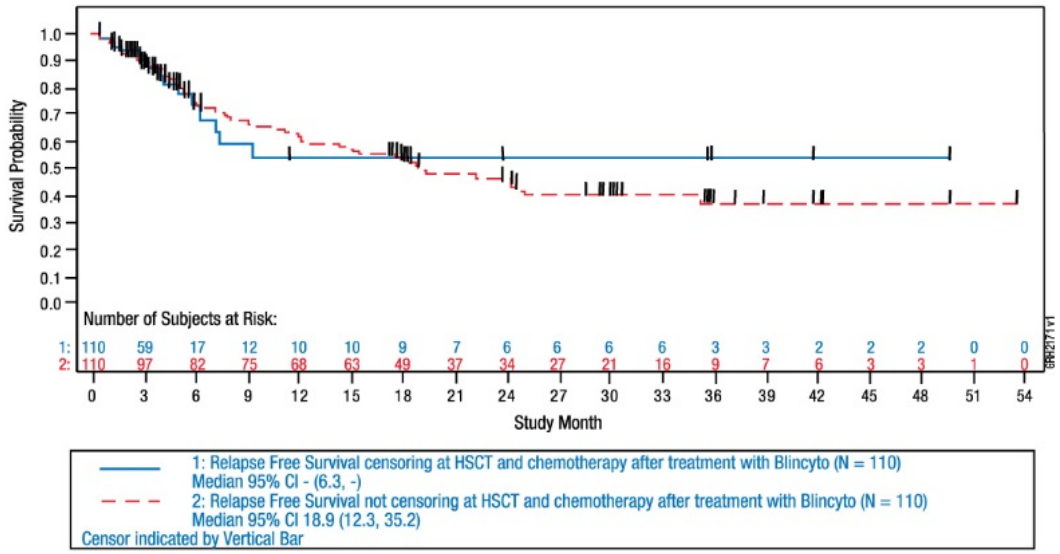


Figure 5. Kaplan Meier Curve of Relapse-free Survival From Day 45 (Landmark Analysis: Complete MRD Responder Versus MRD (Nonresponder)

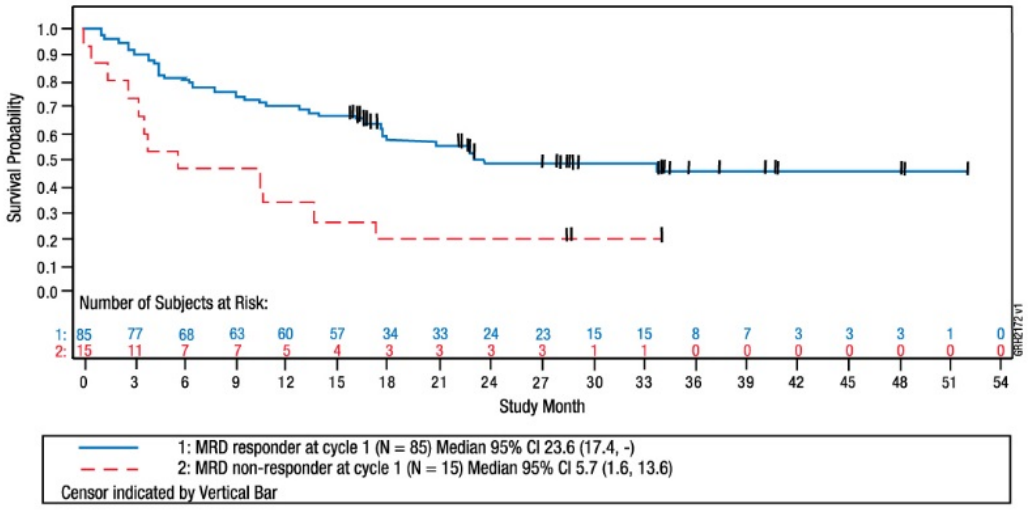
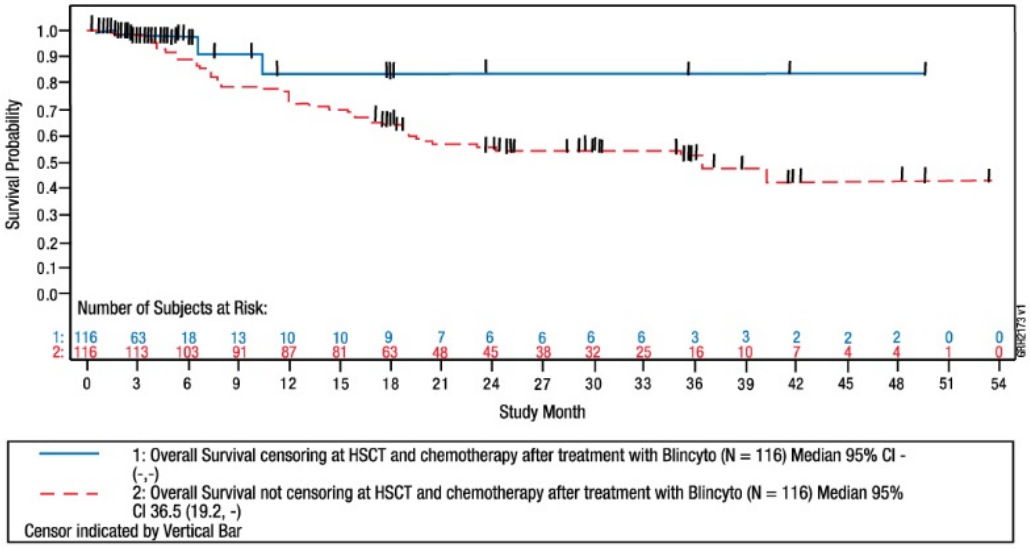


Figure 6. Kaplan-Meier Curve of Overall Survival



Acute Lymphoblastic Leukaemia in Paediatric Patients

The use of Blinyto in paediatric patients is approved on the basis of phase II, non-randomised evidence in patients with relapsed and/or refractory B cell precursor ALL. Patients should be advised that data is expected from an ongoing phase III study designed to provide further efficacy and safety data in first relapse.

In Study 6 the safety and efficacy of Blincyto were evaluated in an open-label, multicentre, single-arm study in 93 paediatric patients with relapsed or refractory B-cell precursor ALL (second or later bone marrow relapse, in any marrow relapse after allogeneic HSCT, or refractory to other treatments, and have > 25% blasts in bone marrow).

Blincyto was administered as a continuous intravenous infusion at doses of 5 to 30 micrograms/m^2/day. The recommended dose for this study was determined to be 5 micrograms/m^2/day on Days 1-7 and 15 micrograms/m^2/day on Days 8-28 for cycle 1, and 15 micrograms/m^2/day on Days 1-28 for subsequent cycles. Dose adjustment was possible in case of adverse events. Patients who responded to Blincyto but later relapsed had the option to be retreated with Blincyto.

The treated population included 70 patients who received at least one infusion of Blincyto at the recommended dose; the median number of treatment cycles was one (range: 1 to 5). Among treated patients, the median age was 8 years (range: 7 months to 17 years), 40 out of 70 (57.1%) had undergone allogeneic HSCT prior to receiving Blincyto, and 39 out of 70 (55.7%) had refractory disease. 50% leukaemic blasts in bone marrow) at baseline with a median of 75.5% bone marrow blasts.

Twenty-three out of 70 (32.9%) patients achieved CR/CRh* within the first two treatment cycles with 12 out of 23 patients achieving CR. Seventeen out of the 23 (73.9%) occurred within cycle 1 of treatment. In addition to the 12 patients who achieved CR within the first two treatment cycles, 3 patients achieved CR (with full recovery of peripheral blood counts) during subsequent cycles, resulting in a combined CR rate of 21.4% (15 out of 70; 95% CI: 12.5% - 32.9%). Eleven of the 23 patients (47.8%) who achieved CR/CRh* received an allogeneic HSCT. See Table 16 for the efficacy results from Study 6.

Table 16. Efficacy Results in Patients < 18 Years of Age With Relapsed or Refractory B-cell Precursor Acute Lymphoblastic Leukaemia (ALL)

	N = 70
CR[a]/CRh*[b], n (%) [95% CI]	23 (32.9%) [22.1% – 45.1%]
CR, n (%) [95% CI]	12 (17.1%) [9.2% – 28.0%]
CRh*, n (%) [95% CI]	11 (15.7%) [8.1% – 26.4%]
MRD Response for CR/CRh*[c]	12/23 (52.2%) [30.6 – 73.2]
CR, n1/n2[d] (%) [95% CI]	7/12 (58.3%) [27.7-84.8]
CRh*, n1/n2[d] (%) [95% CI]	5/11 (45.5%) [16.7-76.6]
Median Relapse[e]-free Survival (RFS)[d] for CR/CRh* [95% CI]	6.0 months [1.4 to 12.0 months]
Median Overall Survival [95% CI]	7.5 months [4.0 to 11.8 months]

a. CR was defined as M1 marrow (£ 5% of blasts in the bone marrow), no evidence of circulating blasts or extra-medullary disease, and full recovery of peripheral blood counts (platelets > 100,000/microliter and absolute neutrophil counts [ANC] > 1,000/microlitre).

b. CRh* was defined as M1 marrow (£ 5% of blasts in the bone marrow), no evidence of circulating blasts or extra-medullary disease, and partial recovery of peripheral blood counts (platelets > 50,000/microlitre and ANC > 500/microlitre).

c. MRD (minimal residual disease) response was defined as MRD by PCR or flow cytometry < 1 x 10-4

d. n1: number of patients who achieved MRD response and the respective remission status; n2: number of patients who achieved the respective remission status. One CR/CRh* responder with missing MRD data was considered as a MRD-nonresponder.

e. Relapse was defined as haematological relapse (blasts in bone marrow greater than 25% following CR) or an extramedullary relapse

5.2 Pharmacokinetic properties

Absorption

The pharmacokinetics of blinatumomab appear linear over a dose range from 5 to 90 micrograms/m^2/day (approximately equivalent to 9 to 162 micrograms/day) in adult patients. Following continuous intravenous infusion, the steady state serum concentration (C_{ss}) was achieved within a day and remained stable over time. The increase in mean C_{ss} values was approximately proportional to the dose in the range tested. At the clinical doses of 9 micrograms/day and 28 micrograms/day for the treatment of relapsed/refractory acute lymphoblastic leukaemia (ALL), the mean (SD) C_{ss} was 228 (356) pg/mL and 616 (537) pg/mL, respectively.

The exposure of blinatumomab in patients with MRD-positive B-cell precursor ALL was similar to patients with relapsed or refractory ALL.

Distribution

The estimated mean (SD) volume of distribution based on terminal phase (V_z) was 4.35 (2.45) L with continuous intravenous infusion of Blincyto.

Metabolism

The metabolic pathway of blinatumomab has not been characterised. Like other protein therapeutics, blinatumomab is expected to be degraded into small peptides and amino acids via catabolic pathways.

Excretion

The estimated mean (SD) systemic clearance with continuous intravenous infusion in patients receiving blinatumomab in clinical studies was 3.11 (2.98) L/hour. The mean (SD) half-life was2.10 (1.41) hours. Negligible amounts of blinatumomab were excreted in the urine at the tested clinical doses.

Body surface area, gender, and age

A population pharmacokinetic analysis was performed to evaluate the effects of demographic characteristics on blinatumomab pharmacokinetics. Results suggest that age (0.62 to 80 years of age) and gender do not influence the pharmacokinetics of blinatumomab.

Body surface area (0.37 to 2.70 m^2) influences the pharmacokinetics of blinatumomab, however the clinical relevance of this effect is unknown.

Special populations

Paediatric

The pharmacokinetics of blinatumomab appear linear over a dose range from 5 to 30 micrograms/m^2/day in paediatric patients. At the recommended doses, the mean (SD) steady state concentration (C_{ss}) values were 162 (179) and 533 (392) pg/mL at 5 and 15 micrograms/m^2/day doses, respectively. The estimated mean (SD) volume of distribution (V_z), clearance (CL) and terminal half-life ($t_{1/2,z}$) were 3.91 (3.36) L/m^2, 1.88 (1.90) L/hr/m^2 and 2.19 (1.53) hours, respectively.

Use in hepatic impairment

No formal pharmacokinetic studies using Blincyto have been conducted in patients with hepatic impairment. Baseline alanine aminotransferase (ALT) and aspartate

aminotransferase (AST) levels were used to assess the effect of hepatic impairment on the clearance of Blincyto. Population pharmacokinetic analysis suggested that there was no association between ALT or AST levels and the clearance of blinatumomab.

Use in renal impairment

No formal pharmacokinetic studies of blinatumomab have been conducted in patients with renal impairment. Pharmacokinetic analyses showed an approximately 2-fold difference in mean blinatumomab clearance values between patients with moderate renal dysfunction and normal renal function. Since high inter-subject variability was discerned (CV% up to 96.8%), and clearance values in renal impaired patients were essentially within the range observed in patients with normal renal function, no clinically meaningful impact of renal function on clinical outcomes is expected.

5.3 Preclinical safety data

Genotoxicity

No mutagenicity studies have been conducted with blinatumomab; however, blinatumomab is not expected to alter DNA or chromosomes.

Carcinogenicity

No carcinogenicity studies have been conducted with blinatumomab.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Each single-use vial of Blincyto contains:
Citric acid monohydrate
Trehalose dihydrate
Lysine hydrochloride
Polysorbate 80
Sodium hydroxide

Each single use vial of IV solution stabiliser contains:
Citric acid monohydrate
Lysine hydrochloride
Polysorbate 80
Sodium hydroxide (for pH-adjustment)
Water for Injections

6.2 Incompatibilities

Blincyto must not be mixed with other medicinal products except those mentioned in section 4.2 Dose and method of administration.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

It is recommended to store unopened Blincyto and IV solution stabiliser for Blincyto vials in a refrigerator at 2°C to 8°C in the original carton. Do not freeze. Protect from direct light.

Once removed from the refrigerator, unopened Blincyto and solution stabiliser for Blincyto vials may be stored at or below 25°C for up to 8 hours in the original container. Do not freeze.

After reconstitution and dilution

Storage Requirements for Reconstituted Blincyto and Prepared IV Bag or Cassettes

Maximum storage time of reconstituted Blincyto* solution		**Maximum combined storage and infusion time of diluted Blincyto solution in IV bag or cassette**	
Room Temperature (Below 25°C**)	**Refrigerated** (2°C to 8°C)	**Room Temperature** (Below 25°C**)	**Refrigerated** (2°C to 8°C)
4 hours	24 hours	96 hours***	10 days***

* While stored, protect reconstituted Blincyto from light.
** Do not freeze
*** If IV bag or cassette containing Blincyto solution for infusion is not administered within the timeframes and temperatures indicated, it must be discarded; it should not be refrigerated again.

The maximum storage time of the prepared IV bag at room temperature should not be longer than 6 hours prior to the start of infusion.

Store and transport the prepared IV bag or cassette containing Blincyto solution at 2°C to 8°C (Refrigerate. Do not freeze.)

6.5 Nature and contents of container

Blincyto is supplied in a single-use glass vial

IV solution stabiliser is supplied in a 10 mL single-use glass vial

Pack size: 1 vial Blincyto and 1 vial IV solution stabiliser for Blincyto supplied in a composite pack.

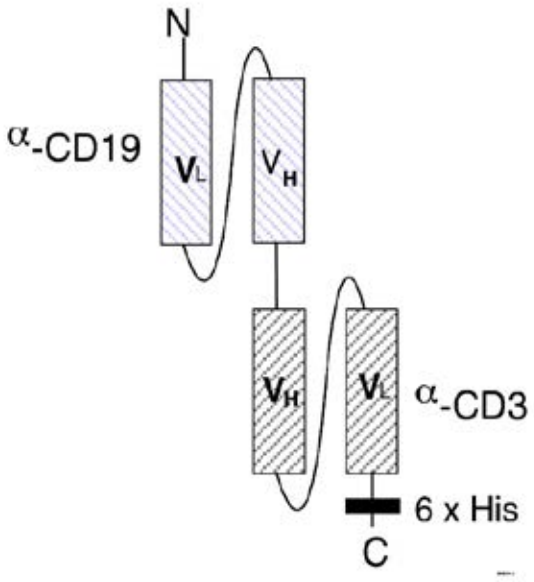
6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

At the end of the infusion, any unused Blincyto solution in the IV bag and IV lines should be disposed of in accordance with local requirements.

6.7 Physicochemical properties

Chemical structure



CAS number

CAS number: 853426-35-4

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 Prescription Medicine

8 SPONSOR

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9 DATE OF FIRST APPROVAL

9 November 2015

10 DATE OF REVISION

7 May 2018

Summary table of changes

Section changed	Summary of new information
4.1	Extension of indications to remove Philadelphia chromosome limitation and add MRD positive population
4.2	Amended to include dosing & administration for MRD positive population
4.4	Updated information on neurological events and immunogenicity
4.8	Inclusion of latest Adverse Reactions; update of selected ARs
5.1	Inclusion of phase III clinical data in Philadelphia chromosome negative population, phase II clinical data in Philadelphia chromosome positive population and phase II clinical data in Minimal Residual Disease positive population
5.2	Inclusion of pharmacokinetic data in Minimal Residual Disease positive population