BLINCYTO®
(blinatumomab)

RESOURCE GUIDE

BLINCYTO® is indicated for the treatment of relapsed or refractory B-cell precursor acute lymphoblastic leukaemia (ALL).[1]

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.[1]

Reference: 1. BLINCYTO® (blinatumomab) Product Information. www.amgen.com.au/Blincyto.PI

BLINCYTO® (blinatumomab)

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Ph–: Philadelphia chromosome negative; **Ph+:** Philadelphia chromosome positive.

ACCESSING BLINCYTO® ON THE PBS

FOR THE TREATMENT OF RELAPSED OR REFRACTORY B-CELL PRECURSOR ALL[1,2]

AUTHORITY REQUIRED[2]

A treatment course consists of up to 2 induction cycles of BLINCYTO® (initial treatment phase), followed by up to 3 consolidation cycles.[1]

INITIAL TREATMENT PHASE[2]

The authority application must be made in writing and must include:

1. A completed authority prescription form;
2. A completed ALL PBS Authority Application – Supporting Information Form;
3. Sufficient information to determine the patient's eligibility according to the PBS criteria as follows:

The patient has relapsed or refractory B-precursor cell ALL with an ECOG performance status ≤2

↓

AND the condition must not be present in the central nervous system or testis

↓

AND >5% blasts in bone marrow

(Note: provide a copy of the most recent bone marrow biopsy report of no more than one month old at the time of application)

↓

AND received a TKI if the condition is Philadelphia chromosome positive

↓

AND received intensive chemotherapy for initial treatment of ALL or for subsequent salvage therapy

(Note: provide date of most recent chemotherapy, and if this was the initial chemotherapy regimen or salvage therapy, including what line of salvage)

↓

AND has NOT received > 1 line of salvage therapy

↓

AND has not received BLINCYTO® previously for the treatment of MRD;
OR has had a relapse-free period of ≥6 months following completion of treatment with BLINCYTO® for MRD

(Note: provide date of completion of BLINCYTO® treatment for MRD and date of subsequent relapse)

- Applications for balance of supply may be made by contacting the Australian Government Department of Human Services on 1800 700 270 (extension 5).
- Patients must not receive more than 2 treatment cycles under the Induction (Initial and Balance of Supply) restrictions.

ECOG, Eastern Cooperative Oncology Group; TKI, tyrosine kinase inhibitor.

References: 1. BLINCYTO® (blinatumomab) Product Information. www.amgen.com.au/Blincyto.PI **2.** Pharmaceutical Benefits Scheme. Available at: www.pbs.gov.au (accesed January 2020).

ACCESSING BLINCYTO® ON THE PBS

FOR THE TREATMENT OF RELAPSED OR REFRACTORY B-CELL PRECURSOR ALL[1,2]

CONSOLIDATION TREATMENT PHASE[2]

After a written authority application for induction treatment has been approved, application for consolidation treatment can be made by calling 1800 700 270 (extension 5) Monday to Friday between 8.00 am and 5.00 pm, Australian Eastern Standard Time.

To be eligible for consolidation treatment, all applications must demonstrate:

Patient must have previously received PBS-subsidised induction treatment with this drug for this condition

The patient must have demonstrated a complete remission

OR

a complete remission with partial haematological recovery

AND not received PBS-subsidised treatment with this drug if progressive disease develops while on this drug

AND treatment must not exceed 3 treatment cycles under this restriction in a lifetime

Note: BLINCYTO® is not PBS subsidised if administered to an in-patient in a public hospital setting.

References: 1. BLINCYTO® (blinatumomab) Product Information. www.amgen.com.au/Blincyto.PI **2.** Pharmaceutical Benefits Scheme. Available at: www.pbs.gov.au (accesed January 2020).

ACCESSING BLINCYTO® ON THE PBS

FOR THE TREATMENT OF MRD POSITIVE B-CELL PRECURSOR ALL IN PATIENTS IN COMPLETE HAEMATOLOGICAL REMISSION[1,2]

AUTHORITY REQUIRED[2]

A treatment course consists of up to 2 induction cycles of BLINCYTO® (initial treatment phase), followed by up to 2 consolidation cycles.[1]

INITIAL TREATMENT PHASE[2]

The authority application must be made in writing and must include:

1. A completed authority prescription form;
2. A completed MRD+ ALL PBS Authority Application – Supporting Information Form;
3. Sufficient information to determine the patient's eligibility according to the PBS criteria as follows:

The patient has MRD* with an ECOG performance status 0 or 1

(Note: provide the percentage blasts in bone marrow count that is ≤4 weeks old at the time of application)

↓

AND achieved complete remission following intensive combination chemotherapy for initial treatment of ALL or for subsequent salvage therapy

(Note: provide the date of most recent chemotherapy, and if this was the initial chemotherapy regimen or salvage therapy)

↓

AND the condition must not be present in the central nervous system or testis

- Applications for balance of supply may be made by contacting the Australian Government Department of Human Services on 1800 700 270 (extension 5).
- Patients must not receive more than 2 treatment cycles under the Induction (Initial and Balance of Supply) restrictions.

*Defined as $\geq 10^{-4}$ (0.01%) blasts based on measurement in bone marrow, documented after an interval of ≥2 weeks from the last course of systemic chemotherapy given as intensive combination chemotherapy treatment of ALL or as subsequent salvage therapy, whichever was the later, and measured using polymerase chain reaction or flow cytometry.

References: 1. BLINCYTO® (blinatumomab) Product Information. www.amgen.com.au/Blincyto.PI **2.** Pharmaceutical Benefits Scheme. Available at: www.pbs.gov.au (accesed January 2020).

ACCESSING BLINCYTO® ON THE PBS

FOR THE TREATMENT OF MRD POSITIVE B-CELL PRECURSOR ALL IN PATIENTS IN COMPLETE HAEMATOLOGICAL REMISSION[1,2]

CONTINUING TREATMENT[2]

After a written authority application for induction treatment has been approved, application for continuing treatment can be made by calling 1800 700 270 (extension 5) Monday to Friday between 8.00 am and 5.00 pm, Australian Eastern Standard Time.

To be eligible for continuing treatment, all applications must demonstrate:

Patient must have previously received PBS-subsidised induction treatment with this drug for this condition

↓

AND have demonstrated a complete remission

↓

AND be MRD negative*

*Either undetectable using the same method used to determine original eligibility or $<10^{-4}$ (0.01%) blasts based on measurement in bone marrow.

↓

AND not developed disease progression while receiving PBS-subsidised treatment with this drug for this condition

↓

AND treatment must not exceed 2 treatment cycles under this restriction in a lifetime

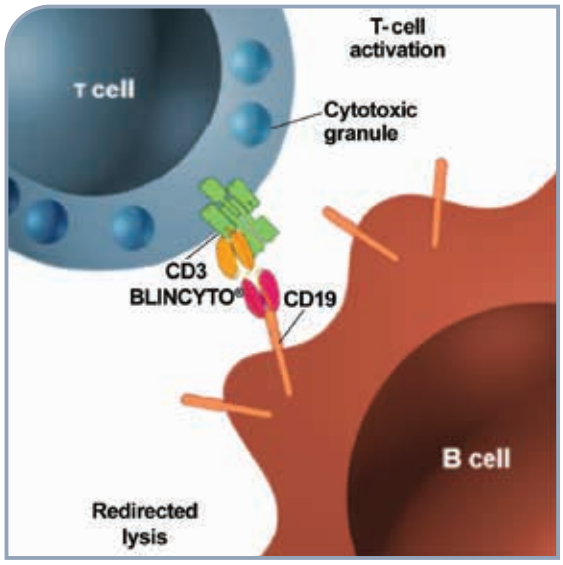
Note: BLINCYTO® is not PBS subsidised if administered to an in-patient in a public hospital setting.

BLINCYTO® (blinatumomab)

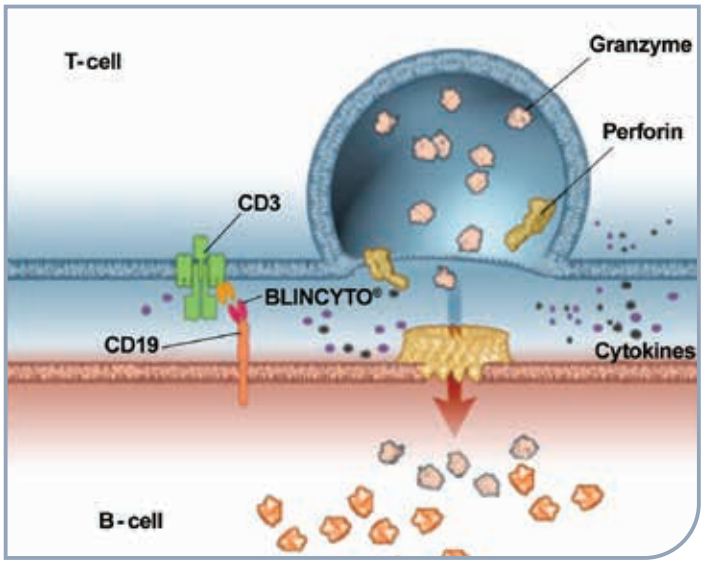
References: 1. BLINCYTO® (blinatumomab) Product Information. www.amgen.com.au/Blincyto.PI **2.** Pharmaceutical Benefits Scheme. Available at: www.pbs.gov.au (accesed January 2020).

BLINCYTO® MECHANISM OF ACTION

BLINCYTO® is an immunotherapy.[1-3] It is a bispecific T-cell engager (BiTE®) antibody construct that binds to CD19 on the surface of cells of B-lineage origin, and CD3 expressed on the surface of T-cells.[1-3] BLINCYTO® mediates the formation of a bridge in the form of an immune synapse between the T-cell and malignant B-cell.[1-3] Subsequent lytic proteins released by the T-cell induce target cell death.[1-3]



BLINCYTO® mediates the formation of a bridge in the form of an immune synapse between the T-cell and malignant B-cell.[1-3]



Subsequent lytic proteins released by the T-cell induce target cell death.[1-3]

Adapted from Baeuerle & Reinhardt, 2009.[4]

BiTE®: Amgen's proprietary technology that engages the body's own immune system to target malignant cells.[4]

CD: cluster of differentiation

References: 1. BLINCYTO® (blinatumomab) Product Information. www.amgen.com.au/Blincyto.PI **2.** Nagorsen D, Baeuerle PA. *Exp Cell Res* 2011;317:1255–60. **3.** Raponi S *et al. Leuk Lymphoma* 2011;52:1098–107. **4.** Baeuerle PA, Reinhardt C. *Cancer Res* 2009;69:4941–4.

EFFICACY SUMMARY

BLINCYTO® ACHIEVES DEEP AND DURABLE REMISSIONS IN THE MRD+ AND RELAPSED OR REFRACTORY SETTINGS[1-5]

BLINCYTO® was evaluated in five multicentre, open-label clinical trials in patients with B-ALL (one Phase III and four Phase II clinical trials).[1-5]

PHASE 3 TRIAL

THE TOWER STUDY: Ph- RELAPSED/REFRACTORY B-ALL[1]

A phase III trial comparing BLINCYTO® versus standard-of-care chemotherapy in 405 difficult-to-treat adult patients with Ph– relapsed or refractory B-ALL, including those with early first relapse, post-transplant relapse, second or greater relapse, and primary refractory disease

PHASE 2 TRIALS

Ph- RELAPSED OR REFRACTORY B-ALL[2]

A phase II trial in 189 adult Ph– relapsed or refractory B-ALL patients characterised by unfavourable prognostic factors

PAEDIATRIC RELAPSED OR REFRACTORY B-ALL[3]

A phase I/II trial in heavily pretreated paediatric relapsed or refractory B-ALL patients (n=70 received the recommended dose) including those with relapse after HSCT, with refractory disease, and in second or later relapse

THE BLAST STUDY: MRD+ B-ALL[4]

A phase II trial of 116 adult patients in haematologic CR (first or later) who remained MRD+ after intensive chemotherapy

Ph+ RELAPSED OR REFRACTORY B-ALL[5]

A phase II trial of 45 adult patients with Ph+ relapsed or refractory B-ALL who progressed after or were refractory or intolerant to second- or later-generation TKI therapy

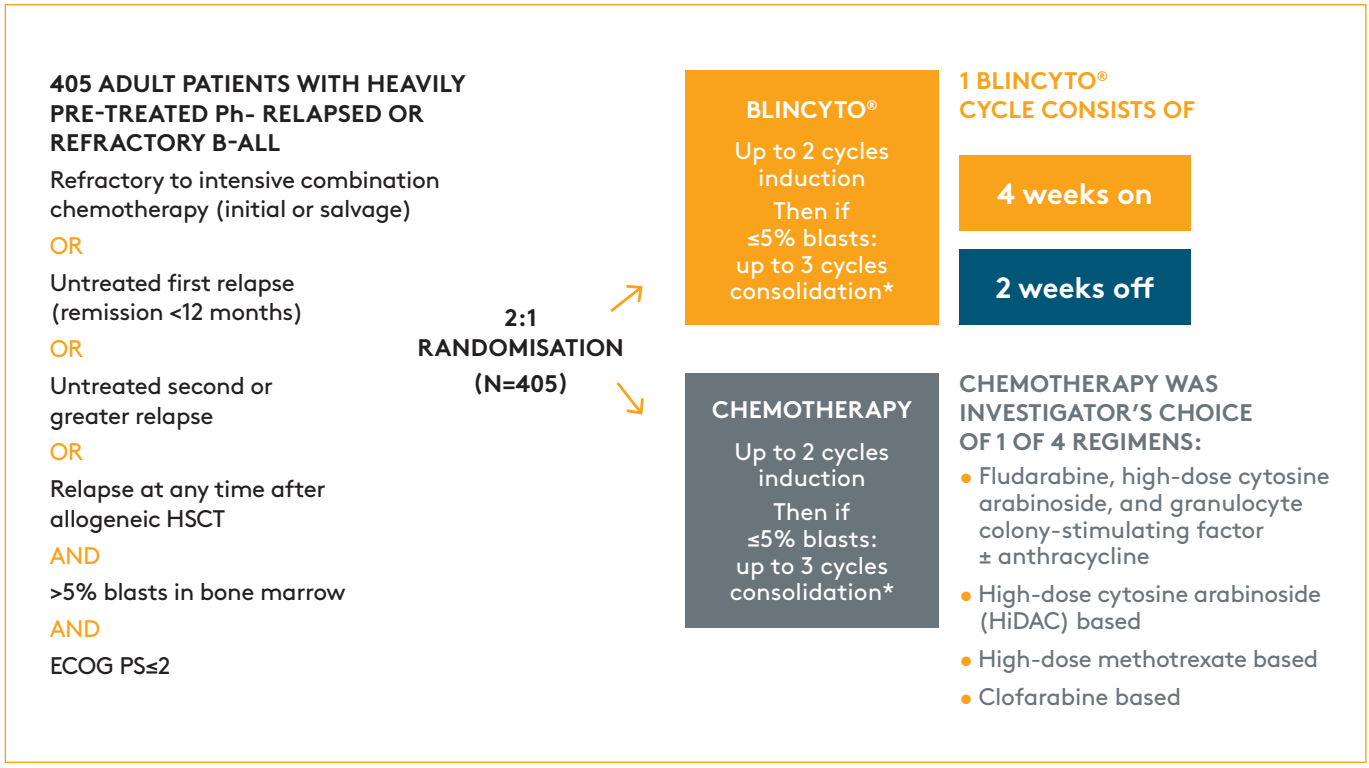
CR: complete remission; **HSCT:** haematopoietic stem cell transplantation; **TKI:** tyrosine kinase inhibitor.

References: 1. Kantarjian H *et al. N Eng J Med* 2017;369:836–47. **2.** Topp MS *et al. Lancet Oncol* 2015;16:57–66. **3.** von Stackelberg A *et al. J Clin Oncol* 2016;34:4381–9. **4.** Gökbuget N *et al. Blood* 2018;131:1522–31. **5.** Martinelli G *et al. J Clin Oncol* 2017;35:1795–802.

EFFICACY IN Ph- RELAPSED OR REFRACTORY B-ALL

BLINCYTO® WAS STUDIED IN THE INTERNATIONAL, RANDOMISED, OPEN-LABEL, PHASE 3 STUDY (TOWER)[1]

Kantarjian H *et al. N Engl J Med* 2017;376:836–47.



Both study arms were well matched at baseline, in terms of demographic and disease characteristics. BLINCYTO® was given via cIV infusion; dose 9 mcg/day during Week 1 of Cycle 1, and 28 mcg/day thereafter.
*If ≤ 5% blasts in bone marrow after consolidation therapy, patients could continue to receive maintenance therapy.

STUDY ENDPOINTS[1]

Primary	• Overall survival (OS)
Key secondary	• Complete remission (CR) with full haematological recovery within 12 weeks of treatment initiation • CR with full, partial or incomplete haematological recovery (CR/CRh/CRi) within 12 weeks of treatment initiation • Event-free survival (events included relapse after achieving CR/CRh/CRi or death; patients who did not achieve CR/CRh/CRi were assigned an event-free duration of 1 day)

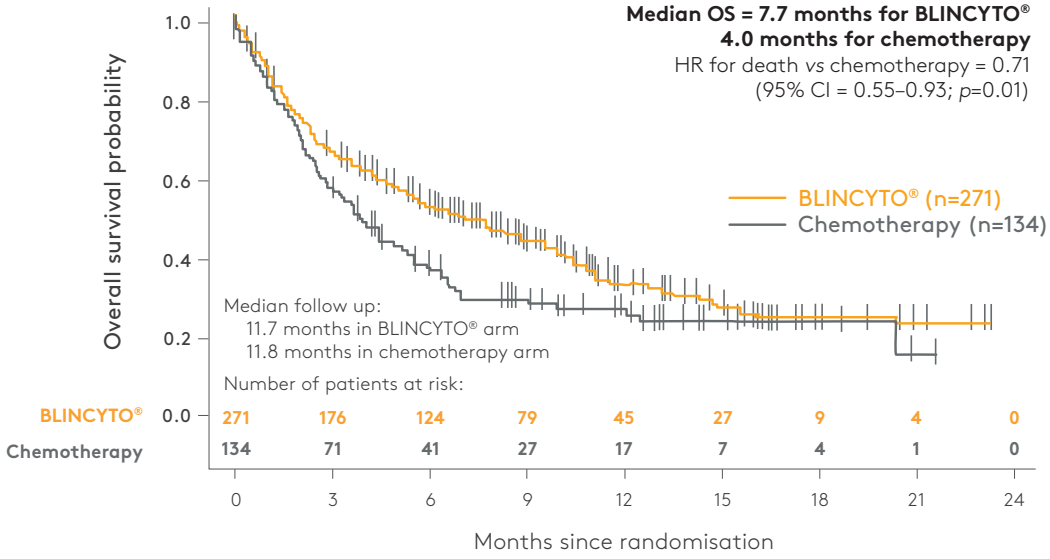
ECOG PS: Eastern Cooperative Oncology Group performance status; **cIV:** continuous intravenous.

Reference: 1. Kantarjian H *et al. N Engl J Med* 2017;376:836–47.

EFFICACY IN Ph- RELAPSED OR REFRACTORY B-ALL

BLINCYTO® ALMOST DOUBLED MEDIAN OVERALL SURVIVAL COMPARED WITH CHEMOTHERAPY (PRIMARY ENDPOINT; ITT)[1]

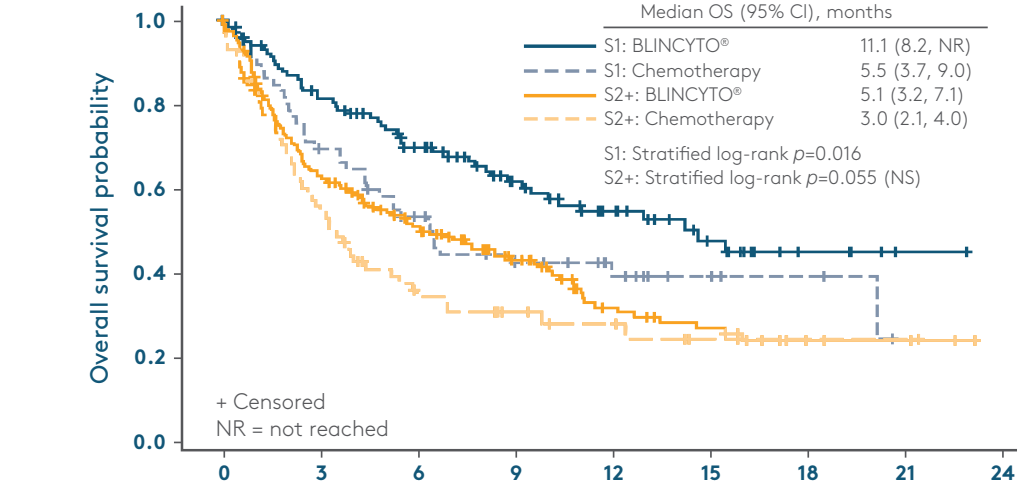
OVERALL SURVIVAL



Adapted from: Kantarjian *et al.* 2017.[1] Caution: Small patient numbers after 15 months.

EARLY USE OF BLINCYTO® (AS FIRST SALVAGE) MORE THAN DOUBLED OVERALL SURVIVAL COMPARED WITH CHEMOTHERAPY[1,2]

OVERALL SURVIVAL AMONG PATIENTS AS FIRST SALVAGE (S1) OR PRIOR (S2+) SALVAGE TREATMENT[2]



No of patients:									
S1: BLINCYTO®	104	80	59	39	26	14	5	1	0
S1: Chemotherapy	63	39	26	18	11	5	3	0	
S2+: BLINCYTO®	167	96	65	40	19	13	4	3	0
S2+: Chemotherapy	71	32	15	9	6	2	1	1	0

Adapted from: Dombret *et al.* 2019.[2] Analysis of salvage status adjudicated separately from prior randomisation status.

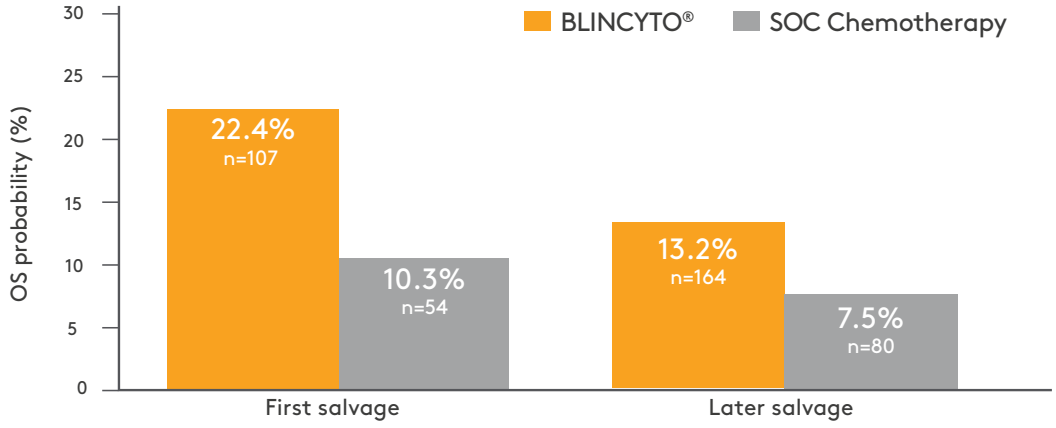
Improved median OS among patients who received BLINCYTO® vs SOC and who had no prior salvage treatment supports early use of BLINCYTO® in adults with Ph– relapsed or refractory B-ALL.[1,2]

ITT: Intent-to-treat; **SOC:** Standard of care; **NS:** not significant.

References: 1. Kantarjian H *et al. N Engl J Med* 2017;376:836–47. **2.** Dombret H *et al. Leuk Lymphoma* 2019;60:2214–22.

EFFICACY IN Ph- RELAPSED OR REFRACTORY B-ALL

PREDICTED 5-YEAR OS VERSUS SOC[1]

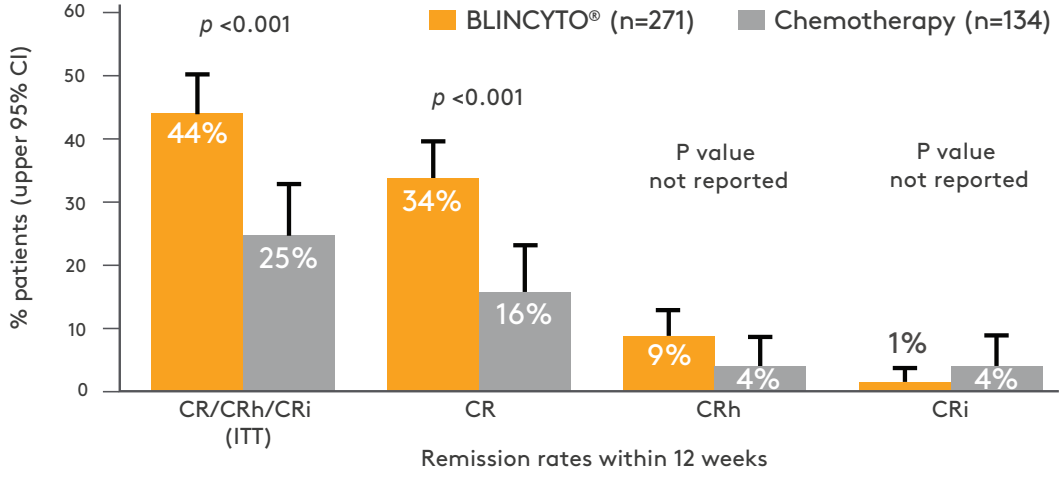


In an analysis† estimating long-term survival outcomes in the TOWER trial, patients treated with BLINCYTO® had a higher probability of 5-year OS versus SOC, regardless of use in first or later salvage (P values not reported).

†A partitioned survival model with a lifetime (50-year) time horizon was used to estimate expected life-years and quality-adjusted life-years gained for BLINCYTO® versus SOC in subgroups of patients who had not previously received salvage therapy versus those who had received at least one prior line of salvage therapy (i.e. early versus late treatment).

Adapted from Severin *et al.* 2018.[1]

REMISSION RATES WITHIN 12 WEEKS OF TREATMENT INITIATION (SECONDARY ENDPOINTS)[2]



Adapted from: Kantarjian *et al.* 2017.[2]

Among patients who achieved CR/CRh/CRi:[2]

- The median duration of remission in the BLINCYTO® arm was 7.3 months (95% CI, 5.8–9.9) versus 4.6 months (95% CI, 1.8–19.0) with chemotherapy
- 76% of patients in the BLINCYTO® group achieved MRD negativity versus 48% with chemotherapy (treatment difference: 28%; 95% CI, 9–47).

CR: Complete remission (≤ 5% bone marrow blasts and no evidence of disease), with full haematologic recovery (platelets >100,000/mcL and absolute neutrophil count [ANC] >1,000/mcL). **CRh:** CR, with partial haematologic recovery (platelets >50,000/mcL, ANC >500/mcL). **CRi:** CR, with incomplete haematologic recovery (platelets >100,000/mcL or ANC >1,000/mcL). **ITT:** Intention-to-treat population. **MRD:** Minimal residual disease ($<10^{-4}$ bone marrow blasts).

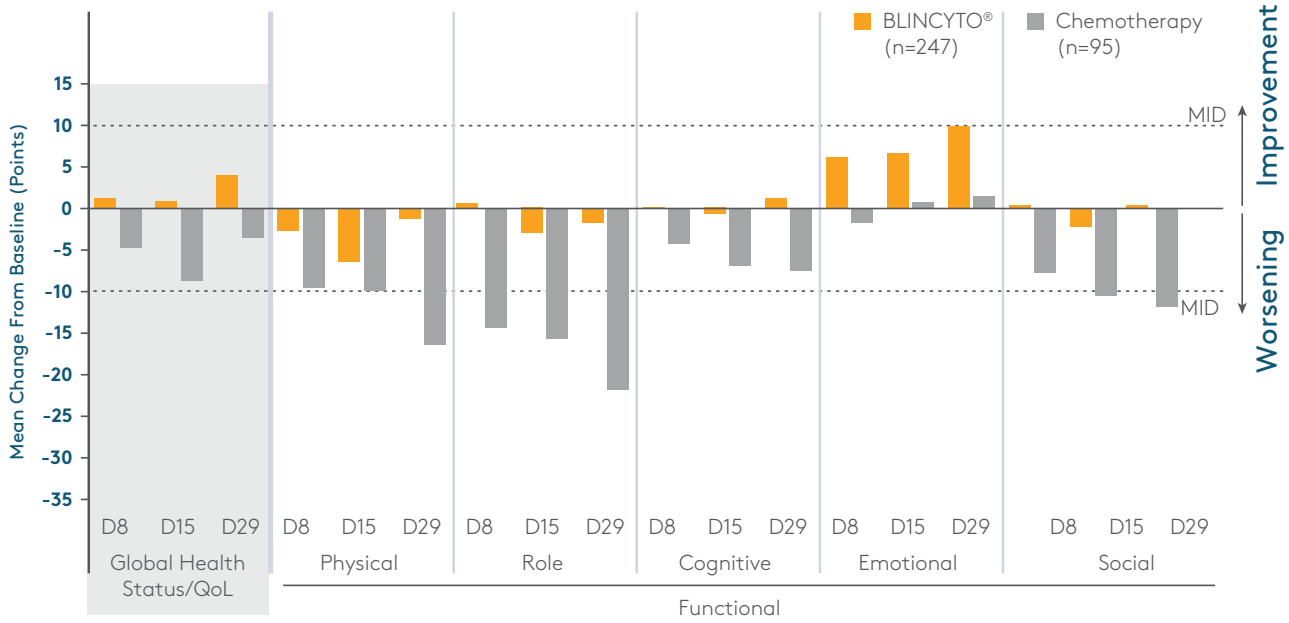
References: 1. Severin F, *et al.* Poster presented at: 23rd Annual Meeting of the European Hematology Association; June 14-17, 2018; Stockholm, Sweden. Abstract #PS1427. **2.** Kantarjian H *et al. N Engl J Med* 2017;376:836–47.

EFFICACY IN Ph- RELAPSED OR REFRACTORY B-ALL

PATIENTS RECEIVING BLINCYTO® REPORTED BETTER POST-TREATMENT HRQoL THAN THOSE RECEIVING CHEMOTHERAPY ACROSS ALL QLQ-C30 SUBSCALES*[1]

*Based on descriptive mean change from baseline.

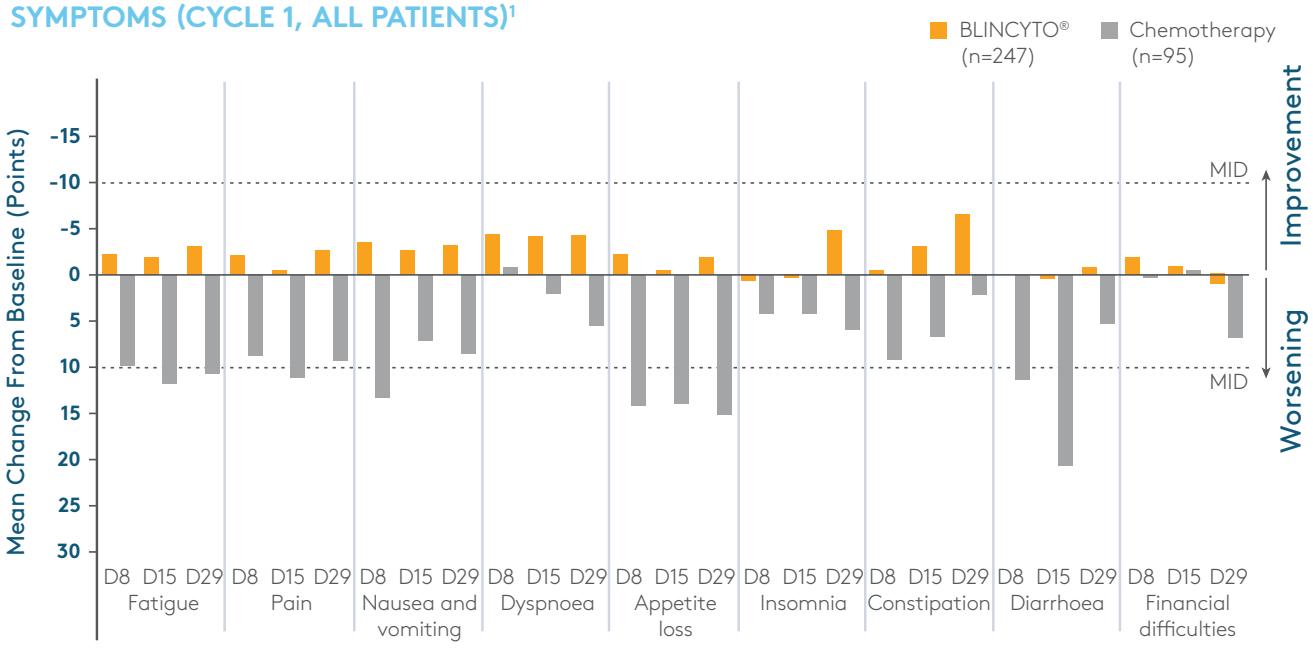
GLOBAL HEALTH STATUS AND FUNCTIONAL SCALE (CYCLE 1, ALL PATIENTS)[1]



Adapted from: Topp *et al.* 2018.
EORTC QLQ-C30 Analysis Set.

P values not provided.

SYMPTOMS (CYCLE 1, ALL PATIENTS)[1]



Adapted from: Topp *et al.* 2018.
EORTC QLQ-C30 Analysis Set

P values not provided.

"Differences in HRQL favoring blinatumomab vs chemotherapy were observable as early as 8 days after treatment initiation."[1]

HRQL: health-related quality of life; **HRQoL:** health-related quality of life; **D:** day; **EORTC QLQ-C30:** European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; **GHS:** global health status; **MID:** minimally important difference.

Reference: 1. Topp MS *et al. Blood* 2018;131:2906–14.

SAFETY IN Ph– RELAPSED OR REFRACTORY B-ALL

BLINCYTO®: CHEMOTHERAPY-FREE IMMUNOTHERAPY WITH A MANAGEABLE TOLERABILITY PROFILE[1]

Event, no. (%)	BLINCYTO® (n = 267)	Chemotherapy (n = 109)
Any adverse event	263 (99)	108 (99)
Event leading to premature discontinuation of trial treatment	33 (12)	9 (8)
Serious adverse event	165 (62)	49 (45)
Fatal serious adverse event	51 (19)	19 (17)
Any adverse event grade ≥3	231 (87)	100 (92)
Grade ≥3 adverse events of interest reported in ≥3% of patients in either group		
Neutropenia	101 (38)	63 (58)
Infection	91 (34)	57 (52)
Elevated liver enzyme	34 (13)	16 (15)
Neurological event	25 (9)	9 (8)
Cytokine release syndrome	13 (5)	0 (0)
Infusion reaction	9 (3)	1 (1)
Lymphopenia	4 (1)	4 (4)
Any decrease in platelet count	17 (6)	13 (12)
Any decrease in white cell count	14 (5)	6 (6)

Data are summarised for all patients who received at least one dose of trial treatment.
Adpated from Kantarjian *et al.* 2017.

After adjusting for treatment exposure, the rate of serious adverse events in the BLINCYTO® arm was 349.4 per 100 patient-years, compared with 641.9 per 100 patient-years in the chemotherapy arm (p-value not reported).[1]

Reference: 1. Kantarjian H *et al. N Engl J Med* 2017;376:836–47.

EFFICACY IN Ph- RELAPSED OR REFRACTORY B-ALL

BLINCYTO® WAS STUDIED IN AN INTERNATIONAL, OPEN-LABEL, MULTICENTRE, SINGLE-ARM PIVOTAL PHASE II TRIAL[1]

Topp MS *et al. Lancet Oncol* 2015;16:57–66.

STUDY DESIGN[1]

189 adult Ph- RELAPSED OR REFRACTORY B-ALL patients characterised by unfavourable prognostic factors

Primary refractory after induction

OR

Relapsed within 12 months of first remission

OR

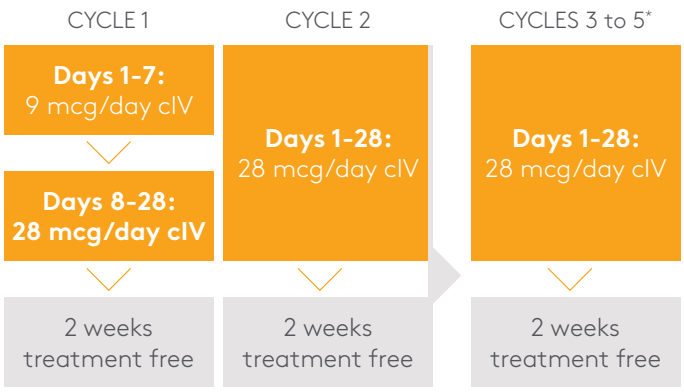
Relapsed within 12 months of allogeneic HSCT

OR

Not responded to or relapsed after first salvage or beyond

AND

≥10% blasts in bone marrow



Eligible patients achieving CR or CRh were offered allogeneic HSCT

Adapted from Topp *et al.* 2015.[1]

* Patients who achieved CR or CRh within the first two cycles could receive up to three additional cycles.

STUDY ENDPOINTS[1]

Primary	• CR or CRh within the first two cycles
Secondary	• CR • CRh • OS • RFS • HSCT realisation • Incidence of adverse events
Exploratory	• MRD response (defined as MRD $<10^{-4}$ by PCR)

PCR: polymerase chain reaction.

Reference: 1. Topp MS *et al. Lancet Oncol* 2015;16:57–66.

EFFICACY IN Ph- RELAPSED OR REFRACTORY B-ALL

PATIENT POPULATION[1]

Patients were selected for negative prognostic factors putting them at high risk of unfavourable outcome.[1]

- All patients had relapsed or refractory B-ALL, including 80% who had already received one or more lines of salvage therapy
- Overall, 69% of patients had ≥50% bone marrow blast count at baseline and 34% had relapsed after previous HSCT

BASELINE CHARACTERISTICS[1]	
Total no. patients	189
Sex, n (%)	
Male	119 (63)
Female	70 (37)
Age, n (%)	
Median years (range)	39 (18-79)
18 to <35	90 (48)
35 to <55	46 (24)
55 to <65	28 (15)
≥65	25 (13)
Previous Lines Of Salvage, n (%)	
0	38 (20)
≥1	151 (80)
1 2 >2	77 (41) 42 (22) 32 (17)
Disease State, n (%)	
Previous Allogeneic HSCT	64 (34)
No Previous Allogeneic HSCT	125 (66)
No Previous Salvage 1 Previous Salvage ≥2 Previous Salvage	29 (15) 55 (29) 41 (22)
Bone Marrow Blast Count*, n (%)	
<50%	59 (31)
≥50%	130 (69)

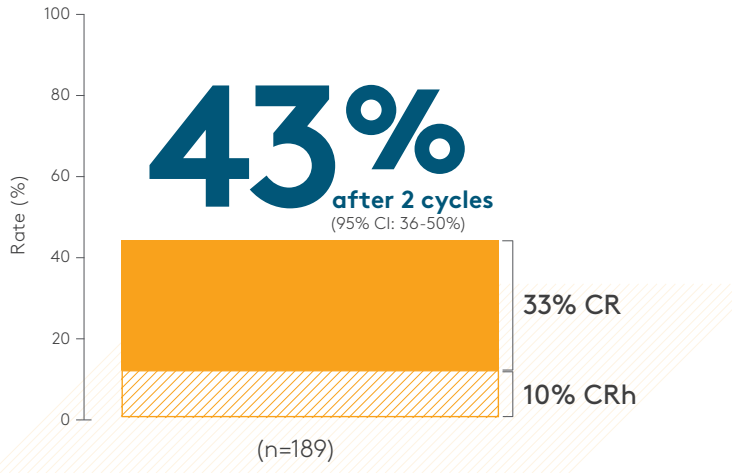
*Per central laboratory assessment for all 189 samples. In 154 patients, the assessment of bone-marrow blast count was done after or without the dexamethasone prephase treatment; in 35 patients, it was done before the dexamethasone prephase treatment.

Reference: 1. Topp MS *et al. Lancet Oncol* 2015;16:57–66.

EFFICACY IN Ph- RELAPSED OR REFRACTORY B-ALL

BLINCYTO®: REMISSION RATES (CR/CRh)[1]

PRIMARY ENDPOINT: CR/CRh RATE WITHIN THE FIRST TWO CYCLES[1]

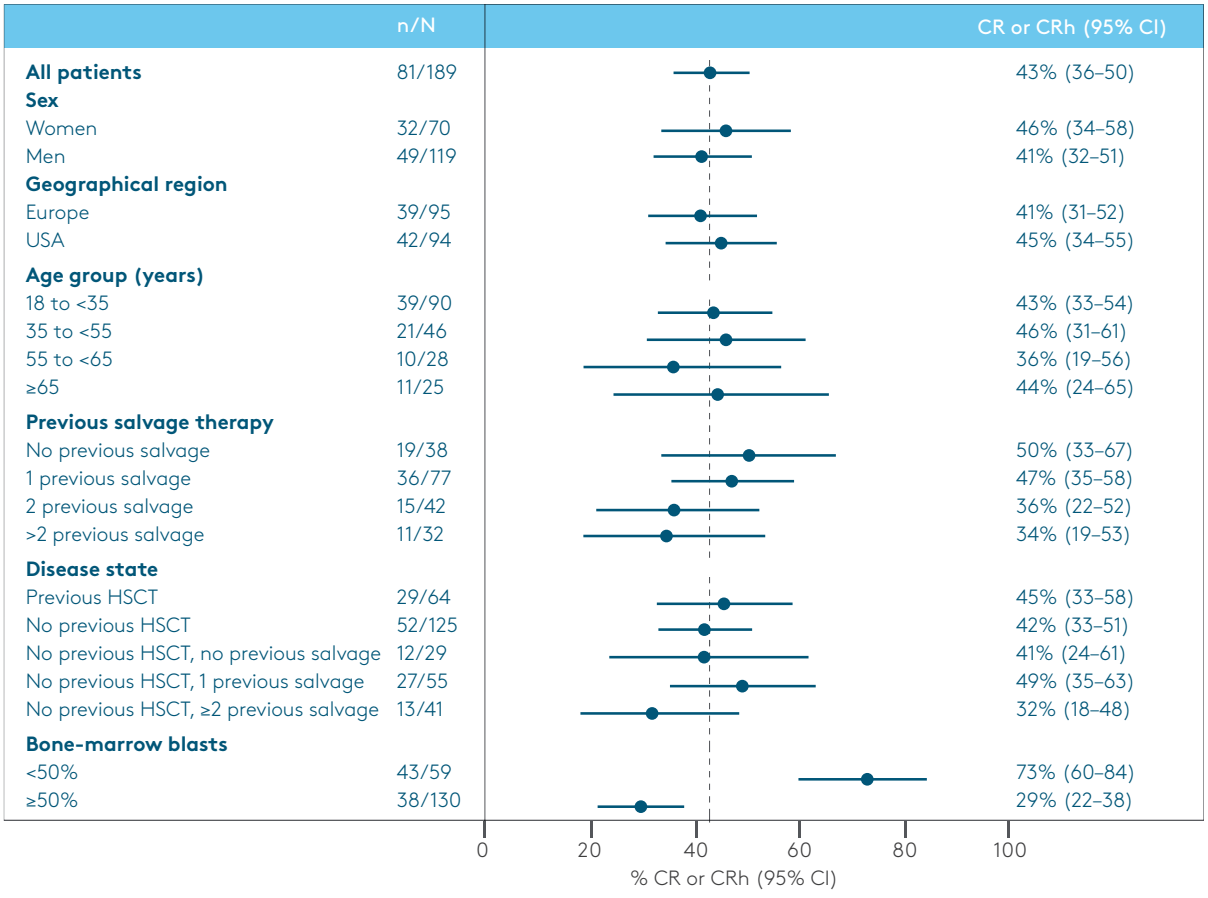


- **43%** of patients achieved CR/CRh within 2 cycles[1]
- Responses were demonstrated regardless of age and treatment history, including patients aged ≥65 years and those who received previous allogeneic HSCT[1]

Adapted from Topp *et al.* 2015.[1]

- **82%** of patients who achieved CR/CRh in 2 cycles were **MRD negative** (95% CI: 72-90%)[1]
- **40%** of patients who achieved CR/CRh in 2 cycles proceeded to **allogeneic HSCT** [1]

CR/CRh RATES AFTER 2 TREATMENT CYCLES WERE CONSISTENT ACROSS PRESPECIFIED AGE AND TREATMENT HISTORY SUBGROUPS[1]



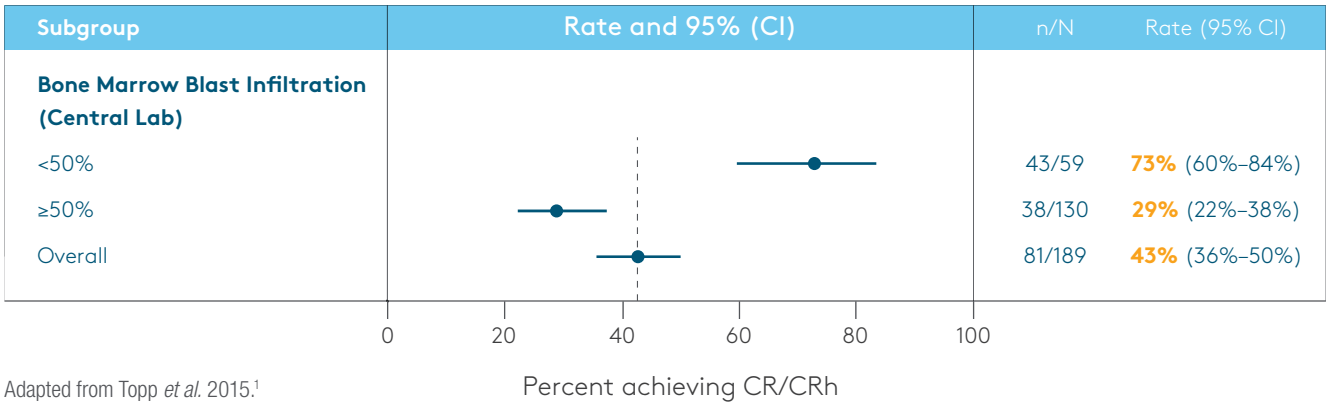
The dashed line represents the point estimate for CR or CRh for the entire patient population.
Adapted from Topp *et al.* 2015.[1]

Reference: 1. Topp MS *et al. Lancet Oncol* 2015;16:57–66.

EFFICACY IN Ph- RELAPSED OR REFRACTORY B-ALL

- Patients with the highest tumour burden as measured by the percentage of bone marrow blast cells at baseline (≥50%) reported CR/CRh rate of 29%[1]
- Patients with low tumour burden (<50% blasts) responded best to treatment, with CR/CRh rate of 73%[1]

CR/CRh DURING FIRST 2 CYCLES BY TUMOUR BURDEN AT BASELINE[1]



Adapted from Topp *et al.* 2015.[1]

SECONDARY ENDPOINTS AND MRD RESPONSE[1]

Secondary endpoints

40%
proceeded to TRANSPLANT

Of those with CR/CRh (n=32/81)

5.9 months
median RELAPSE-FREE SURVIVAL

Of those with CR/CRh (n=82)

6.1 months
median OVERALL SURVIVAL

All patients (n=189)

MRD response

82%
MRD negative

Of those with CR/CRh and MRD evaluable (n=73)

6.9 months
median RELAPSE-FREE SURVIVAL in MRD responders

Patients with MRD response (n=60)

11.5 months
median OVERALL SURVIVAL in MRD responders

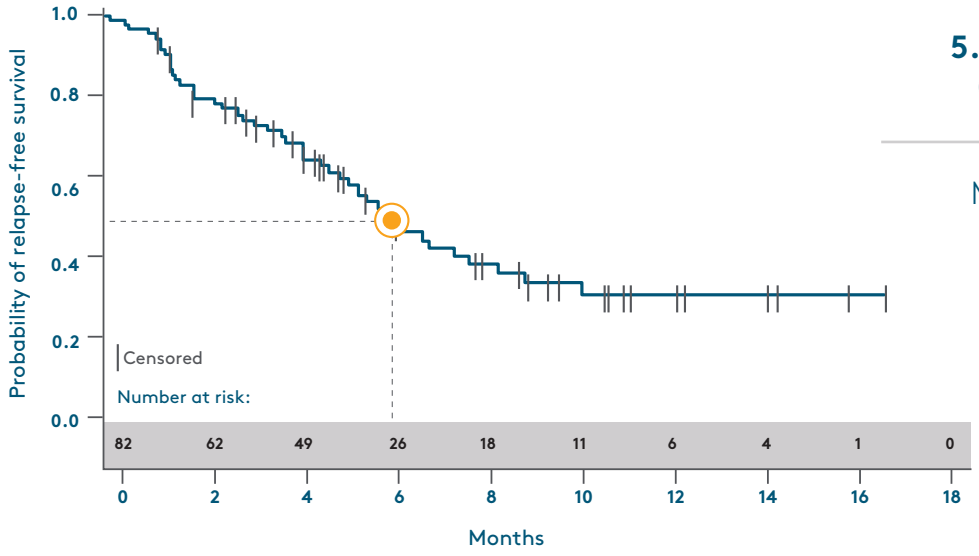
Patients with MRD response (n=60)

Reference: 1. Topp MS *et al. Lancet Oncol* 2015;16:57–66.

EFFICACY IN Ph- RELAPSED OR REFRACTORY B-ALL

BLINCYTO®: DURABLE RESPONSES FOR PATIENTS ACHIEVING CR/CRh[1]

SECONDARY ENDPOINT: RELAPSE-FREE SURVIVAL AMONG PATIENTS IN CR/CRh[1]

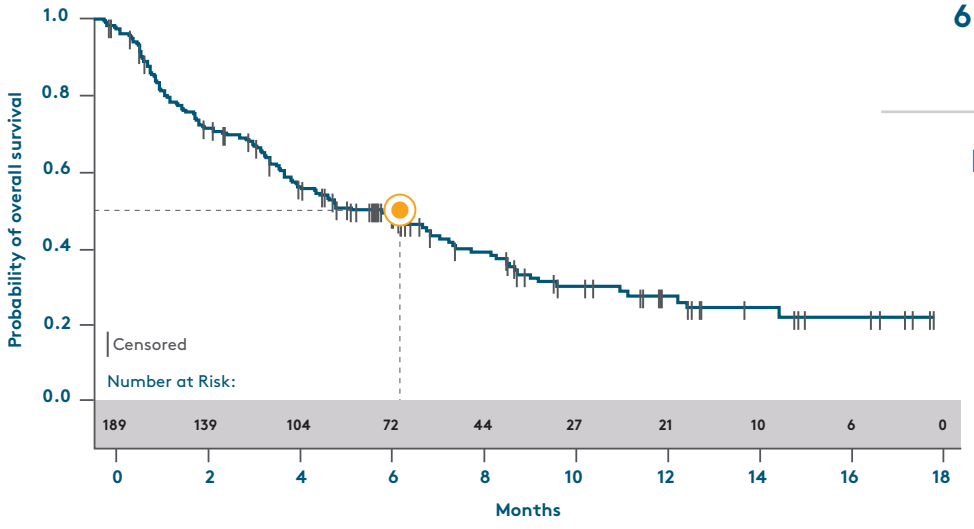


5.9 months median
(95% CI: 4.8–8.3)

Median follow-up:
8.9 months

Adapted from Topp *et al.* 2015.[1]

SECONDARY ENDPOINT: OVERALL SURVIVAL (ALL PATIENTS)[1]



6.1 months median
(95% CI: 4.2-7.5)

Median follow-up:
9.8 months

Adapted from Topp *et al.* 2015.[1]

- **6.9 months** median RFS for MRD responders (95% CI 5.5–10.1) vs 2.3 months for MRD non-responders (95% CI 1.2–not estimable)[1]
- Median overall survival for MRD responders versus MRD non-responders was **11.5 months** (95% CI 8.5–not estimable) versus 6.7 months (95% CI 2.0–not estimable)[1]

Reference: 1. Topp MS *et al. Lancet Oncol* 2015;16:57–66.

SAFETY IN Ph- RELAPSED OR REFRACTORY B-ALL

BLINCYTO®: CHEMOTHERAPY-FREE IMMUNOTHERAPY WITH A MANAGEABLE TOLERABILITY PROFILE[1]

ADVERSE EVENTS IRRESPECTIVE OF CAUSALITY[1]

n (%)	Any grade	Worst grade 3	Worst grade 4	Worst grade 5
Patients with adverse events	188 (99)	71 (38)	56 (30)	28 (15)
Patients with neurologic events	98 (52)	20 (11)	4 (2)	0 (0)
Adverse event of worst grade ≥3 occurring in ≥5% of patients				
Febrile neutropenia	53 (28)	46 (24)	2 (1)	0 (0)
Neutropenia	33 (17)	9 (5)	21 (11)	0 (0)
Anaemia	38 (20)	25 (13)	2 (1)	0 (0)
Pneumonia	18 (10)	13 (7)	2 (1)	2 (1)
Thrombocytopenia	21 (11)	2 (1)	14 (7)	0 (0)
Hyperglycaemia	24 (13)	15 (8)	0 (0)	0 (0)
Leucopenia	19 (10)	7 (4)	8 (4)	0 (0)
ALT increased	24 (13)	12 (6)	1 (<1)	0 (0)
Hypokalaemia	45 (24)	10 (5)	3 (2)	0 (0)
Pyrexia	113 (60)	13 (7)	0 (0)	0 (0)
Sepsis	13 (7)	3 (2)	4 (2)	4 (2)
Hypophosphataemia	13 (7)	8 (4)	2 (1)	0 (0)

Events for all patients (n=189) during the treatment period and until the end-of-core-study visit (30 days after last treatment or before allogeneic HSCT). Individual neurological events are not shown.

Adapted from Topp *et al.* 2015.

Please see Adverse Event Management section for further details.

ALT: alanine aminotransferase.

Reference: 1. Topp MS *et al. Lancet Oncol* 2015;16:57–66.

EFFICACY IN Ph+ RELAPSED OR REFRACTORY B-ALL

BLINCYTO® WAS STUDIED IN AN OPEN-LABEL, MULTICENTRE, SINGLE-ARM PHASE II STUDY IN PATIENTS WITH Ph+ RELAPSED OR REFRACTORY B-ALL (ALCANTARA)[1]

Martinelli G *et al. J Clin Oncol* 2017; 35:1795–802.

ALCANTARA STUDY DESIGN[1]

Adults ≥18 years of age with relapsed or refractory Ph+ B-ALL:

- Relapsed after or refractory to at least 1 second- or later-generation TKI **OR**
- Intolerant to second- or later-generation TKI and intolerant or refractory to imatinib

WITH

- >5% bone marrow blasts
- ECOG performance status ≤2

AND WITHOUT

- History or presence of clinically relevant CNS pathology (eg, epilepsy, stroke, dementia)
- Active acute or chronic GVHD or systemic treatment for GVHD within 2 weeks before treatment start
- Allogeneic HSCT within 12 weeks of starting treatment in this trial

BLINCYTO® single-agent immunotherapy

- cIV infusion for 2 induction cycles followed by up to 3 consolidation cycles
- **Treatment cycle:** 4 weeks on drug, 2 weeks off
- **Dosing:** 9 mcg/day on Days 1-7 of Cycle 1 and 28 mcg/day on subsequent days

Adapted from Martinelli *et al.* 2017.[1]
‡Patients who achieved CR or CRh within the first two cycles could receive up to three additional cycles.

STUDY ENDPOINTS[1]

Primary endpoint	• CR or CRh during the first two cycles
Major secondary endpoints	• MRD response rate (MRD negativity) • Rate of allogeneic HSCT • RFS • OS

CR was defined as ≤5% blasts in the bone marrow, no evidence of disease, and full recovery of peripheral blood counts (platelets >100,000/mcL and ANC >1,000/mcL).

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

A stringent definition of complete MRD response (no amplification of BCR-ABL by PCR with 10^{-5} sensitivity) was used.[1]

Reference: 1. Martinelli G *et al. J Clin Oncol* 2017; 35:1795–802.

EFFICACY IN Ph+ RELAPSED OR REFRACTORY B-ALL

PATIENT POPULATION[1]

BLINCYTO® WAS STUDIED IN A POOR PROGNOSIS Ph+ RELAPSED OR REFRACTORY B-ALL POPULATION[1]

BASELINE DEMOGRAPHIC AND DISEASE CHARACTERISTICS	
Sex, n (%)	
Male	24 (53)
Median age (range), years	55 (23-78)
Age, n (%)	
18 to <55 years	22 (49)
≥55 years	23 (51)
Prior TKI exposure, n (%)	45 (100)
Dasatinib	39 (87)
Imatinib*	25 (56)
Ponatinib	23 (51)
Nilotinib	16 (36)
T315I mutation, n (%)	10 (27)†
Prior allogeneic HSCT, n (%)	20 (44)
Median baseline bone marrow blast, % (range)	80 (6-98)

84% of patients had received ≥2 prior TKI treatments.

51% of patients were resistant or intolerant to ponatinib.

27% of patients had the T315I mutation.

*One patient was resistant to imatinib and never exposed to another TKI (protocol deviation).
†37 patients had evaluable mutational analysis data.

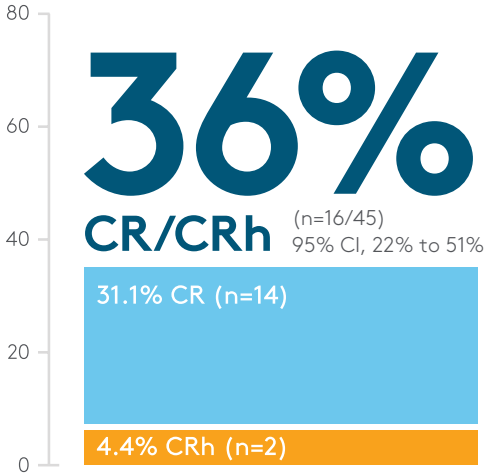
Reference: 1. Martinelli G *et al. J Clin Oncol* 2017; 35:1795–802.

EFFICACY IN Ph+ RELAPSED OR REFRACTORY B-ALL

BLINCYTO® INDUCED CR/CRh IN MORE THAN ONE THIRD OF PATIENTS[1]

PRIMARY ENDPOINT: CR/CRh RATE WITHIN THE FIRST 2 BLINCYTO® TREATMENT CYCLES[1]

Primary Endpoint: CR/CRh Rate Within 2 Treatment Cycles



2 additional patients achieved CR with an incomplete haematologic recovery.

Consistent Response Across Subgroups[1]

40% (n=4/10) CR/CRh among patients with **T315I mutation**

47% (n=8/17) CR/CRh among patients treated with **≥3 prior second- or later-generation TKIs**

35% (n=8/23) CR/CRh among patients with **ponatinib resistance/intolerance**

44% of responders (n=7/16) proceeded to transplant.[1]

Adapted from Martinelli *et al.* 2017.[1]

Reference: 1. Martinelli G *et al. J Clin Oncol* 2017; 35:1795–802.

EFFICACY IN Ph+ RELAPSED OR REFRACTORY B-ALL

THE MAJORITY OF PATIENTS WHO ACHIEVED CR/CRh WITH BLINCYTO® HAD A COMPLETE MRD RESPONSE[1]

88%
(n=14/16)

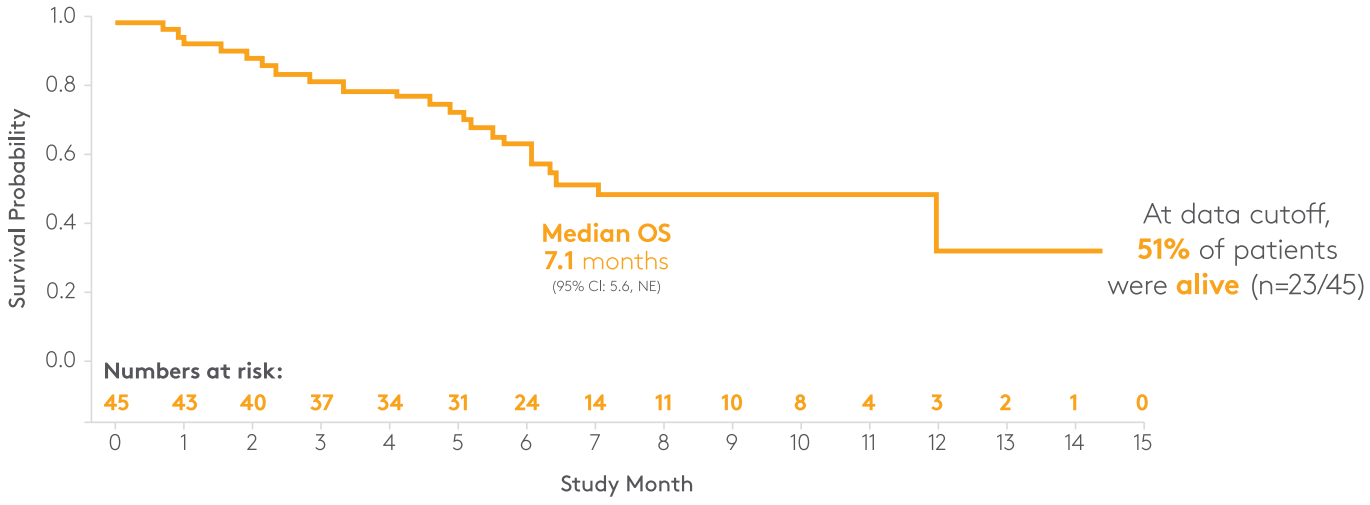
of patients with CR/CRh were
MRD negative within 2 treatment cycles.[1]

- Complete MRD response (MRD negativity) was defined as no RT-PCR amplification of BCR-ABL at a sensitivity of 10^{-5}.[1]

Haematologic and molecular responses were independent of mutational status, including presence of the T315I mutation.[1]

MEDIAN OS FOR ALL PATIENTS WAS 7.1 MONTHS[1]

OS among patients treated with BLINCYTO®[1]



Adapted from Martinelli *et al.* 2017.[1]

Median RFS among patients who achieved CR/CRh was 6.7 months (95% CI, 4.4 to NE).[1]

NE: not evaluable.

Reference: 1. Martinelli G *et al. J Clin Oncol* 2017; 35:1795–802.

SAFETY IN Ph+ RELAPSED OR REFRACTORY B-ALL

BLINCYTO®: CHEMOTHERAPY-FREE IMMUNOTHERAPY WITH A MANAGEABLE TOLERABILITY PROFILE[1]

ADVERSE EVENTS AND NEUROLOGIC EVENTS (REGARDLESS OF CAUSALITY)[1]

	GRADE					
	Any		3		4	
Event	**No.**	**%**	**No.**	**%**	**No.**	**%**
Patients with adverse events	**45**	**100**	**33**	**73**	**16**	**36**
Adverse events of grade ≥3 occurring in ≥5% of patients*						
Pyrexia	26	58	5	11	0	0
Febrile neutropenia	18	40	12	27	0	0
Headache	14	31	3	7	0	0
Anaemia	13	29	7	16	1	2
Thrombocytopenia	10	22	5	11	7	16
Pain	7	16	4	9	0	0
Increased AST	6	13	3	7	2	4
Increased ALT	5	11	5	11	0	0
Device-related infection	5	11	3	7	0	0
Neutropenia	3	7	0	0	3	7
Patients with neurologic events	**21**	**47**	**3**	**7**	**0**	**0**
Neurologic events occurring in two or more patients						
Paresthesia	6	13	0	0	0	0
Confused state	5	11	0	0	0	0
Dizziness	4	9	0	0	0	0
Tremor	4	9	0	0	0	0
Aphasia	2	4	1	2	0	0
Cerebellar syndrome	2	4	0	0	0	0
Memory impairment	2	4	0	0	0	0
Nervous system disorder	2	4	1	2	0	0

*Cutoff based on grade ≥3 adverse events.
Adapted from Martinelli *et al.* 2017.
Please see Adverse Events Management section for further details.

- The most common treatment-emergent adverse events with BLINCYTO® included pyrexia (58%), febrile neutropenia (40%), and headache (31%)[1]
- 5 (11%) fatal treatment-emergent adverse events occurred, 1 of which was considered related to BLINCYTO® treatment (septic shock)[1]

Reference: 1. Martinelli G *et al. J Clin Oncol* 2017; 35:1795–802.

EFFICACY IN PAEDIATRIC RELAPSED OR REFRACTORY B-ALL

BLINCYTO® WAS STUDIED IN AN OPEN-LABEL, MULTICENTRE, SINGLE-ARM, PHASE I/II STUDY IN HEAVILY PRETREATED PAEDIATRIC PATIENTS[1]

von Stackelberg A *et al. J Clin Oncol* 2016;34:4381–9.

STUDY DESIGN[1]

93 patients aged <18 yrs with B-ALL

Primary refractory, in first relapse after full salvage induction, in second or later relapse, or in any relapse after allogeneic HSCT:

- Median age was 8 years
- 57% of patients had received prior HSCT
- 56% of patients had refractory disease
- 74% of patients had marrow blast count ≥ 50%
- 70 patients received the recommended dose

Exclusion criteria include:

- Active acute or extensive chronic GVHD after HSCT
- Active CNS or testicular involvement

Adapted from von Stackelberg *et al,* 2016.[1]

BLINCYTO® single-agent immunotherapy

- **Administration:** cIV
- **Treatment Cycle:** 4 weeks on drug, 2 weeks off; up to 2 induction cycles followed by up to 3 consolidation cycles

Follow up: Up to 24 months after start of study treatment

The recommended dose of BLINCYTO® was determined to be 5 mcg/m^2/day on days 1-7 and 15 mcg/m^2/day on days 8-28 for cycle 1, and then 15 mcg/m^2/day on days 1-28 for subsequent cycles.

STUDY ENDPOINTS[1]

Primary	• Phase I: maximum tolerated dose • Phase II: rate of CR within the first 2 cycles of BLINCYTO® treatment
Secondary	• HSCT realisation • Time to relapse • Duration of CR • OS • RFS • Incidence and severity of adverse events
Exploratory	• MRD response rate (conversion to MRD negativity within the first 2 treatment cycles)

Safety and efficacy data shown include all patients (n=70) who received the recommended dose in Phase I or II.
CR defined as no evidence of circulating blasts or extramedullary disease and <5% of blasts in bone marrow.
MRD negativity defined as <1 x 10^{-4} detectable blasts as determined by flow cytometry.
GVHD: graft versus host disease; **CNS:** central nervous system.

Reference: 1. von Stackelberg A *et al. J Clin Oncol* 2016;34:4381–9.

EFFICACY IN PAEDIATRIC RELAPSED OR REFRACTORY B-ALL

PATIENT POPULATION[1]

BLINCYTO® WAS STUDIED IN A HEAVILY PRETREATED PAEDIATRIC POPULATION.[1]

BASELINE CHARACTERISTICS (N=70)	
Sex, n (%)	
Male	47 (67)
Age, n (%)	
<2 years	10 (14)
2-6 years	20 (29)
7-17 years	40 (57)
Previous relapse, n (%)	
0 (primary refractory disease)	2 (3)
1	31 (44)
2	29 (41)
≥3	8 (11)
Previous allogeneic HSCT, n (%)	40 (57)
Baseline bone marrow blast count, n (%)	
<50%	18 (26)
≥50%	52 (74)

71% had relapsed within 6 months of their last treatment

56% had refractory disease

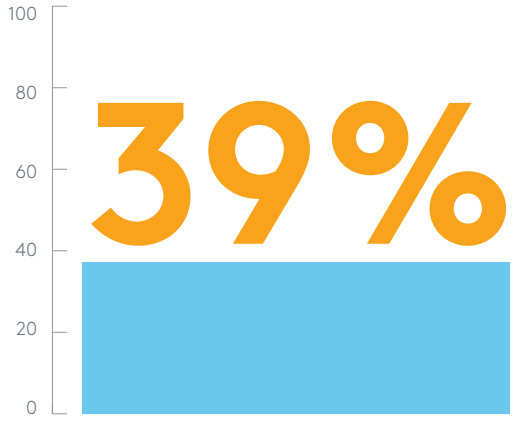
53% were in second or later relapse

57% had relapsed after HSCT

Reference: 1. von Stackelberg A *et al. J Clin Oncol* 2016;34:4381–9.

EFFICACY IN PAEDIATRIC RELAPSED OR REFRACTORY B-ALL

39% OF PAEDIATRIC PATIENTS TREATED WITH BLINCYTO® ACHIEVED CR WITHIN THE FIRST 2 TREATMENT CYCLES[1]



(n=27/70; 95% CI: 27%, 51%; primary endpoint)

74% achieved CR in Cycle 1 (n=20/27); 26% in Cycle 2 (n=7/27).

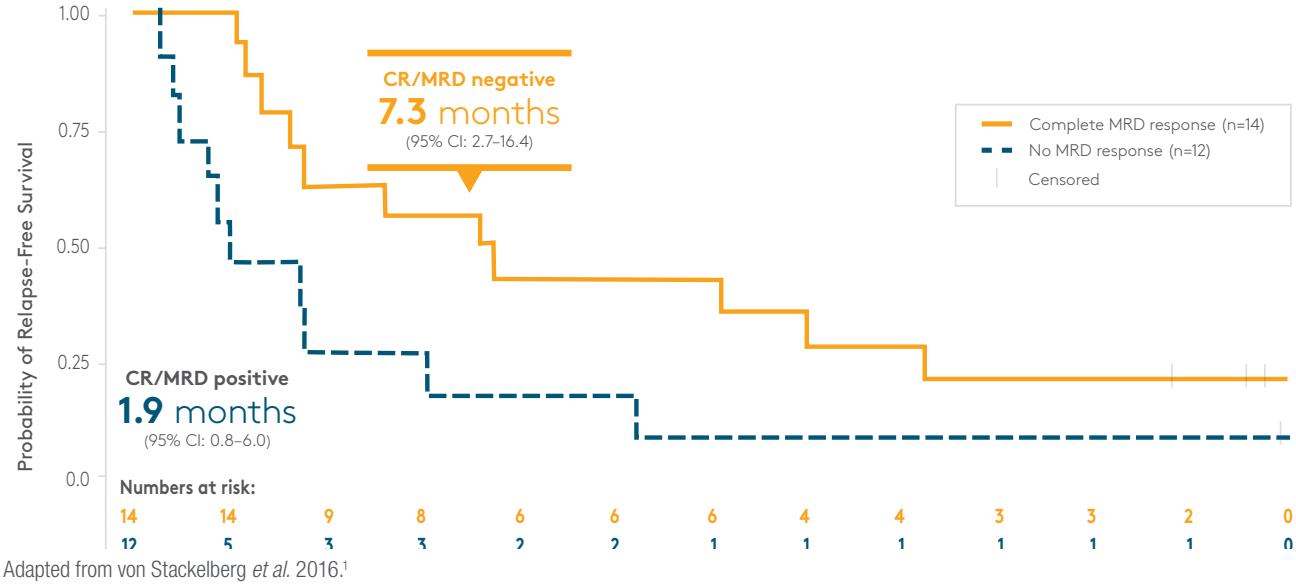
CR defined as no evidence of circulating blasts or extramedullary disease and <5% of blasts in bone marrow (M1). Patients in the study were considered very high risk on the basis of baseline tumour load, multiple prior relapses, short interval between latest treatment and start of BLINCYTO®, previous allogeneic HSCT, and/or cytogenetic profile.

Adapted from von Stackelberg *et al.* 2016.[1]

- **52%** of patients who achieved a CR were **MRD negative** (95% CI: 32%, 71%)[1]
- **48%** of patients who achieved a CR went on to receive **allogeneic HSCT**[1]

MEDIAN RELAPSE-FREE SURVIVAL WITH BLINCYTO® WAS 7.3 MONTHS IN MRD- PATIENTS VS 1.9 MONTHS FOR MRD+ PATIENTS[1]

MEDIAN RELAPSE-FREE SURVIVAL (RFS) BASED ON MRD STATUS OF PATIENTS IN CR[1]



Adapted from von Stackelberg *et al.* 2016.[1]

- Median RFS for patients who achieved CR was **4.4 months**[1]

Reference: 1. von Stackelberg A *et al. J Clin Oncol* 2016;34:4381–9.

SAFETY IN PAEDIATRIC RELAPSED OR REFRACTORY B-ALL

BLINCYTO®: CHEMOTHERAPY-FREE IMMUNOTHERAPY WITH A MANAGEABLE TOLERABILITY PROFILE[1]

- The most common adverse events were clinically manageable and included pyrexia, anaemia, nausea and headache
- Most adverse events occurred in the first few days of Cycle 1

ADVERSE EVENTS OCCURRING IN ≥20% OF PAEDIATRIC PATIENTS REGARDLESS OF RELATIONSHIP TO TREATMENT[1]	
Adverse event (any grade*)	**No. (%) of paediatric patients† (N=70)**
Pyrexia	56 (80)
Anaemia	29 (41)
Nausea	23 (33)
Headache	21 (30)
Hypertension	18 (26)
Vomiting	17 (24)
Hypokalaemia	15 (21)
Thrombocytopenia	15 (21)
Back pain	14 (20)
Cough	14 (20)
Febrile neutropenia	14 (20)

*Based on the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE). Grade 3 is severe, Grade 4 is life-threatening, and Grade 5 is fatal.
†All patients treated at 5/15 mcg/m^2/day in phase I and II.

Adapted from von Stackelberg A *et al.* 2016.

Please see Adverse Event Management section for further details.

Reference: 1. von Stackelberg A *et al. J Clin Oncol* 2016;34:4381–9, and data supplement.

EFFICACY IN MRD+ B-ALL

BLINCYTO® WAS STUDIED IN AN INTERNATIONAL, OPEN-LABEL, MULTICENTRE, SINGLE-ARM PHASE II STUDY IN PATIENTS WITH MRD+ B-ALL (BLAST)[1]

Gökbuget N *et al. Blood* 2018;131:1522–31.

- This single-arm phase II study was the first international, multicentre trial with MRD-based patient inclusion and with the endpoint of complete MRD response after the first cycle of treatment[1]

BLAST STUDY DESIGN[1]

Adults ≥18 years of age with B-ALL[1]:

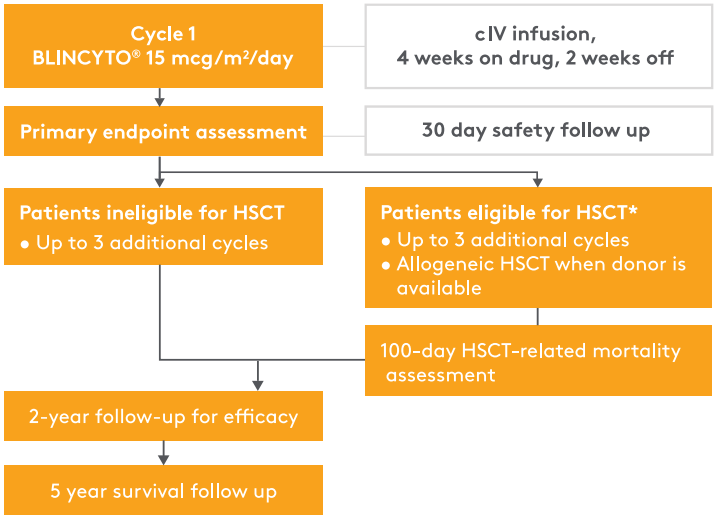
- In haematologic CR
  - <5% blasts in bone marrow
  - ANC ≥1,000/mcL
  - Platelets ≥50,000/mcL
  - Haemoglobin ≥9 g/dL
- With an MRD level of ≥10*$^{-3}$ after ≥3 intensive chemotherapy treatments

AND WITHOUT

- Prior allogeneic HSCT
- Current extramedullary disease or CNS pathology, including active ALL in the CNS
- Prior chemotherapy (within 2 weeks) or radiotherapy (within 4 weeks)

*In an assay with a minimum sensitivity of 10^{-4}.

BLAST TREATMENT OVERVIEW[1]



*HSCT was offered to eligible patients at any time after cycle 1.
Adapted from Gökbuget *et al.* 2018[1]

MRD EVALUATION[1]

- Patients were enrolled based on PCR- or flow cytometry-determined MRD level of ≥10^{-3}
- The reference lab confirmed MRD level and status at inclusion by quantitative PCR of individual clonal immunoglobulin and/or T-cell receptor gene rearrangements according to standardised methodology

STUDY ENDPOINTS[1]

Primary	• Complete MRD response rate after 1 cycle (minimum sensitivity 10^{-4})
Secondary	• OS • Haematologic RFS at 18 months • Duration of complete MRD response • Time to haematologic relapse • Incidence and severity of adverse events

A stringent definition of complete MRD response (no detectable leukaemic blasts by PCR with at least 10^{-4} sensitivity) was used.[1]

ANC: absolute neutrophil count; **CNS:** central nervous system.

Reference: 1. Gökbuget N *et al. Blood* 2018;131:1522–31.

EFFICACY IN MRD+ B-ALL

PATIENT POPULATION[1]

BLINCYTO® WAS STUDIED IN PATIENTS WITH PERSISTENT OR RECURRENT MRD AFTER A MINIMUM OF 3 BLOCKS OF INTENSIVE CHEMOTHERAPY[1]

BASELINE CHARACTERISTICS OF PATIENTS (N=116)	
Sex, n (%)	
Male	68 (59)
Median age (range), years	45 (18-76)
Age, n (%)	
≥18 to <35 years	36 (31)
≥35 to <55 years	41 (35)
≥55 to <65 years	24 (21)
≥65 years	15 (13)
Median (range) time from prior treatment, months	2 (0-55)
Relapse history, n (%)	
In first complete remission (CR1)	75 (65)
In second complete remission (CR2)	39 (34)
In third complete remission (CR3)	2 (2)
Baseline MRD levels, n (%)*	
$\geq 10^{-1}$ to <1	9 (8)
$\geq 10^{-2}$ to $<10^{-1}$	45 (39)
$\geq 10^{-3}$ to $<10^{-2}$	52 (45)

65% were in CR1

36% were in CR2 or CR3

47% had high MRD burden ($\geq 10^{-2}$)

*10 (9%) patients had MRD $<10^{-3}$, below the lower limit of quantification, or unknown MRD.

NOTE: Percentages may not add up 100% due to rounding.

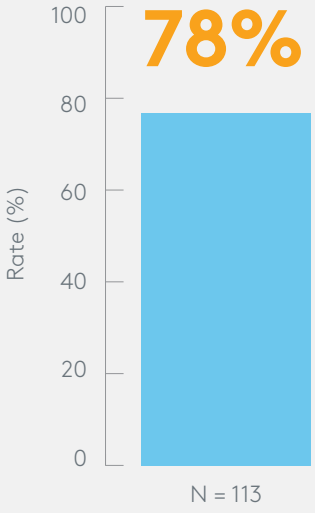
The majority of patients studied were in first complete remission (MRD positive after frontline chemotherapy).[1]

Reference: 1. Gökbuget N *et al. Blood* 2018;131:1522–31.

78% OF ADULT PATIENTS WITH MRD+ B-ALL ACHIEVED A COMPLETE MRD RESPONSE AFTER ONE CYCLE OF BLINCYTO®[1]

BLAST study: An open-label, single-arm phase II trial of 116 poor-prognosis patients in haematologic complete response (first or later) who remained MRD+ after intensive chemotherapy[1]

COMPLETE MRD RESPONSE (PRIMARY ENDPOINT FULL ANALYSIS SET)[1]



78% **after 1 cycle**
(95% CI: 69–85%)

Complete MRD response:
MRD negative with
sensitivity of 10^{-4} (1:10,000) by PCR

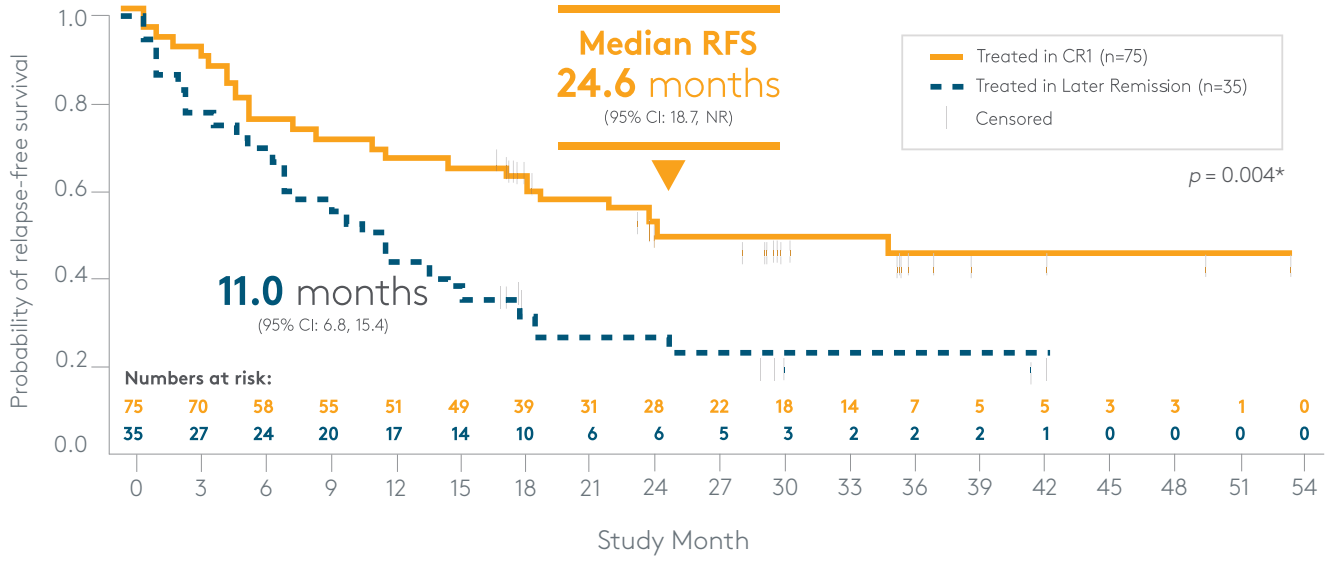
Adapted from Gökbuget *et al.* 2018.[1]

Complete MRD response was numerically higher in B-ALL patients treated with BLINCYTO® in first complete remission vs later complete remission, suggested that intervening earlier with BLINCYTO® may be beneficial[1]

BLINCTYO®-TREATED PATIENTS ACHIEVED OVER 2X LONGER RELAPSE-FREE SURVIVAL (RFS) WHEN TREATED IN CR1 VS LATER CR

(24.6 vs 11 months; unadjusted HR, 2.09; 95% CI, 1.26–3.48; p=0.004)[1,2]

RFS IN PATIENTS TREATED WITH BLINCYTO® IN CR1 VS LATER REMISSION[1]

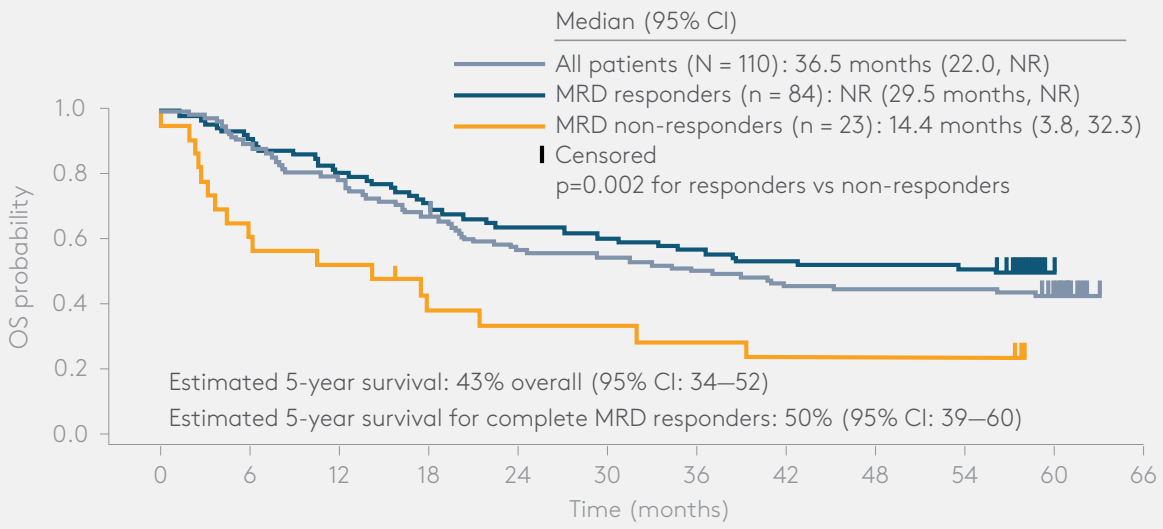


*Log Rank P value
Adapted from Gökbuget N *et al.* 2018.[1]

Reference: 1. Gökbuget N *et al. Blood* 2018;131:1522–31. **2.** BLINCYTO® (blinatumomab) Product Information. www.amgen.com.au/Blincyto.PI.

MEDIAN OVERALL SURVIVAL WAS NOT REACHED WITH 5 YEARS OF FOLLOW-UP IN BLAST STUDY PATIENTS WHO ACHIEVED COMPLETE MRD RESPONSE WITH BLINCYTO®[1,2]

OVERALL SURVIVAL BY COMPLETE MRD RESPONSE STATUS AT A MEDIAN FOLLOW-UP OF 59.8 MONTHS[1†]



Adapted from Gökbuget *et al.* 2019.[1] Landmark analysis from day 45; complete MRD response was defined as no target amplification, with a minimum sensitivity of 10^{-4}.
†After cycle 1 of BLINCYTO® treatment.

Median overall survival was also not reached among:[1]

- Patients who achieved a complete MRD response with BLINCYTO® in CR1
- Patients who received HSCT in CCR after BLINCYTO®

NCCN guidelines recommend BLINCYTO® for MRD+ patients with B-cell precursor ALL in complete haematological remission[2]

Reference: 1. Gökbuget N, *et al.* Presented at: 24th Congress of the European Hematology Association; June 13-16, 2019; Amsterdam, the Netherlands. Oral Presentation S1619. **2.** NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Acute Lymphoblastic Leukemia. Version 1.2020 — January 15, 2020

SAFETY IN MRD+ B-ALL

BLINCYTO®: CHEMOTHERAPY-FREE IMMUNOTHERAPY WITH A MANAGEABLE TOLERABILITY PROFILE[1]

ALL ADVERSE EVENTS REGARDLESS OF CAUSALITY THAT OCCURRED DURING THE TREATMENT PERIOD PLUS 30 DAYS (FULL ANALYSIS SET)[1]

	ALL PATIENTS (N = 116)	
	Any Grade	Grade 3/4
Any adverse event, n (%)	**116 (100)**	**69 (60)**
Non-neurologic adverse events, worst grade ≥3 occurring in ≥3% of patients		
Pyrexia	103 (89)	9 (8)
Headache	44 (38)	4 (3)
Neutropenia	18 (16)	18 (16)
Leukopenia	8 (7)	7 (6)
Anaemia	7 (6)	5 (4)
ALT increased	7 (6)	6 (5)
Thrombocytopenia	6 (5)	5 (5)
AST increased	5 (4)	4 (4)
Any neurologic adverse event, n (%)*	**61 (53)**	**15 (13)**
Neurologic events, worst grade ≥3		
Tremor	35 (30)	6 (5)
Aphasia	15 (13)	1 (1)
Dizziness	9 (8)	1 (1)
Confused state	6 (5)	1 (1)
Encephalopathy	6 (5)	5 (5)
Seizure	3 (3)	2 (2)
Disorientation	3 (3)	1 (1)
Depressed level of consciousness	1 (1)	1 (1)
Generalised tonic-clonic seizure	1 (1)	1 (1)

Thirty-six patients (31%) had treatment interruptions because of treatment-emergent adverse events, mainly as a result of neurologic events and flu-like symptoms. Those occurring in ≥2% of patients included pyrexia (8%) and aphasia, encephalopathy, overdose, tremor, ALT increased, AST increased, and chills (3% each).

*Among all patients. Multiple events may have occurred in some patients.
Adapted from Gökbuget N *et al.* 2018.
Please see Adverse Event Management section for further details.

- Serious adverse events were managed with treatment interruption or discontinuation[1]
- Most patients who interrupted treatment due to grade 3/4 neurologic events resumed BLINCYTO® treatment after the event resolved[1]

BLINCYTO® is the first and only PBS-listed therapy for the treatment of MRD+ B-ALL.[2]

AST: aspartate aminotransferase; **ALT:** alanine aminotransferase.
References: 1. Gökbuget N *et al. Blood* 2018;131:1522–31. **2.** Pharmaceutical Benefits Scheme. Available from www.pbs.gov.au. Accessed January 2020.

SAFETY AND TOLERABILITY SUMMARY

BLINCYTO®: CHEMOTHERAPY-FREE IMMUNOTHERAPY WITH A MANAGEABLE TOLERABILITY PROFILE[1]

SAFETY PROFILE IN ADULT Ph- RELAPSED OR REFRACTORY B-ALL PATIENTS

In the randomised phase III clinical study (n=267) of adult patients with Ph- relapsed or refractory B-ALL, the most common adverse reactions were:[1]

- 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%)
- Increased liver enzymes (16.9%)

The most serious adverse reactions that occurred during BLINCYTO® treatment were:[1]

- Infections (28.1%)
- Neutropenia/febrile neutropenia (10.5%)
- Neurologic events (6.7%)
- Cytokine release syndrome (3.7%)
- Tumour lysis syndrome (1.1%)

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.[1]

Reference: 1. BLINCYTO® (blinatumomab) Product Information. www.amgen.com.au/Blincyto.PI.

SAFETY AND TOLERABILITY SUMMARY

BLINCYTO®: CHEMOTHERAPY-FREE IMMUNOTHERAPY WITH A GENERALLY MANAGEABLE TOLERABILITY PROFILE[1]

SAFETY PROFILE IN PAEDIATRIC RELAPSED OR REFRACTORY B-ALL PATIENTS

The adverse reactions in BLINCYTO®-treated paediatric patients were similar in type to those seen in adult patients.[1]

Adverse reactions that were observed more frequently (≥10% difference) in the paediatric population compared to the adult population were:[1]

- Anaemia
- Thrombocytopenia
- Leukopenia
- Pyrexia
- Infusion-related reaction
- Hypertension
- Weight increased

SAFETY PROFILE IN ADULT Ph+ RELAPSED OR REFRACTORY B-ALL AND MRD+ B-ALL PATIENTS

The adverse reaction profile in BLINCYTO®-treated Ph+ relapsed or refractory B-ALL patients and MRD+ B-ALL adult patients was similar in type to those seen in the randomised phase III clinical study in Ph– relapsed or refractory B-ALL.[1]

The most common adverse reactions among adult patients were:[1]

- Pyrexia (90.5%)
- Headache (39.4%)
- Tremor (29.2%)
- Chills (28.5%)
- Fatigue (26.3%)
- Nausea (23.4%)
- Vomiting (21.2%)
- Hypokalaemia (20.4%)
- Diarrhoea (20.4%).

The most common serious adverse reaction during BLINCYTO® treatment among adult patients was pyrexia (12.4%)[1]

Reference: 1. BLINCYTO® (blinatumomab) Product Information. www.amgen.com.au/Blincyto.PI.

SUMMARY DOSAGE AND ADMINISTRATION[1]

cIV

- Because of its short half-life (<3 hours), BLINCYTO® must be adminstered as a cIV infusion delivered at a constant flow rate using an infusion pump

4 WEEK CYCLE

- A single cycle is 4 weeks of BLINCYTO® cIV infusion
- Each cycle is separated by a 2-week treatment-free interval

CYCLES

- **Patients with relapsed or refractory B-ALL** may receive up to 5 cycles of BLINCYTO® treatment
- For maintenance therapy, a cycle of treatment of BLINCYTO® consists of 28 days of cIV infusion followed by a 56-day treatment-free interval (Maintenance therapy with BLINCYTO® is not covered by the PBS listing)
- **Patients with MRD+ B-ALL** may receive up to 4 cycles of BLINCYTO® treatment

DOSING

Patients ≥45 kg receive a fixed dose and for patients <45 kg, the dose is calculated using the patient's body surface area (BSA)

- **FOR RELAPSED OR REFRACTORY B-ALL PATIENTS**

≥45 kg:
- Cycle 1 days 1–7: 9 mcg/day
- Cycle 1 days 8–28: 28 mcg/day
- Subsequent cycles days 1–28: 28 mcg/day

<45 kg:
- Cycle 1 days 1–7: 5 mcg/m^2/day (not to exceed 9 mcg/day)
- Cycle 1 days 8–28: 15 mcg/m^2/day (not to exceed 28 mcg/day)
- Subsequent cycles days 1–28: 15 mcg/m^2/day (not to exceed 28 mcg/day)

- **FOR MRD+ B-ALL PATIENTS**

≥45 kg:
- 28 mcg/day

<45 kg:[2]
- 15 mcg/m^2/day (not to exceed 28 mcg/day)

- The dose may be adjusted in the case of adverse events

PRE-MEDICATION

- **Adult relapsed or refractory B-ALL patients** should be premedicated with 20 mg IV dexamethasone 1 hour prior to initiation of each cycle to help minimise infusion reactions
- **Paediatric relapsed or refractory B-ALL patients** should be premedicated with dexamethasone 10 mg/m^2 (not to exceed 20 mg) orally or intravenously 6–12 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)
- For patients with ≥50% leukaemic blasts in bone marrow or >15,000/mcL peripheral blood leukaemic blast counts treat with dexamethasone (not to exceed 24 mg/day)
- **Adult patients with MRD+ B-ALL** should be premedicated with prednisone 100 mg intravenously or equivalent (e.g., dexamethasone 16 mg) 1 hour prior to the first dose of BLINCYTO® of each cycle
- Intrathecal chemotherapy prophylaxis is recommended before and during BLINCYTO® therapy to prevent CNS ALL relapse
- **Paediatric patients with MRD+ B-ALL** should be premedicated with 5 mg/m^2 of dexamethasone (not to exceed 20 mg) prior to the first dose of BLINCYTO® in the first cycle and when restarting an infusion after an interruption of ≥4 hours in the first cycle[2]

HOSPITAL ADMISSION

- **For relapsed or refractory B-ALL patients,** hospitalisation is recommended at a minimum for the first 9 days of cycle 1 and the first 2 days of cycle 2
- **For MRD+ B-ALL patients,** hospitalisation is recommended at a minimum for the first 3 days of the first cycle and the first 2 days of cycle 2
- For all subsequent cycle starts and reinitiation (e.g. if treatment is interrupted for ≥4 hours), supervision by a healthcare professional or hospitalisation is recommended

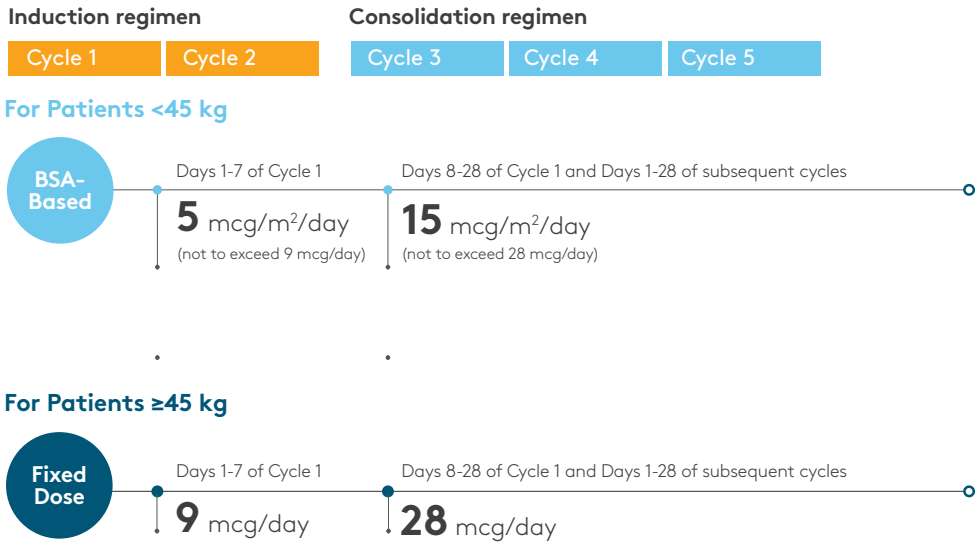
References: 1. BLINCYTO® (blinatumomab) Product Information. www.amgen.com.au/Blincyto.PI. **2.** BLINCYTO® (blinatumomab) US Prescribing Information. Available at: https://pi.amgen.com/~/media/amgen/repositorysites/pi-amgen-com/blincyto/blincyto_pi_hcp_english.pdf (accessed February 2020).

DOSAGE AND ADMINISTRATION

DOSING AND PREMEDICATION IN PATIENTS WITH RELAPSED OR REFRACTORY B-ALL[1]

TREATMENT CYCLES

- A single cycle of treatment consists of 4 weeks of continuous IV infusion followed by a 2-week treatment-free interval
- A treatment course consists of up to 2 induction cycles of BLINCYTO®, followed by up to 3 consolidation cycles



It is important to initiate treatment at the recommended starting dose in order to mitigate the risk of CRS.

PREMEDICATION

Intrathecal chemotherapy prophylaxis is recommended before and during BLINCYTO® therapy to prevent CNS ALL relapse.

Adult relapsed or refractory B-ALL patients should be premedicated with 20 mg IV dexamethasone 1 hour prior to initiation of each cycle to help minimise infusion reactions.

Paediatric relapsed or refractory B-ALL patients should be premedicated with dexamethasone 10 mg/m² (not to exceed 20 mg) orally or intravenously 6–12 hours prior to the start of BLINCYTO® (cycle 1 day 1), followed by premedication with dexamethasone 5 mg/m² orally or intravenously within 30 minutes of the start of BLINCYTO® (cycle 1 day 1).

PRE-PHASE TREATMENT FOR PATIENTS WITH HIGH TUMOUR BURDEN

For patients with ≥50% leukaemic blasts or >15,000/mcL peripheral blood leukaemic blast counts treat with dexamethasone (not to exceed 24 mg/day).

HOSPITALISATION

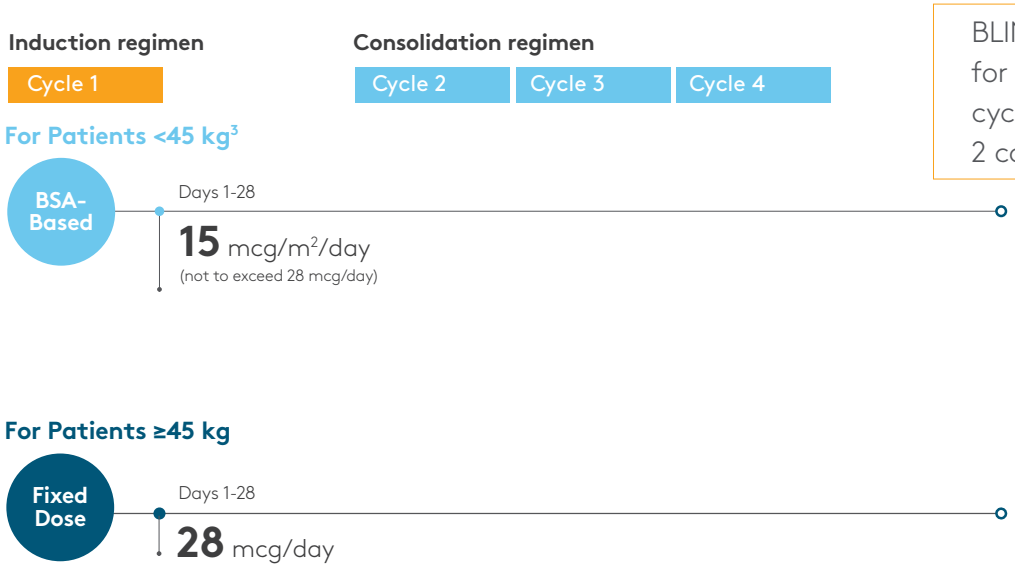
- Hospitalisation is recommended at a minimum for the first 9 days of the first treatment cycle and the first 2 days of the second cycle
- For all subsequent cycle starts and reinitiation (e.g. if treatment is interrupted for ≥4 hours), supervision by a healthcare professional or hospitalisation is recommended

Reference: 1. BLINCYTO® (blinatumomab) Product Information. www.amgen.com.au/Blincyto.PI.

DOSAGE AND ADMINISTRATION

DOSING AND PREMEDICATION IN PATIENTS WITH MRD+ B-ALL[1]

- A single cycle of treatment consists of 4 weeks of continuous IV infusion followed by a 2-week treatment-free interval
- A treatment course consists of up to 1 induction cycle of BLINCYTO®, followed by up to 3 consolidation cycles



BLINCYTO® is PBS listed for up to 2 induction cycles followed by up to 2 consolidation cycles.[2]

PREMEDICATION

Intrathecal chemotherapy prophylaxis is recommended before and during BLINCYTO® therapy to prevent CNS ALL relapse.

Adult patients with MRD+ B-ALL should be premedicated with prednisone 100 mg intravenously or equivalent (e.g., dexamethasone 16 mg) 1 hour prior to the first dose of BLINCYTO® of each cycle.

Paediatric patients with MRD+ B-ALL should be premedicated with 5 mg/m² of dexamethasone (not to exceed 20 mg) prior to the first dose of BLINCYTO® in the first cycle and when restarting an infusion after an interruption of ≥4 hours in the first cycle.[3]

HOSPITALISATION

- 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 hours), supervision by a healthcare professional or hospitalisation is recommended

References: 1. BLINCYTO® (blinatumomab) Product Information. www.amgen.com.au/Blincyto.PI. **2.** Pharmaceutical Benefits Scheme. Available at: www.pbs.gov.au (accesed January 2020). **3.** BLINCYTO® (blinatumomab) US Prescribing Information. Available at: https://pi.amgen.com/~/media/amgen/repositorysites/pi-amgen-com/blincyto/blincyto_pi_hcp_english.pdf. (accessed February 2020)

DOSAGE AND ADMINISTRATION

INFUSION PROCESS[1]

Because of its short half life (<3 hours) BLINCYTO® must be administered as a cIV infusion delivered at a constant flow rate using an infusion pump.[1]

BLINCYTO® may be administered either from an IV bag or from a cassette.[1]

Infusion bags are prepared to infuse over 24, 48, 72 or 96 hours and each duration has a specific constant infusion rate to ensure the correct dose of BLINCYTO® is administered.[1]

Different infusion durations are designed to help treatment fit around the schedules of the care team and patient.

Clearly label the prepared IV infusion bag or cassette with the dose, infusion rate and duration of infusion.[1]

IV LINE

IMPORTANT NOTE: Do not flush infusion lines into the patient, as it will cause an inadvertent bolus of drug to be administered. BLINCYTO® should be infused through a dedicated lumen.[1]

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.[1]

BLINCYTO® is compatible with polyolefin, PVC non-di-ethylhexylphthalate (non-DEHP), or ethyl vinyl acetate (EVA) infusion bags/pump cassettes.[1]

CHANGE OF IV BAG OR CASSETTE

The IV bag or cassette must be changed at least every 96 hours by a healthcare professional for sterility reasons.[1]

If using IV bags, to minimise the number of aseptic transfers, it is recommended to use a 250 mL-prefilled IV bag.[1] 250 mL prefilled IV bags typically contain overfill with a total volume of 265 mL to 275 mL.[1] **BLINCYTO® dose calculations are based on a starting volume of 265 mL to 275 mL 0.9% sodium chloride.**[1]

PUMP SPECIFICATIONS

The infusion pump should be:[1]

- **Programmable:** to set infusion rate and duration
- **Lockable:** to avoid patients accidentally changing settings
- **Non-elastomeric:** to provide a constant infusion rate
- **Fitted with an alarm:** to alert patients and care team to problems with the pump

Reference: 1. BLINCYTO® (blinatumomab) Product Information. www.amgen.com.au/Blincyto.PI.

DOSAGE AND ADMINISTRATION

IMPORTANT CONSIDERATIONS WHEN USING BLINCYTO®

Use aseptic technique[1]

To prevent **accidental contamination**, prepare BLINCYTO® according to aseptic standards (see Product Information for more information)

Follow instructions carefully[1]

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)

Do not flush the infusion line[1]

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

Patients should not adjust the pump setting[2]

Inform patients that any changes to pump function may result in **dosing errors**. If there is a problem with the infusion pump or the pump alarms, patients should **contact their doctor or nurse immediately**

In the event of overdose:[1]

- **Temporarily interrupt** the infusion
- **Monitor** the patient

Consider re-initiation of BLINCYTO® at the correct therapeutic dose

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).[1]

References: 1. BLINCYTO® (blinatumomab) Product Information. www.amgen.com.au/Blincyto.PI
2. BLINCYTO® (blinatumomab) Consumer Medicine Information. www.amgen.com.au/Blincyto.CMI

DOSAGE AND ADMINISTRATION

VOLUME CALCULATIONS IN PATIENTS WITH RELAPSED OR REFRACTORY B-ALL WEIGHING ≥45 KG[1]

IV BAGS

Infusion time (rate)	24 hours (10 mL/h)		48 hours (5 mL/h)		72 hours (3.3 mL/h)		96 hours (2.5 mL/h)	
Dose (per day)	9 mcg	28 mcg	9 mcg	28 mcg	9 mcg	28 mcg	9 mcg	28 mcg
Number of reconstituted BLINCYTO® vials needed								
Volume of reconstituted BLINCYTO® required	0.83 mL	2.6 mL	1.7 mL	5.2 mL	2.5 mL	8 mL	3.3 mL	10.7 mL

250 ML CASSETTES

Cassette duration	24 hours		48 hours		72 hours		96 hours	
Dose (per day)	9 mcg	28 mcg	9 mcg	28 mcg	9 mcg	28 mcg	9 mcg	28 mcg
Number of reconstituted BLINCYTO® vials needed								
Volume of reconstituted BLINCYTO® required	0.75 mL	2.3 mL	1.5 mL	4.7 mL	2.25 mL	7 mL	3 mL	9.3 mL

Reference: 1. BLINCYTO® (blinatumomab) Product Information. www.amgen.com.au/Blincyto.PI.

DOSAGE AND ADMINISTRATION

VOLUME CALCULATIONS IN PATIENTS WITH RELAPSED OR REFRACTORY B-ALL WEIGHING <45 KG[1]

IV BAGS

Infusion time (rate)	24 hours (10 mL/hour)		48 hours (5 mL/hour)		72 hours (3.3 mL/hour)		96 hours (2.5 mL/hour)	
Dose (per day)	5 mcg/m²	15 mcg/m²	5 mcg/m²	15 mcg/m²	5 mcg/m²	15 mcg/m²	5 mcg/m²	15 mcg/m²
Number of reconstituted BLINCYTO® vials needed				 to		 to		 to
Volume of reconstituted BLINCYTO® required for BSA 0.4–1.59 m²*	0.2–0.7 mL	0.6–2.1 mL	0.4–1.4 mL	1.2–4.2 mL	0.6–2.1 mL	1.8–6.3 mL	0.8–2.8 mL	2.4–8.3 mL

250 ML CASSETTES

Cassette duration	24 hours		48 hours		72 hours		96 hours	
Dose (per day)	5 mcg/m²	15 mcg/m²	5 mcg/m²	15 mcg/m²	5 mcg/m²	15 mcg/m²	5 mcg/m²	15 mcg/m²
Number of reconstituted BLINCYTO® vials needed				 to		 to		 to
Volume of reconstituted BLINCYTO® required for BSA 0.4–1.59 m²*	0.19–0.65 mL	0.56–1.9 mL	0.37–1.3 mL	1.1–3.9 mL	0.56–1.9 mL	1.7–5.8 mL	0.74–2.6 mL	2.2–7.7 mL

BSA: body surface area. *See Product Information for exact dose of reconstituted BLINCYTO®.

Reference: 1. BLINCYTO® (blinatumomab) Product Information. www.amgen.com.au/Blincyto.PI.

DOSAGE AND ADMINISTRATION

VOLUME CALCULATIONS IN PATIENTS WITH MRD+ B-ALL WEIGHING ≥45 KG[1]

IV BAGS

Infusion time (rate)	24 hours (10 mL/h)	48 hours (5 mL/h)	72 hours (3.3 mL/h)	96 hours (2.5 mL/h)
Dose (per day)	28 mcg	28 mcg	28 mcg	28 mcg
Number of reconstituted BLINCYTO® vials needed				
Volume of reconstituted BLINCYTO® required	2.6 mL	5.2 mL	8 mL	10.7 mL

250 ML CASSETTES

Cassette duration	24 hours	48 hours	72 hours	96 hours
Dose (per day)	28 mcg	28 mcg	28 mcg	28 mcg
Number of reconstituted BLINCYTO® vials needed				
Volume of reconstituted BLINCYTO® required	2.3 mL	4.7 mL	7 mL	9.3 mL

Reference: 1. BLINCYTO® (blinatumomab) Product Information. www.amgen.com.au/Blincyto.PI.

DOSAGE AND ADMINISTRATION

VOLUME CALCULATIONS IN PATIENTS WITH MRD+ B-ALL WEIGHING <45 KG[1,2]

IV BAGS

Infusion time (rate)	24 hours (10 mL/hour)	48 hours (5 mL/hour)	72 hours (3.3 mL/hour)	96 hours (2.5 mL/hour)
Dose (per day)	15 mcg/m²	15 mcg/m²	15 mcg/m²	15 mcg/m²
Number of reconstituted BLINCYTO® vials needed		 to	 to	 to
Volume of reconstituted BLINCYTO® required for BSA 0.4–1.59 m²*	0.6–2.1 mL	1.2–4.2 mL	1.8–6.3 mL	2.4–8.3 mL

250 ML CASSETTES

Cassette duration	24 hours	48 hours	72 hours	96 hours
Dose (per day)	15 mcg/m²	15 mcg/m²	15 mcg/m²	15 mcg/m²
Number of reconstituted BLINCYTO® vials needed		 to	 to	 to
Volume of reconstituted BLINCYTO® required for BSA 0.4–1.59 m²*	0.56–1.9 mL	1.1–3.9 mL	1.7–5.8 mL	2.2–7.7 mL

BSA: body surface area. *See Product Information for exact dose of reconstituted BLINCYTO®.

Reference: 1. BLINCYTO® (blinatumomab) Product Information. www.amgen.com.au/Blincyto.PI. **2.** BLINCYTO® (blinatumomab) US Prescribing Information. Available at: https://pi.amgen.com/~/media/amgen/repositorysites/pi-amgen-com/blincyto/blincyto_pi_hcp_english.pdf (accessed February 2020).

DOSAGE AND ADMINISTRATION

BLINCYTO® INFUSION CHECKLIST[1]

INFUSION CHECKLIST[1]

- ✓ The patient has received appropriate dexamethasone premedication if starting a new cycle
- ✓ The infusion will take place through a dedicated lumen
- ✓ The BLINCYTO® solution has been prepared at a concentration of 9 mcg/day (starting dose) or 28 mcg/day (full dose), as appropriate for patients weighing ≥45 kg and 5 mcg/m^2/day (starting dose; not to exceed 9 mcg/day) or 15 mcg/m^2/day (full dose; not to exceed 28 mcg/day), as appropriate, for patients weighing <45 kg
- ✓ The IV tubing is attached to the bag along with an in-line, sterile, non-pyrogenic, low protein binding 0.2 micron in-line filter
- ✓ Excess air has been removed (particularly important for use with an ambulatory infusion pump)
- ✓ The IV line has been primed with the prepared solution for infusion
- ✓ The infusion bag size is correct (250 mL with usual overfill volume of 265 to 275 mL)
- ✓ The duration of infusion has been confirmed (24, 48, 72, or 96 h)
- ✓ The infusion rate has been verified
- ✓ The pump has been correctly programmed and the tubing and filter are properly set up

THERAPY INTERRUPTION

- Healthcare professional supervision or hospitalisation is recommended in instances where treatment is being re-initiated following an interruption of ≥4 hours[1]

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).[1]

MEDICATION OVERDOSE

Stop the infusion immediately	**Consult the treating physician**	**Assess for treatment-related adverse events**	**If none, consider, with the treating physician, resuming therapy at the correct dose**	**If the overdose results in an adverse event, monitor the patient until all signs of toxicity are resolved**

Reference: 1. BLINCYTO® (blinatumomab) Product Information. www.amgen.com.au/Blincyto.PI.

DOSAGE AND ADMINISTRATION

BLINCYTO® IV PREPARATION[1]

STEPS TO PREPARE BLINCYTO® IV SOLUTION UNDER CONDITIONS USING ASEPTIC TECHNIQUES[1]

Step 1	• Transfer appropriate amount of BLINCYTO® IV solution stabiliser to the 0.9% Sodium Chloride infusion bag • Gently mix the contents of the bag to avoid foaming • Discard remaining BLINCYTO® IV solution stabiliser vial if applicable
Step 2	• Reconstitute BLINCYTO® lyophilised powder vial with 3 mL of Preservative Free Sterile Water for injection • Do not reconstitute BLINCYTO® with BLINCYTO® IV solution stabiliser • Do not shake • Gently swirl contents to avoid excess foaming • Reconstitute the required number of BLINCYTO® vials • Visually inspect the reconstituted solution for particulate matter and to confirm colour. The solution should be clear to slightly opalescent, colourless to slightly yellow
Step 3	• Transfer appropriate amount of reconstituted BLINCYTO® solution into the 0.9% Sodium Chloride infusion bag containing IV solution stabilser • Gently mix the contents of the bag to avoid foaming
Step 4	• Attach the IV tubing with the sterile 0.2 micron in-line filter to the prepared infusion bag
Step 5	• Remove air from the prepared BLINCYTO® infusion solution bag
Step 6	• Prime the IV tubing with the prepared BLINCYTO® infusion solution • Do not prime the IV tubing with 0.9% Sodium Chloride solution for injection
Step 7	• Store the prepared BLINCYTO® infusion solution bags at 2^{0}C to 8^{0}C for a maximum of 10 days if not immediately used • Clearly label the prepared IV infusion bag with the dose, infusion rate and duration of infusion

Note: for comprehensive preparation instructions, please refer to the BLINCYTO® Product Information.

Reference: 1. BLINCYTO® (blinatumomab) Product Information. www.amgen.com.au/Blincyto.PI.

DOSAGE AND ADMINISTRATION

BLINCYTO® CASSETTE PREPARATION[1]

STEPS TO PREPARE BLINCYTO® CASSETTE UNDER CONDITIONS USING ASEPTIC TECHNIQUES[1]

Step 1	• Transfer appropriate amount of 0.9% Sodium Chloride solution to the cassette
Step 2	• Transfer appropriate amount of BLINCYTO® IV solution stabiliser to the cassette • Gently mix the contents of the cassette to avoid foaming • Discard remaining BLINCYTO® IV solution stabiliser vial if applicable
Step 3	• Reconstitute BLINCYTO® lyophilised powder vial with 3 mL of Preservative Free Sterile Water for injection • Do not reconstitute BLINCYTO® with BLINCYTO® IV solution stabiliser • Do not shake • Gently swirl contents to avoid excess foaming • Reconstitute the required number of BLINCYTO® vials as needed • Visually inspect the reconstituted solution for particulate matter and to confirm colour. The solution should be clear to slightly opalescent, colourless to slightly yellow
Step 4	• Transfer appropriate amount of reconstituted BLINCYTO® solution into the cassette • Gently mix the contents of the cassette to avoid foaming • Redraw approximately 10 mL of fluid from the cassette and inject back to ensure no BLINCYTO® remains in the cassette line. Gently mix again
Step 5	• Remove air from the cassette using a syringe
Step 6	• Attach the IV tubing with the sterile 0.2 micron in-line filter to the cassette using a syringe
Step 7	• Prime the IV tubing with the prepared BLINCYTO® solution for infusion • Do not prime the IV tubing with 0.9% Sodium Chloride solution for injection
Step 8	• Store at 2°C to 8°C for a maximum of 10 days if not used immediately • Clearly label the prepared cassette with the dose, infusion rate and duration of infusion

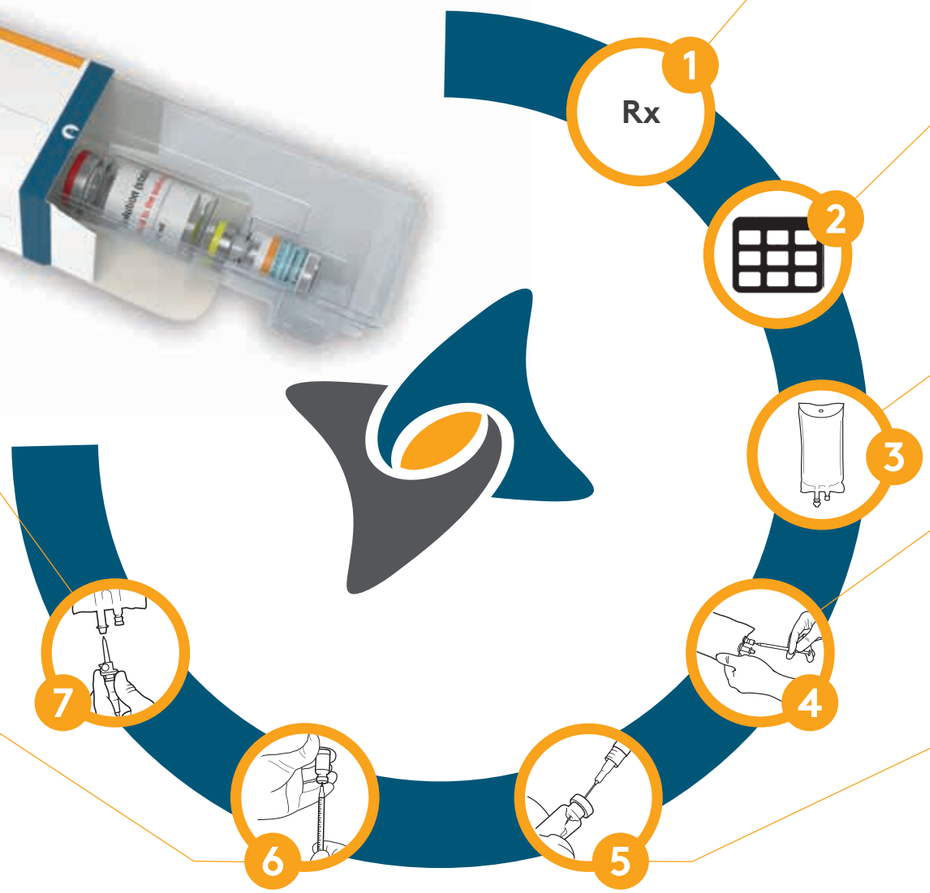
Note: for comprehensive preparation instructions, please refer to the BLINCYTO® Product Information.

Reference: 1. BLINCYTO® (blinatumomab) Product Information. www.amgen.com.au/Blincyto.PI.

DOSAGE AND ADMINISTRATION

PREPARATION OF BLINCYTO® INFUSION SOLUTION FOR IV ADMINISTRATION[1]

Example packaging only.
Package appearance may
differ by country.



REMOVE AIR AND PRIME IV LINE

- Under aseptic conditions, attach the IV tubing to the infusion bag with the sterile 0.2 micron in-line filter.
- Remove air from the infusion bag.
- Prime the IV line only with the prepared solution for infusion.
- **Do not prime with sodium chloride 9 mg/mL (0.9%) solution for injection.**

TRANSFER CORRECT VOLUME OF RECONSTITUTED BLINCYTO®

- Refer to the volume calculation table
- Using a syringe, aseptically transfer the correct volume of reconstituted BLINCYTO® into the infusion bag.
- More than one vial of reconstituted BLINCYTO® may be required, as described in the **volume** calculation table.
- Gently mix the contents of the bag to avoid foaming.
- Discard remaining BLINCYTO® reconstituted solution.

PREPARATION STEPS

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

CHECK PRESCRIBED DOSE AND INFUSION TIME

CHECK VOLUMES REQUIRED

- Using the volume calculation table, check the volume of reconstituted BLINCYTO® that will be required.
- Bear in mind that more than one vial of BLINCYTO® may need to be reconstituted to prepare one BLINCYTO® infusion bag.

PREPARE THE INFUSION BAG

- 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.

TRANSFER SOLUTION (STABILISER)

- 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.

RECONSTITUTE BLINCYTO® WITH WATER FOR INJECTIONS

Do not reconstitute BLINCYTO® powder for concentrate with the solution (stabiliser).

- Using a syringe, reconstitute one 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.**
- The addition of water for injections to the powder for concentrate results in a total volume of 3.1 mL per PI for a final BLINCYTO® concentration of 12.5 mcg/mL.
- 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 the solution is cloudy or has precipitated.**

INFORMATION TO TELL ADMINISTERING HCP

1 The line has been primed with drug and is ready for infusion.

2 The line should not be flushed into the patient, as it will cause an inadvertent bolus of drug to be administered. BLINCYTO® should be infused through a dedicated lumen.

3 The infusion bag can remain at room temperature up to 96 hours (including infusion time). Any unused drug should be discarded after 96 hours; it should not be refrigerated again. The infusion bag does not need to be protected from light.

4 The entire volume in the prepared infusion bag (265 mL to 275 mL) is greater than the volume that will be administered to the patient (240 mL). Because of this overfill, infusion bags may not completely empty during the infusion period.

Note: BLINCYTO® is NOT cytotoxic chemotherapy. Priming with prepared solution will not place persons handling the line at risk of cytotoxic exposure.

STORAGE

- Store at 2°C to 8°C if not used immediately.

HCP: healthcare professional

Reference: 1. BLINCYTO® (blinatumomab) Product Information. www.amgen.com.au/Blincyto.PI.

DOSAGE AND ADMINISTRATION

DEFINING A BLINCYTO® SCHEDULE[1]

It is recommended that the multidisciplinary care team, including prescribing physician, pharmacist and nurse, work with the patient to define a schedule for infusion bag changes.

Below is part of an EXAMPLE schedule for a **adult patient with relapsed or refractory B-ALL weighing ≥45 kg** starting treatment. Please note it is NOT a recommendation of how patients should receive BLINCYTO®; individual hospital regulations and processes as well as each patient's situation need to be taken into consideration.[1]

Day			Treatment setting	Bag prepared by pharmacist	Bag changed by HCP
1	Tuesday	AM	Hospitalisation for 9 days	72-hour bag	
		PM			72-hour bag
2	Wednesday	AM			
		PM			
3	Thursday	AM			
		PM			
4	Friday	AM		96-hour bag	
		PM			96-hour bag
5	Saturday	AM			
		PM			
6	Sunday	AM			
		PM			
7	Monday	AM			
		PM			
8	Tuesday	AM		72-hour bag	
		PM			72-hour bag
9	Wednesday	AM			
		PM			
10	Thursday	AM	Patient returns home		
		PM			
11	Friday	AM	Outpatient visit	96-hour bag	
		PM			96-hour bag
12	Saturday	AM			
		PM			
13	Sunday	AM			
		PM			
14	Monday	AM			
		PM			
15	Tuesday	AM	Outpatient visit	72-hour bag	
		PM			72-hour bag
16	Wednesday	AM			
		PM			
17	Thursday	AM			
		PM			
18	Friday	AM	Outpatient visit	96-hour bag	
		PM			96-hour bag
19	Saturday	AM			
		PM			
20	Sunday	AM			
		PM			
21	Monday	AM			
		PM			
22	Tuesday	AM	Outpatient visit	72-hour bag	
		PM			72-hour bag
23	Wednesday	AM			
		PM			
24	Thursday	AM			
		PM			
25	Friday	AM	Outpatient visit	96-hour bag	
		PM			96-hour bag
26	Saturday	AM			
		PM			
27	Sunday	AM			
		PM			
28	Monday	AM	End of cycle visit		
		PM			
2-week treatment-free interval					

Reference: 1. BLINCYTO® (blinatumomab) Product Information. www.amgen.com.au/Blincyto.PI.

DOSAGE AND ADMINISTRATION

AFTER RECONSTITUTION AND DILUTION[1]

Storage requirements for reconstituted BLINCYTO® and prepared IV bag or cassettes[1]

Maximum storage time of reconstituted BLINCYTO®* solution		Maximum combined storage and infusion time of diluted BLINCYTO®* solution in IV bags or cassette	
Room Temperature (Below 25ºC**)	Refrigerated (2ºC to 8ºC)	Room Temperature (Below 25ºC**)	Refrigerated (2ºC to 8ºC)
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.[1]

Store and transport the prepared IV bag or cassette containing BLINCYTO® solution at 2ºC to 8ºC (Refrigerate. Do not freeze).[1]

DISPOSAL

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.[1]

SPILLAGE

BLINCYTO® is not a cytotoxic chemotherapy.[2] In case of spillage, please follow your hospital or facility's protocol for immunotherapies or biological medicines.

References: 1. BLINCYTO® (blinatumomab) Product Information. www.amgen.com.au/Blincyto.PI. **2.** Amgen Data on File.

DOSAGE AND ADMINISTRATION

BLINCYTO® PRESENTATION AND STORAGE[1]

Pack size: 1 vial BLINCYTO® and 1 vial IV solution stabiliser for BLINCYTO® supplied in a composite pack.[1]

Each BLINCYTO® pack contains:[1]

- BLINCYTO® supplied in a single-use glass vial as a sterile, preservative-free, white to off-white lyophilised powder (38.5 mcg/vial); and
- IV solution stabiliser supplied in a 10 mL single-use glass vial as a sterile, preservative-free, colourless to slightly yellow, clear solution. **Do not use the IV solution stabiliser to reconstitute BLINCYTO®**

Example packaging only.
Package appearance may differ by country.

It is recommended to store unopened BLINCYTO® and 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.[1]

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).[1]

Reference: 1. BLINCYTO® (blinatumomab) Product Information. www.amgen.com.au/Blincyto.PI.

ADVERSE EVENT MANAGEMENT SUMMARY

ADVERSE EVENTS MAY BE CLINICALLY MANAGED WITH TREATMENT INTERRUPTION AND/OR DOSE ADJUSTMENTS[1]

A benefit–risk assessment is recommended to determine whether to reinitiate or permanently discontinue BLINCYTO® treatment.[1]

Warning: The following have occurred in patients receiving BLINCYTO®:[1]

- 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.[1]

- Patients should be closely monitored for signs or symptoms of[1]:
  - Cytokine release syndrome (CRS)
  - Neurological events
  - Infections
  - Tumour lysis syndrome (TLS)
- Management of these events may require either temporary interruption or discontinuation of BLINCYTO®[1]
- The following should also be monitored during BLINCYTO® infusion and treated appropriately:[1]
  - Laboratory parameters (including, but not limited to white blood cell count [WBC] and absolute neutrophil count [ANC])
  - Alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), and total blood bilirubin

Reference: 1. BLINCYTO® (blinatumomab) Product Information. www.amgen.com.au/Blincyto.PI.

ADVERSE EVENT MANAGEMENT

BLINCYTO® ADVERSE EVENT MANAGEMENT

NEUROLOGICAL EVENTS

In patients with relapsed or refractory B-ALL:

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.[1]

Serious and grade ≥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.[1]

The majority of neurologic events (80.7%) were clinically reversible.[1]

The median time to the first event was within the first two weeks of treatment.[1]

One case of fatal encephalopathy has been reported in an earlier phase II single-arm study.[1]

In patients with MRD+ B-ALL:

Neurologic events were reported for 71.5% of adult patients with MRD+ B-ALL of which 22.6% were considered serious.[1]

Grade ≥3 and grade ≥4 events, respectively, were reported for 16.1% and 2.2% of adult patients with MRD+ B-ALL.[1]

Patients receiving BLINCYTO® should be clinically monitored for signs and symptoms of neurologic events.[1]

Management of these signs and symptoms may require either temporary interruption or discontinuation of BLINCYTO®.[1]

Reference: 1. BLINCYTO® (blinatumomab) Product Information. www.amgen.com.au/Blincyto.PI.

ADVERSE EVENT MANAGEMENT

BLINCYTO® ADVERSE EVENT MANAGEMENT

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.[1]

Patients with Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≥2 experienced a higher incidence of serious infections than those with ECOG PS <2.[1]

Monitor patients for signs and symptoms of infection and treat appropriately.

Management of infections may require either temporary interruption or discontinuation of BLINCYTO®.

CYTOKINE RELEASE SYNDROME (CRS)

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 lymphohistiocytosis/macrophage activation syndrome have been reported in the setting of CRS.[1]

To mitigate the risk of CRS, it is important to initiate BLINCYTO® (Cycle 1, Days 1–7) at the recommended starting dose.

Patients should be closely monitored for signs or symptoms of these events.

Management of these events may require either temporary interruption or discontinuation of BLINCYTO®.

TUMOUR LYSIS SYNDROME (TLS)

TLS, which may be life-threatening or fatal, has been observed in patients receiving BLINCYTO®.[1]

Appropriate prophylactic measures including hydration should be used for the prevention of TLS during BLINCYTO® treatment.

Patients receiving BLINCYTO® should be closely monitored for signs and symptoms of TLS.

Management of these events may require either temporary interruption or discontinuation of BLINCYTO®.

Reference: 1. BLINCYTO® (blinatumomab) Product Information. www.amgen.com.au/Blincyto.PI.

ADVERSE EVENT MANAGEMENT

BLINCYTO® ADVERSE EVENT MANAGEMENT

NEUTROPENIA/FEBRILE NEUTROPENIA

Neutropenia and febrile neutropenia, including life-threatening cases, have been observed in patients receiving BLINCYTO®.[1]

Monitor laboratory parameters (including, but not limited to WBC count and ANC) during BLINCYTO® infusion and treat appropriately.

ELEVATED LIVER ENZYMES

Treatment with BLINCYTO® was associated with transient elevations in liver enzymes.[1]

The majority of the events were observed within the first week of BLINCYTO® initiation and did not require interruption or discontinuation of BLINCYTO®.[1]

In the pivotal clinical study with BLINCYTO®, (n=267), 21.7% of patients reported elevated liver enzymes.[1]

Serious and grade ≥3 adverse reactions (such as ALT increased, AST increased, and blood bilirubin increased) were observed in 1.1% and 12.7% of patients respectively.[1]

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®.[1]

Elevated liver enzyme events were reported for 12.4% of adult patients with MRD+ B-ALL.[1]

Grade ≥3 and grade ≥4 events, respectively, were reported for 8.0% and 4.4% of adult patients with MRD+ B-ALL.[1]

The duration of hepatic adverse reactions has generally been brief and with rapid resolution, often when continuing uninterrupted treatment with BLINCYTO®.[1]

Monitor ALT, AST, GGT and total blood bilirubin prior to the start of and during BLINCYTO® treatment[1]

Reference: 1. BLINCYTO® (blinatumomab) Product Information. www.amgen.com.au/Blincyto.PI.

ADVERSE EVENT MANAGEMENT

BLINCYTO® ADVERSE EVENT MANAGEMENT

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.[1]

Evaluate patients who develop signs and symptoms of pancreatitis.[1]

Management of pancreatitis may require either temporary interruption or discontinuation of BLINCYTO®.[1]

INFUSION REACTIONS

Patients should be observed closely for infusion reactions, especially during the first infusion of the first cycle and treated appropriately.[1]

Management of infusion reactions may require either temporary interruption or discontinuation of BLINCYTO®.[1]

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).[1]

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.[1]

RECOMMENDATIONS ABOUT IMMUNISATION

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®.[1]

RECOMMENDATIONS ABOUT CONTRACEPTION

Women of childbearing potential should use contraception during and for at least 48 hours after treatment with BLINCYTO®.[1]

Reference: 1. BLINCYTO® (blinatumomab) Product Information. www.amgen.com.au/Blincyto.PI.

ADVERSE EVENT MANAGEMENT

BLINCYTO® ADVERSE EVENT MONITORING CHECKLIST[1]

What to monitor	How to monitor
Neurological events	• Check for signs of confusion, disorientation, dizziness, tremor and/or seizure, prior to treatment and throughout the treatment cycle including the treatment-free interval. • Consider utilising a writing test periodically to support this monitoring and early detection of neurologic events.
Infection	• Monitor body temperature for fever • Check catheter site for inflammation or swelling
Infusion reactions, especially during the first cycle	• Check body temperature for fever, blood pressure for hypotension, blood tests for increased total bilirubin, and ask patients if nauseous or experiencing any other symptoms
Cytokine release syndrome	• Check body temperature for fever, blood pressure for hypotension, blood tests for increased total bilirubin, and ask patients if nauseous or experiencing any other symptoms
Tumour lysis syndrome	• Urine output and fluid balance should be recorded and assessed frequently • Check for hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia
Laboratory parameters (including WBC and ANC)	• Perform blood tests
Liver enzymes (ALT, AST, GGT and total blood bilirubin)	• Perform blood tests

Reference: 1. BLINCYTO® (blinatumomab) Product Information. www.amgen.com.au/Blincyto.PI.

ADVERSE EVENT MANAGEMENT

BLINCYTO® DOSE ADJUSTMENTS FOR ADVERSE EVENTS[1]

Permanently discontinue BLINCYTO® if Grade 4* CRS occurs.[1]

Dose should be withheld if Grade 3* (severe) CRS occurs.[1]

Once resolved, restart BLINCYTO® in patients weighing ≥45 kg at 9 mcg/day and escalate to 28 mcg/day after 7 days if the toxicity does not recur.[1]

In patients weighing <45 kg, restart BLINCYTO® at 5 mcg/m^2/day and escalate to 15 mcg/m^2/day after 7 days if the toxicity does not recur.[1]

Permanently discontinue BLINCYTO® if Grade 4* neurological event or more than one seizure occurs.[1]

Dose should be withheld if Grade 3* (severe) neurological event occurs until no more than Grade 1 (mild) and for at least 3 days.[1]

Upon improvement to no more than Grade 1 (mild) and after at least 3 days, in patients weighing ≥45 kg, treatment should be reinitiated at 9 mcg/day and escalated to 28 mcg/day after 7 days if the toxicity does not recur. If the toxicity occurred at 9 mcg/day, or if the toxicity takes more than 7 days to resolve, discontinue BLINCYTO® permanently.[1]

Upon improvement to no more than Grade 1 (mild) and after at least 3 days, in patients weighing <45 kg, treatment should be reinitiated at 5 mcg/m^2/day and escalated to 15 mcg/m^2/day after 7 days if the toxicity does not recur. If the toxicity occurred at 5 mcg/m^2/day, or if the toxicity takes more than 7 days to resolve, discontinue BLINCYTO® permanently.[1]

For reinitiation, premedication with 24 mg dexamethasone with a 4-day taper is required.[1]
As secondary prophylaxis, appropriate anticonvulsant medication should be considered in patients weighing ≥45 kg.[1]

Consider permanent discontinuation of BLINCYTO® if Grade 4* adverse reaction occurs.[1]

Dose should be withheld if Grade 3* (severe) adverse reaction occurs.[1]

Once no more than Grade 1 (mild), restart BLINCYTO® in patients weighing ≥45 kg at 9 mcg/day and escalate to 28 mcg/day after 7 days if the toxicity does not recur.[1]

In patients weighing <45 kg, restart BLINCYTO® at 5 mcg/m^2/day and escalate to 15 mcg/m^2/day after 7 days if the toxicity does not recur.[1]

BLINCYTO® should be permanently discontinued if any of the following occur:[1]

- Grade 4* (life-threatening) neurologic event
- More than one seizure
- Neurologic event leading to treatment interruption that requires greater than a week to resolve
- Grade 3* (severe) neurologic event that occurs at 9 mcg/day dose in patients weighing ≥45 kg or 5 mcg/m^2/day dose in those weighing <45 kg leading to treatment interruption
- Grade 4* events other than neurologic events or CRS

A benefit-risk assessment is recommended to determine whether to reinitiate or permanently discontinue BLINCYTO® treatment.[1]

For more information about the safety profile of BLINCYTO®, please refer to the Approved Product Information.[1]

*Grading based on NCI CTCAE 4.0. Grade 3 is severe, and grade 4 is life-threatening.

Reference: 1. BLINCYTO® (blinatumomab) Product Information. www.amgen.com.au/Blincyto.PI.

ADVERSE EVENT MANAGEMENT

USE OF OUTPATIENT CARE[1,2]

OUTPATIENT OPTIONS

When not hospitalised, depending on local availability and requirements and following the decision of the treating physician, patients under treatment with BLINCYTO® may receive ongoing care at an outpatient clinic or another appropriate facility e.g. an infusion centre.

COORDINATION OF CARE TEAM

It is recommended that when transitioning to outpatient care, the care team should be informed about:	**Treatment storage, handling and administration**
	Changing infusion bags or cassettes (e.g. to avoid weekends and holidays)
	Programming of ambulatory pumps
	Infusion bag or cassette storage temperature and expiry date
	Clarity of solution per visual inspection (should be colourless, not cloudy and with no particulates)

Additionally, the person responsible for the patient in the home setting must be able to recognise the symptoms of all adverse events, especially those of grade 3 or higher, including CRS, serious infection and infusion reactions.

REASONS TO RETURN TO HOSPITAL

It is recommended that the patient should return to the primary site of care in the following, but not limited to, cases:

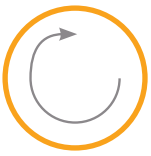
- Unexpected medical events
- Emergence of serious adverse events
- Infusion pump problems
- Maintenance of the infusion set such as pump and port needle change, as needed

Reference: 1. BLINCYTO® (blinatumomab) Product Information. www.amgen.com.au/Blincyto.PI. **2.** Amgen data on file.

ADVERSE EVENT MANAGEMENT

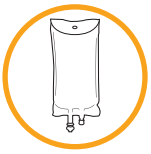
INFORMATION FOR PATIENTS TREATED WITH BLINCYTO®

THIS SECTION CONTAINS SOME USEFUL INFORMATION FOR YOUR PATIENTS ABOUT THEIR TREATMENT WITH BLINCYTO®



TREATMENT CYCLES[1]

Treatment happens in cycles where 1 cycle consists of 4 weeks of continuous treatment. Each cycle is followed by a 2-week treatment-free interval. Patients with R/R B-ALL may receive up to a maximum of 5 cycles of BLINCYTO® treatment. Patients with MRD+ B-ALL may receive up to a maximum of 4 cycles of BLINCYTO® treatment.



THE INFUSION[1]

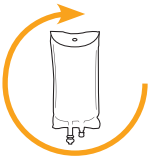
Treatment is given by cIV. This means it enters the body through a tube (often called a "line") that connects to a catheter, which is a special tube that goes into a vein. The medicine slowly enters the body 24 hours a day through this tube.

THE PUMP[2,3]

The pump pushes the treatment from the bag into the body at just the right speed so that the right amount prescribed by the doctor is given.

- ✓ Make sure the tubing stays connected to the pump at all times
- ✓ Do not let the tubing become tangled or twisted at any time
- ✓ Do not lie on the tubing
- ✓ Do not pull the tubing or unplug the pump at any time
- ✓ If there is blood in the tubing, speak to a doctor or nurse as soon as possible
- ✓ Keep the pump, the tubing, and the covering at the insertion site dry at all times

Do not attempt to change the settings on the pump, as this may cause too much or too little treatment to be given.[2]



IV BAG CHANGE OR CASSETTE

- The IV bag or cassette must be changed at least every 96 hours by a healthcare professional for sterility reasons[1]
- The IV bag change must occur within 4 hours of the designated time regardless of the remaining volume in the existing infusion bag[3]

References: 1. BLINCYTO® (blinatumomab) Product Information. www.amgen.com.au/Blincyto.PI. **2.** BLINCYTO® (blinatumomab) Consumer Medicine Information. www.amgen.com.au/Blincyto.CMI. **3.** Amgen Data on File.

ADVERSE EVENT MANAGEMENT

INFORMATION FOR PATIENTS TREATED WITH BLINCYTO®[1]

SIDE EFFECTS

Like all medicines, BLINCYTO® can cause side effects, although not everybody gets them. Some of these side effects may be serious. The doctor will decide what to do based on the type of side effect and how serious it is. If it is a serious side effect, the doctor may temporarily or permanently stop treatment.

Patients should tell their doctor immediately if they 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

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). The doctor will take regular blood tests during treatment with BLINCYTO®.

For very common side effects, common side effects or uncommon side effects, please refer the patient to the Consumer Medicine Information.

If patients experience any side effects, including any not mentioned here, they should talk to their doctor or nurse.

WHEN TO GET HELP

Patients should call their healthcare provider or get emergency medical help immediately if:[1]

- They have any side effects that bother them or do not go away
- They experience seizures, difficulty in speaking or slurred speech, confusion and disorientation, or loss of balance
- They develop chills or shivering, or feel warm; they should take their temperature as they may have a fever – these may be symptoms of an infection
- They develop a reaction at any time during the infusion. Symptoms may include dizziness, face swelling, difficulty breathing, wheezing or rash
- They develop severe and persistent stomach pain, with or without nausea and vomiting. These may be symptoms of a serious and potentially fatal condition known as pancreatitis (inflammation of the pancreas)
- They think they may have been given more treatment than they should, for example, the infusion bag empties before the scheduled bag change
- There is a problem with the pump or the pump alarm sounds
- The pump stops unexpectedly. Advise patients not to try to restart the pump. Their doctor will decide when the next dose should be given

Reference: 1. BLINCYTO® (blinatumomab) Consumer Medicine Information. www.amgen.com.au/Blincyto.CMI.

BLINCYTO® (blinatumomab)

Important Risk Minimisation Information for Doctors

This educational brochure contains important information regarding the administration of BLINCYTO and the risks of medication errors, neurologic events and cytokine release syndrome

This educational material is essential to ensure the safe and effective use of the product and appropriate management of the important selected risks and therefore it is advised to be read carefully before prescribing and administering the medicine

Please ensure each patient or caregiver is provided a copy of the patient educational material and Consumer Medicine Information for reference

This document is not a comprehensive list of Safety events; please refer to the Product Information for further information.

Please refer to the full Approved Product Information before prescribing, available from Amgen Australia Pty Ltd or http://www.amgen.com.au/Blincyto.PI

For more information on BLINCYTO® or to report any adverse events or product complaints involving BLINCYTO please contact Australia Medical Information on 1800 803 638.

Important information regarding BLINCYTO therapy

The following actions should be taken to prevent or minimise the risk of medication errors, neurologic events and cytokine release syndrome.

Medication errors

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

BLINCYTO Recommended Dosage for Relapsed or Refractory B-cell Precursor ALL:

Patient Weight	Treatment Cycle 1			Subsequent Treatment 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 micrograms/day	28 micrograms/day	14-day treatment-free interval	28 micrograms/day	14-day treatment-free interval
Less than 45 kg *(BSA-based dose)*	5 micrograms/m^2/day *(not to exceed 9 micrograms/day)*	15 micrograms/m^2/day *(not to exceed 28 micrograms/day)*		15 micrograms/m^2/day *(not to exceed 28 micrograms/day)*	

BLINCYTO Recommended Dosage for MRD-positive B-cell Precursor ALL:

Patient Weight	**Treatment Cycle(s)**	
	Days 1-28	**Days 29-42**
Greater than or equal to 45 kg *(fixed-dose)*	28 micrograms/day	14-day treatment-free interval

- See Dosage and Administration section of the PI
- To minimise the occurrence of medication errors, please counsel patients on the following:
  - Instruct patients not to unlock the pump
  - If the pump does not appear to perform properly at any time (e.g. alarm goes off), instruct patients and caregivers not to try to fix the pump and tell them to contact you or the nurse immediately
  - Instruct patients not to change any pump settings on purpose (with the exception of stopping the pump in case of emergency)

Neurologic events	• See dosage adjustments section of Product Information for management of severe (Grade 3) and life-threatening (Grade 4) neurologic events
	• Monitor patients for signs and symptoms of neurologic events (e.g. confusion, disorientation, dizziness, tremor, seizure) prior to and throughout the treatment cycle
	• The majority of events resolved following interruption of BLINCYTO, but some resulted in treatment discontinuation
	• Consider utilising a writing test periodically to evaluate for the early detection of neurologic events
	• Be aware that elderly patients may experience a higher rate of neurologic events, including cognitive disorder, encephalopathy, and confusion
	• **Withhold dose if Grade 3 (severe) neurologic event occurs and discontinue BLINCYTO permanently if Grade 4 (life-threatening) neurologic event occurs**
	• The median time to onset of any neurologic toxicity was 9 days, however symptoms may appear earlier or later
	• It is essential to counsel patients regarding the potential neurologic effects and to advise patients:
	  ○ **Not to drive, operate heavy machines or engage in hazardous activities while receiving BLINCYTO**
	  ○ To contact you if they experience neurologic symptoms
	• 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)

Cytokine Release Syndrome (CRS)	• Cytokine Release Syndrome (CRS) which may be life-threatening or fatal has been reported in patients receiving BLINCYTO • Monitor for signs and symptoms of CRS, some of which may be pyrexia, asthenia, headache, hypotension, total bilirubin increased, and nausea; In some cases, disseminated intravascular coagulation, capillary leak syndrome, and haemophagocytic lymphohistiocytosis/macrophage activation syndrome have been reported in the setting of CRS • Highest elevation of cytokines was observed 2 days following the start of BLINCYTO • Management of these events may require temporary interruption or permanent discontinuation of BLINCYTO. Discontinue BLINCYTO permanently if a Grade 4 non-neurologic event occurs • Refer to Dosage and Administration section of Product Information for further information on management of non-neurologic events

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 Precautions and Dosage and Administration).*

Indication: treatment of relapsed or refractory (R/R) B-cell precursor acute lymphoblastic leukaemia (ALL); treatment of minimal residual disease (MRD) positive ALL in patients in complete haematological remission. **Contraindications:** hypersensitivity to blinatumomab, CHO-derived proteins or any excipient. **Precautions:** neurologic events; increased risk for serious infections; cytokine release syndrome; infusion reactions; tumour lysis syndrome, pancreatitis. Management of these adverse reactions may require interruption or discontinuation of treatment. Neutropenia and febrile neutropenia; elevated liver enzymes; leukoencephalopathy; medication errors – strictly follow preparation and administration instructions. Pregnancy Category: C. Use contraception during and for 48 hours after treatment. Discontinue breast-feeding during and for at least 48 hours after treatment. Do not use recommended adult fixed dose in paediatric patients. No data in patients aged less than 28 days. **Interactions:** low potential of clinically meaningful drug interaction with BLINCYTO-mediated cytokine elevation. Vaccination with live viral vaccines not recommended 2 weeks prior to or during treatment, and until recovery of B lymphocytes to normal range following last treatment cycle. **Adverse Reactions:** Common: infections, pyrexia, infusion-related reactions, headache, anaemia, febrile neutropenia, neutropenia, thrombocytopenia, oedema, increased liver enzymes, fatigue, nausea, tremor, hypokalaemia, diarrhoea, chills. See also Precautions for serious adverse reactions. **Dosage & Administration:** R/R ALL: Single cycle is 4 weeks continuous intravenous (cIV) infusion then 2 week treatment free interval. *For patients greater than or equal to 45 kg (fixed dose):* Cycle 1 - starting dose 9 micrograms/day for days 1-7, then 28 micrograms/day for days 8-28. All other cycles 28 micrograms/day for 4 weeks. *For patients less than 45 kg (body surface area based dose*): Cycle 1 - starting dose 5 micrograms/m^2/day for days 1-7 (do not exceed 9 micrograms/day), then 15 micrograms/m^2/day (do not exceed 28 micrograms/day);all other cycles, 15 micrograms/m^2/day (do not exceed 28 micrograms/day). For maintenance, 28 day cIV infusion, then 56 days treatment free. Hospitalise at least first 9 days of Cycle 1 and first 2 days of Cycle 2. Supervision or hospitalisation for other cycle starts and reinitiation. Adults: premedicate with 20 mg IV dexamethasone prior to initiation of each cycle. Intrathecal chemotherapy prophylaxis recommended before and during therapy. Treat with dexamethasone (≤ 24 mg/day) if high tumour burden. Paediatrics: premedicate with dexamethasone 10 mg/m^2 (not to exceed 20 mg) oral or IV 6 to 12 hours prior to start of BLINCYTO (Cycle 1 day 1), followed by premedication with dexamethasone 5 mg/m^2 oral or IV within 30 minutes of start of BLINCYTO (Cycle 1 day 1). MRD+ ALL: 28 day cIV infusion then 14 days treatment free, for up to 4 cycles; premedicate with prednisone 100 mg IV or equivalent 1 hour prior to start of BLINCYTO each cycle; hospitalise first 3 days Cycle 1 and first 2 days Cycle 2, supervise/hospital for subsequent cycle starts and reinitiation – see full PI. R/R & MRD+ ALL - Interrupt Blincyto if grade 3 neurological events, Cytokine Release Syndrome or other clinically relevant adverse reactions occur see full PI. Refer to full Product Information before prescribing; available from Amgen Australia Pty Ltd, Ph: 1800 803 638 or at www.amgen.com.au/Blincyto.PI

BLINCYTO® (blinatumomab)

Important Risk Minimisation Information for Nurses

This educational brochure contains important information regarding the administration of BLINCYTO and the risks of medication errors, neurologic events and cytokine release syndrome

This educational material is essential to ensure the safe and effective use of the product and appropriate management of the important selected risks and therefore it is advised to be read carefully before administering the medicinal product.

Please ensure each patient or caregiver is provided with a copy of the patient educational material and Consumer Medicine Information for reference

If you have any questions about the administration and adverse events of BLINCYTO, please refer to the Product Information (PI) available from Amgen Australia Pty Ltd or http://www.amgen.com.au/Blincyto.PI

For more information on BLINCYTO or to report any adverse events or product complaints involving BLINCYTO please contact Australia Medical Information on 1800 803 638

Important information regarding BLINCYTO therapy

The following actions should be taken to prevent or minimize the risk of medication errors and to provide important counseling information on neurologic events and cytokine release syndrome (CRS)

Administration	IV lines	• Do not flush the infusion lines into the patient, as it will cause an inadvertent bolus of BLINCYTO to be administered. BLINCYTO should be infused through a dedicated lumen.

	Pump specifications and settings	• Only program the pump based on the printed infusion rate on the label attached to the infusion bag.
		• Do not calculate the infusion rate yourself.
		• Lock the pump and make sure the battery is adequately charged with each bag change.
		• If the pump does not appear to perform properly (for example: alarm goes off) at any time, instruct patients and caregivers not to try to fix the pump, tell them to get help from the treating physician or from you immediately
		• Instruct patient:
		  • not to unlock the pump
		  • not to change any pump settings on purpose (with the exception of stopping the pump in case of emergency)
		• Remember to check if the remaining volume of infusion bag correlates with the set infusion rate prior to each bag change. If the remaining volume of infusion bag does not correlate with the set infusion rate prior to each bag change, please record discrepancy and contact the physician for further instruction.

	IV bag or cassette change	• The IV bag or cassette must be changed at least every 96 hours by a healthcare professional for sterility reasons. • The IV bag change must occur within 4 hours of the designated time regardless of the remaining volume in the existing infusion bag.
	Therapy interruption	• Healthcare professional supervision or hospitalisation is recommended in instances where treatment is being re-initiated following an interruption of 4 or more hours.
	Catheter site care	• BLINCYTO solution is a preservative-free solution. Aseptic technique must always be adhered to when administering BLINCYTO. • Instruct the patients and caregivers on how to perform catheter site care as required

Counselling	Neurologic events	• It is essential to monitor patients for signs and symptoms of neurologic events (e.g. confusion, disorientation, dizziness, tremor, seizure) prior to treatment and throughout the treatment cycle including the treatment-free interval. **Should any of these signs and symptoms occur please ensure an urgent clinical assesment is obtained.**
		• Consider utilising a writing test periodically to support this monitoring and early detection of neurologic events.
		• Be aware that serious neurologic events have occurred at a higher frequency in elderly patients (≥ 65 years of age)
		• Counsel patients on the potential neurologic effects and advise patients:
		  • **Not to drive, use heavy machinery, or engage in hazardous activities while receiving BLINCYTO.**
		  • To contact you or the doctor if they experience neurologic symptoms.

	Cytokine Release Syndrome (CRS)	• Cytokine Release Syndrome (CRS) which may be life-threatening or fatal has been reported in patients receiving BLINCYTO. • It is essential to monitor patients closely for signs and symptoms of CRS (e.g pyrexia, asthenia, headache, hypotension, total bilirubin increased, and nausea, in some cases disseminated intravascular coagulation and capillary leak syndrome). **Should any of these signs and symptoms occur, please ensure an urgent clinical assesment is obtained.** • Advise patients to contact you or their doctor if they experience any unusual symptoms

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 Precautions and Dosage and Administration).*

Indication: treatment of relapsed or refractory (R/R) B-cell precursor acute lymphoblastic leukaemia (ALL); treatment of minimal residual disease (MRD) positive ALL in patients in complete haematological remission. **Contraindications:** hypersensitivity to blinatumomab, CHO-derived proteins or any excipient. **Precautions:** neurologic events; increased risk for serious infections; cytokine release syndrome; infusion reactions; tumour lysis syndrome, pancreatitis. Management of these adverse reactions may require interruption or discontinuation of treatment. Neutropenia and febrile neutropenia; elevated liver enzymes; leukoencephalopathy; medication errors – strictly follow preparation and administration instructions. Pregnancy Category: C. Use contraception during and for 48 hours after treatment. Discontinue breast-feeding during and for at least 48 hours after treatment. Do not use recommended adult fixed dose in paediatric patients. No data in patients aged less than 28 days. **Interactions:** low potential of clinically meaningful drug interaction with BLINCYTO-mediated cytokine elevation. Vaccination with live viral vaccines not recommended 2 weeks prior to or during treatment, and until recovery of B lymphocytes to normal range following last treatment cycle. **Adverse Reactions:** Common: infections, pyrexia, infusion-related reactions, headache, anaemia, febrile neutropenia, neutropenia, thrombocytopenia, oedema, increased liver enzymes, fatigue, nausea, tremor, hypokalaemia, diarrhoea, chills. See also Precautions for serious adverse reactions. **Dosage & Administration:** R/R ALL: Single cycle is 4 weeks continuous intravenous (cIV) infusion then 2 week treatment free interval. *For patients greater than or equal to 45 kg (fixed dose):* Cycle 1 - starting dose 9 micrograms/day for days 1-7, then 28 micrograms/day for days 8-28. All other cycles 28 micrograms/day for 4 weeks. *For patients less than 45 kg (body surface area based dose*): Cycle 1 - starting dose 5 micrograms/m^2/day for days 1-7 (do not exceed 9 micrograms/day), then 15 micrograms/m^2/day (do not exceed 28 micrograms/day);all other cycles, 15 micrograms/m^2/day (do not exceed 28 micrograms/day). For maintenance, 28 day cIV infusion, then 56 days treatment free. Hospitalise at least first 9 days of Cycle 1 and first 2 days of Cycle 2. Supervision or hospitalisation for other cycle starts and reinitiation. Adults: premedicate with 20 mg IV dexamethasone prior to initiation of each cycle. Intrathecal chemotherapy prophylaxis recommended before and during therapy. Treat with dexamethasone (≤ 24 mg/day) if high tumour burden. Paediatrics: premedicate with dexamethasone 10 mg/m^2 (not to exceed 20 mg) oral or IV 6 to 12 hours prior to start of BLINCYTO (Cycle 1 day 1), followed by premedication with dexamethasone 5 mg/m^2 oral or IV within 30 minutes of start of BLINCYTO (Cycle 1 day 1). MRD+ ALL: 28 day cIV infusion then 14 days treatment free, for up to 4 cycles; premedicate with prednisone 100 mg IV or equivalent 1 hour prior to start of BLINCYTO each cycle; hospitalise first 3 days Cycle 1 and first 2 days Cycle 2, supervise/hospital for subsequent cycle starts and reinitiation – see full PI. R/R & MRD+ ALL - Interrupt Blincyto if grade 3 neurological events, Cytokine Release Syndrome or other clinically relevant adverse reactions occur see full PI. Refer to full Product Information before prescribing; available from Amgen Australia Pty Ltd, Ph: 1800 803 638 or at www.amgen.com.au/Blincyto.PI

BLINCYTO® (blinatumomab)

Important Risk Minimisation Information for Pharmacists

This preparation card contains important information regarding the reconstitution and preparation procedures for BLINCYTO

To ensure the safe and effective use of BLINCYTO and appropriate management of the important selected risks please read carefully before reconstitution and preparation of the medicinal product

If you have any questions about the reconstitution and preparation of BLINCYTO please refer to the Product Information (PI) available from Amgen Australia Pty Ltd or http://www.amgen.com.au/Blincyto.PI

For more information on BLINCYTO or to report any adverse events or product complaints involving BLINCYTO please contact Australia Medical Information on 1800 803 638

BLINCYTO Preparation Card for Pharmacists

Important information about the preparation of BLINCYTO for INTRAVENOUS administration

Note: for comprehensive preparation instructions, please refer to the Blincyto Product Information

Table 1. Preparation of BLINCYTO infusion solution for INTRAVENOUS administration for patients weighing greater than or equal to 45 kg

Dose	Infusion duration (hours)	Normal Saline (250-mL bag)[a]	IV Solution Stabiliser for BLINCYTO (mL)	Number of BLINCYTO vials needed	Reconstituted BLINCYTO solution (mL)	Infusion rate (mL/hr)
9 mcg/day	24	1	5.5	1	0.83	10
	48	1	5.5	1	1.7	5
	72	1	5.5	1	2.5	3.3
	96	1	5.5	2	3.3	2.5
28 mcg/day	24	1	5.5	1	2.6	10
	48	1	5.5	2	5.2	5
	72	1	5.5	3	8.0	3.3
	96	1	5.5	4	10.7	2.5

[a] Normal saline (0.9% sodium chloride)

Use only polyolefin, PVC non-di-ethylhexylphthalate (non-DEHP), or ethyl vinyl acetate (EVA) infusion bags/pump cassettes and polyolefin, PVC non-DEHP, or EVA intravenous tubing with a sterile, non-pyrogenic, low protein-binding 0.2 micron in-line filter

Table 2. Preparation of BLINCYTO infusion solution for INTRAVENOUS administration for patients weighing less than 45 kg for 5 micrograms/m^2/day dose

Infusion Duration	Normal Saline (250-ml bag)[a]	IV Solution Stabiliser for BLINCYTO (mL)	Infusion Rate	BSA (m^2)	Reconstituted BLINCYTO (mL)	Number of BLINCYTO vials needed
24 hours	1	5.5	10 mL/hour	1.50 – 1.59	0.70	1
	1	5.5		1.40 – 1.49	0.65	1
	1	5.5		1.30 – 1.39	0.61	1
	1	5.5		1.20 – 1.29	0.56	1
	1	5.5		1.10 – 1.19	0.52	1
	1	5.5		1.00 – 1.09	0.47	1
	1	5.5		0.90 – 0.99	0.43	1
	1	5.5		0.80 – 0.89	0.38	1
	1	5.5		0.70 – 0.79	0.34	1
	1	5.5		0.60 – 0.69	0.29	1
	1	5.5		0.50 – 0.59	0.25	1
	1	5.5		0.40 – 0.49	0.20	1

Table 2. Preparation of BLINCYTO infusion solution for INTRAVENOUS administration for patients weighing less than 45 kg for 5 micrograms/m^2/day dose

Infusion Duration	Normal Saline (250-ml bag)[a]	IV Solution Stabiliser for BLINCYTO (mL)	Infusion Rate	BSA (m^2)	Reconstituted BLINCYTO (mL)	Number of BLINCYTO vials needed
48 hours	1	5.5	5 mL/hour	1.50 – 1.59	1.4	1
	1	5.5		1.40 – 1.49	1.3	1
	1	5.5		1.30 – 1.39	1.2	1
	1	5.5		1.20 – 1.29	1.1	1
	1	5.5		1.10 – 1.19	1.0	1
	1	5.5		1.00 – 1.09	0.94	1
	1	5.5		0.90 – 0.99	0.85	1
	1	5.5		0.80 – 0.89	0.76	1
	1	5.5		0.70 – 0.79	0.67	1
	1	5.5		0.60 – 0.69	0.58	1
	1	5.5		0.50 – 0.59	0.49	1
	1	5.5		0.40 – 0.49	0.40	1

Table 2. Preparation of BLINCYTO infusion solution for INTRAVENOUS administration for patients weighing less than 45 kg for 5 micrograms/m^2/day dose

Infusion Duration	Normal Saline (250-ml bag)[a]	IV Solution Stabiliser for BLINCYTO (mL)	Infusion Rate	BSA (m^2)	Reconstituted BLINCYTO (mL)	Number of BLINCYTO vials needed
72 hours	1	5.5	3.3 mL/hour	1.50 – 1.59	2.1	1
	1	5.5		1.40 – 1.49	2.0	1
	1	5.5		1.30 – 1.39	1.8	1
	1	5.5		1.20 – 1.29	1.7	1
	1	5.5		1.10 – 1.19	1.5	1
	1	5.5		1.00 – 1.09	1.4	1
	1	5.5		0.90 – 0.99	1.3	1
	1	5.5		0.80 – 0.89	1.1	1
	1	5.5		0.70 – 0.79	1.01	1
	1	5.5		0.60 – 0.69	0.87	1
	1	5.5		0.50 – 0.59	0.74	1
	1	5.5		0.40 – 0.49	0.60	1

Table 2. Preparation of BLINCYTO infusion solution for INTRAVENOUS administration for patients weighing less than 45 kg for 5 micrograms/m^2/day dose

Infusion Duration	Normal Saline (250-ml bag)[a]	IV Solution Stabiliser for BLINCYTO (mL)	Infusion Rate	BSA (m^2)	Reconstituted BLINCYTO (mL)	Number of BLINCYTO vials needed
96 hours	1	5.5	2.5 mL/hour	1.50 – 1.59	2.8	1
	1	5.5		1.40 – 1.49	2.6	1
	1	5.5		1.30 – 1.39	2.4	1
	1	5.5		1.20 – 1.29	2.2	1
	1	5.5		1.10 – 1.19	2.1	1
	1	5.5		1.00 – 1.09	1.9	1
	1	5.5		0.90 – 0.99	1.7	1
	1	5.5		0.80 – 0.89	1.5	1
	1	5.5		0.70 – 0.79	1.3	1
	1	5.5		0.60 – 0.69	1.2	1
	1	5.5		0.50 – 0.59	0.98	1
	1	5.5		0.40 – 0.49	0.80	1

[a] Normal saline (0.9% sodium chloride)

Use only polyolefin, PVC non-di-ethylhexylphthalate (non-DEHP), or ethyl vinyl acetate (EVA) infusion bags/pump cassettes and polyolefin, PVC non-DEHP, or EVA intravenous tubing with a sterile, non-pyrogenic, low protein-binding 0.2 micron in-line filter

Table 3. Preparation of BLINCYTO infusion solution for INTRAVENOUS administration for patients weighing less than 45 kg for 15 micrograms/m^2/day dose

Infusion Duration	Normal Saline (250-ml bag)[a]	IV Solution Stabiliser for BLINCYTO (mL)	Infusion Rate	BSA (m^2)	Reconstituted BLINCYTO (mL)	Number of BLINCYTO vials needed
24 hours	1	5.5	10 mL/hour	1.50 – 1.59	2.1	1
	1	5.5		1.40 – 1.49	2.0	1
	1	5.5		1.30 – 1.39	1.8	1
	1	5.5		1.20 – 1.29	1.7	1
	1	5.5		1.10 – 1.19	1.5	1
	1	5.5		1.00 – 1.09	1.4	1
	1	5.5		0.90 – 0.99	1.3	1
	1	5.5		0.80 – 0.89	1.1	1
	1	5.5		0.70 – 0.79	1.01	1
	1	5.5		0.60 – 0.69	0.87	1
	1	5.5		0.50 – 0.59	0.74	1
	1	5.5		0.40 – 0.49	0.60	1

Table 3. Preparation of BLINCYTO infusion solution for INTRAVENOUS administration for patients weighing less than 45 kg for 15 micrograms/m^2/day dose

Infusion Duration	Normal Saline (250-ml bag)[a]	IV Solution Stabiliser for BLINCYTO (mL)	Infusion Rate	BSA (m^2)	Reconstituted BLINCYTO (mL)	Number of BLINCYTO vials needed
48 hours	1	5.5	5 mL/hour	1.50 – 1.59	4.2	2
	1	5.5		1.40 – 1.49	3.9	2
	1	5.5		1.30 – 1.39	3.6	2
	1	5.5		1.20 – 1.29	3.4	2
	1	5.5		1.10 – 1.19	3.1	2
	1	5.5		1.00 – 1.09	2.8	1
	1	5.5		0.90 – 0.99	2.6	1
	1	5.5		0.80 – 0.89	2.3	1
	1	5.5		0.70 – 0.79	2.0	1
	1	5.5		0.60 – 0.69	1.7	1
	1	5.5		0.50 – 0.59	1.5	1
	1	5.5		0.40 – 0.49	1.2	1

Table 3. Preparation of BLINCYTO infusion solution for INTRAVENOUS administration for patients weighing less than 45 kg for 15 micrograms/m^2/day dose

Infusion Duration	Normal Saline (250-ml bag)[a]	IV Solution Stabiliser for BLINCYTO (mL)	Infusion Rate	BSA (m^2)	Reconstituted BLINCYTO (mL)	Number of BLINCYTO vials needed
72 hours	1	5.5	3.3 mL/hour	1.50 – 1.59	6.3	3
	1	5.5		1.40 – 1.49	5.9	3
	1	5.5		1.30 – 1.39	5.4	2
	1	5.5		1.20 – 1.29	5.0	2
	1	5.5		1.10 – 1.19	4.6	2
	1	5.5		1.00 – 1.09	4.2	2
	1	5.5		0.90 – 0.99	3.8	2
	1	5.5		0.80 – 0.89	3.4	2
	1	5.5		0.70 – 0.79	3.0	2
	1	5.5		0.60 – 0.69	2.6	1
	1	5.5		0.50 – 0.59	2.2	1
	1	5.5		0.40 – 0.49	1.8	1

Table 3. Preparation of BLINCYTO infusion solution for INTRAVENOUS administration for patients weighing less than 45 kg for 15 micrograms/m^2/day dose

Infusion Duration	Normal Saline (250-ml bag)[a]	IV Solution Stabiliser for BLINCYTO (mL)	Infusion Rate	BSA (m^2)	Reconstituted BLINCYTO (mL)	Number of BLINCYTO vials needed
96 hours	1	5.5	2.5 mL/hour	1.50 – 1.59	8.3	3
	1	5.5		1.40 – 1.49	7.8	3
	1	5.5		1.30 – 1.39	7.3	3
	1	5.5		1.20 – 1.29	6.7	3
	1	5.5		1.10 – 1.19	6.2	3
	1	5.5		1.00 – 1.09	5.6	3
	1	5.5		0.90 – 0.99	5.1	2
	1	5.5		0.80 – 0.89	4.6	2
	1	5.5		0.70 – 0.79	4.0	2
	1	5.5		0.60 – 0.69	3.5	2
	1	5.5		0.50 – 0.59	2.9	2
	1	5.5		0.40 – 0.49	2.4	1

[a] Normal saline (0.9% sodium chloride)

Use only polyolefin, PVC non-di-ethylhexylphthalate (non-DEHP), or ethyl vinyl acetate (EVA) infusion bags/pump cassettes and polyolefin, PVC non-DEHP, or EVA intravenous tubing with a sterile, non-pyrogenic, low protein-binding 0.2 micron in-line filter

Table 4. Steps to prepare BLINCYTO INTRAVENOUS solution under aseptic conditions using aseptic techniques

Step 1	• Transfer appropriate amount of BLINCYTO IV solution stabiliser to the 0.9% sodium chloride infusion bag • Gently mix the contents of the bag to avoid foaming • Discard remaining BLINCYTO IV solution stabiliser vial if applicable
Step 2	• Reconstitute BLINCYTO lyophilised powder vial with 3 mL of Preservative Free Sterile Water for injection • Do not reconstitute BLINCYTO with BLINCYTO IV solution stabiliser • Do not shake • Gently swirl contents to avoid excess foaming • Reconstitute the required number of BLINCYTO vials (see table above) • Visually inspect the reconstituted solution for particulate matter and to confirm colour, the solution should be clear to slightly opalescent, colourless to slightly yellow
Step 3	• Transfer appropriate amount of reconstituted BLINCYTO solution into the 0.9% sodium chloride infusion bag containing IV solution stabilser • Gently mix the contents of the bag to avoid foaming
Step 4	• Attach the intravenous tubing with the sterile 0.2 micron in-line filter to the prepared infusion bag
Step 5	• Remove air from the prepared BLINCYTO infusion solution bag
Step 6	• Prime the intravenous tubing with the prepared BLINCYTO infusion solution • Do not prime the intravenous tubing with 0.9% sodium chloride solution for injection
Step 7	• Store the prepared BLINCYTO infusion solution bags at 2°C to 8°C for a maximum of 10 days if not immediately used (for further information, please see Special precautions for storage section in the Product Information) • Clearly label the prepared IV infusion bag or cassette with the dose, infusion rate and duration of infusion

BLINCYTO Preparation Card for Pharmacists

Important information about the preparation of BLINCYTO CASSETTE for INTRAVENOUS administration

Note: for comprehensive preparation instructions, please refer to the BLINCYTO Product Information

Table 5. Preparation of BLINCYTO CASSETTE for patients weighing greater than or equal to 45 kg

Dose	Infusion duration (hours)	Normal Saline (to be added to 250 mL cassette)[a]	IV Solution Stabiliser for BLINCYTO (mL)	Number of BLINCYTO vials needed	Reconstituted BLINCYTO solution (mL)	Infusion rate (mL/hr)
9 mcg/day	24	244.25	5.0	1	0.75	10
	48	243.5	5.0	1	1.5	5
	72	242.75	5.0	1	2.25	3.3
	96	242	5.0	2	3.0	2.5
28 mcg/day	24	242.7	5.0	1	2.3	10
	48	240.3	5.0	2	4.7	5
	72	238	5.0	3	7.0	3.3
	96	235.7	5.0	4	9.3	2.5

[a]Normal saline (0.9% sodium chloride)

Use only polyolefin, PVC non-di-ethylhexylphthalate (non-DEHP), or ethyl vinyl acetate (EVA) infusion bags/pump cassettes and polyolefin, PVC non-DEHP, or EVA intravenous tubing with a sterile, non-pyrogenic, low protein-binding 0.2 micron in-line filter

Table 6. Preparation of BLINCYTO CASSETTE for patients weighing less than 45 kg for 5 mcg/m^2/day dose

Cassette Duration	Normal Saline (to be added to 250 mL cassette)[a]	IV Solution Stabiliser for BLINCYTO (mL)	Infusion Rate	BSA (m^2)	Reconstituted BLINCYTO (mL)	Number of BLINCYTO vials needed
24 hours	244.35	5.0	10 mL/hour	1.50 – 1.59	0.65	1
	244.40	5.0		1.40 – 1.49	0.60	1
	244.44	5.0		1.30 – 1.39	0.56	1
	244.48	5.0		1.20 – 1.29	0.52	1
	244.52	5.0		1.10 – 1.19	0.48	1
	244.56	5.0		1.00 – 1.09	0.44	1
	244.61	5.0		0.90 – 0.99	0.39	1
	244.65	5.0		0.80 – 0.89	0.35	1
	244.69	5.0		0.70 – 0.79	0.31	1
	244.73	5.0		0.60 – 0.69	0.27	1
	244.77	5.0		0.50 – 0.59	0.23	1
	244.81	5.0		0.40 – 0.49	0.19	1

Table 6. Preparation of BLINCYTO CASSETTE for patients weighing less than 45 kg for 5 mcg/m^2/day dose

Cassette Duration	Normal Saline (to be added to 250 mL cassette)[a]	IV Solution Stabiliser for BLINCYTO (mL)	Infusion Rate	BSA (m^2)	Reconstituted BLINCYTO (mL)	Number of BLINCYTO vials needed
48 hours	243.70	5.0	5 mL/hour	1.50 – 1.59	1.3	1
	243.80	5.0		1.40 – 1.49	1.2	1
	243.90	5.0		1.30 – 1.39	1.1	1
	244.00	5.0		1.20 – 1.29	1.0	1
	244.05	5.0		1.10 – 1.19	0.95	1
	244.13	5.0		1.00 – 1.09	0.87	1
	244.21	5.0		0.90 – 0.99	0.79	1
	244.30	5.0		0.80 – 0.89	0.70	1
	244.38	5.0		0.70 – 0.79	0.62	1
	244.46	5.0		0.60 – 0.69	0.54	1
	244.55	5.0		0.50 – 0.59	0.45	1
	244.63	5.0		0.40 – 0.49	0.37	1

Table 6. Preparation of BLINCYTO CASSETTE for patients weighing less than 45 kg for 5 mcg/m^2/day dose

Cassette Duration	Normal Saline (to be added to 250 mL cassette)[a]	IV Solution Stabiliser for BLINCYTO (mL)	Infusion Rate	BSA (m^2)	Reconstituted BLINCYTO (mL)	Number of BLINCYTO vials needed
72 hours	243.10	5.0	3.3 mL/hour	1.50 – 1.59	1.9	1
	243.20	5.0		1.40 – 1.49	1.8	1
	243.30	5.0		1.30 – 1.39	1.7	1
	243.40	5.0		1.20 – 1.29	1.6	1
	243.60	5.0		1.10 – 1.19	1.4	1
	243.70	5.0		1.00 – 1.09	1.3	1
	243.80	5.0		0.90 – 0.99	1.2	1
	243.90	5.0		0.80 – 0.89	1.1	1
	244.07	5.0		0.70 – 0.79	0.93	1
	244.19	5.0		0.60 – 0.69	0.81	1
	244.32	5.0		0.50 – 0.59	0.68	1
	244.44	5.0		0.40 – 0.49	0.56	1

Table 6. Preparation of BLINCYTO CASSETTE for patients weighing less than 45 kg for 5 mcg/m^2/day dose

Cassette Duration	Normal Saline (to be added to 250 mL cassette)[a]	IV Solution Stabiliser for BLINCYTO (mL)	Infusion Rate	BSA (m^2)	Reconstituted BLINCYTO (mL)	Number of BLINCYTO vials needed
96 hours	242.40	5.0	2.5 mL/hour	1.50 – 1.59	2.6	1
	242.60	5.0		1.40 – 1.49	2.4	1
	242.80	5.0		1.30 – 1.39	2.2	1
	242.90	5.0		1.20 – 1.29	2.1	1
	243.10	5.0		1.10 – 1.19	1.9	1
	243.30	5.0		1.00 – 1.09	1.7	1
	243.40	5.0		0.90 – 0.99	1.6	1
	243.60	5.0		0.80 – 0.89	1.4	1
	243.80	5.0		0.70 – 0.79	1.2	1
	243.90	5.0		0.60 – 0.69	1.1	1
	244.09	5.0		0.50 – 0.59	0.91	1
	244.26	5.0		0.40 – 0.49	0.74	1

[a] Normal saline (0.9% sodium chloride)

Use only polyolefin, PVC non-di-ethylhexylphthalate (non-DEHP), or ethyl vinyl acetate (EVA) infusion bags/pump cassettes and polyolefin, PVC non-DEHP, or EVA intravenous tubing with a sterile, non-pyrogenic, low protein-binding 0.2 micron in-line filter

Table 7. Preparation of BLINCYTO CASSETTE for patients weighing less than 45 kg for 15 mcg/m^2/day dose

Cassette Duration	Normal Saline (to be added to 250 mL cassette)[a]	IV Solution Stabiliser for BLINCYTO (mL)	Infusion Rate	BSA (m^2)	Reconstituted BLINCYTO (mL)	Number of BLINCYTO vials needed
24 hours	243.1	5.0	10 mL/hour	1.50 – 1.59	1.9	1
	243.2	5.0		1.40 – 1.49	1.8	1
	243.3	5.0		1.30 – 1.39	1.7	1
	243.4	5.0		1.20 – 1.29	1.6	1
	243.6	5.0		1.10 – 1.19	1.4	1
	243.7	5.0		1.00 – 1.09	1.3	1
	243.8	5.0		0.90 – 0.99	1.2	1
	243.9	5.0		0.80 – 0.89	1.1	1
	244.07	5.0		0.70 – 0.79	0.93	1
	244.19	5.0		0.60 – 0.69	0.81	1
	244.32	5.0		0.50 – 0.59	0.68	1
	244.44	5.0		0.40 – 0.49	0.56	1

Table 7. Preparation of BLINCYTO CASSETTE for patients weighing less than 45 kg for 15 mcg/m^2/day dose

Cassette Duration	Normal Saline (to be added to 250 mL cassette)[a]	IV Solution Stabiliser for BLINCYTO (mL)	Infusion Rate	BSA (m^2)	Reconstituted BLINCYTO (mL)	Number of BLINCYTO vials needed
48 hours	241.1	5.0	5 mL/hour	1.50 – 1.59	3.9	2
	241.4	5.0		1.40 – 1.49	3.6	2
	241.6	5.0		1.30 – 1.39	3.4	2
	241.9	5.0		1.20 – 1.29	3.1	2
	242.1	5.0		1.10 – 1.19	2.9	2
	242.4	5.0		1.00 – 1.09	2.6	1
	242.6	5.0		0.90 – 0.99	2.4	1
	242.9	5.0		0.80 – 0.89	2.1	1
	243.1	5.0		0.70 – 0.79	1.9	1
	243.4	5.0		0.60 – 0.69	1.6	1
	243.6	5.0		0.50 – 0.59	1.4	1
	243.9	5.0		0.40 – 0.49	1.1	1

Table 7. Preparation of BLINCYTO CASSETTE for patients weighing less than 45 kg for 15 mcg/m^2/day dose

Cassette Duration	Normal Saline (to be added to 250 mL cassette)[a]	IV Solution Stabiliser for BLINCYTO (mL)	Infusion Rate	BSA (m^2)	Reconstituted BLINCYTO (mL)	Number of BLINCYTO vials needed
72 hours	239.2	5.0	3.3 mL/hour	1.50 – 1.59	5.8	3
	239.6	5.0		1.40 – 1.49	5.4	2
	240.0	5.0		1.30 – 1.39	5.0	2
	240.3	5.0		1.20 – 1.29	4.7	2
	240.7	5.0		1.10 – 1.19	4.3	2
	241.1	5.0		1.00 – 1.09	3.9	2
	241.5	5.0		0.90 – 0.99	3.5	2
	241.8	5.0		0.80 – 0.89	3.2	2
	242.2	5.0		0.70 – 0.79	2.8	1
	242.6	5.0		0.60 – 0.69	2.4	1
	243.0	5.0		0.50 – 0.59	2.0	1
	243.3	5.0		0.40 – 0.49	1.7	1

Table 7. Preparation of BLINCYTO CASSETTE for patients weighing less than 45 kg for 15 mcg/m^2/day dose

Cassette Duration	Normal Saline (to be added to 250 mL cassette)[a]	IV Solution Stabiliser for BLINCYTO (mL)	Infusion Rate	BSA (m^2)	Reconstituted BLINCYTO (mL)	Number of BLINCYTO vials needed
96 hours	237.3	5.0	2.5 mL/hour	1.50 – 1.59	7.7	3
	237.8	5.0		1.40 – 1.49	7.2	3
	238.3	5.0		1.30 – 1.39	6.7	3
	238.8	5.0		1.20 – 1.29	6.2	3
	239.3	5.0		1.10 – 1.19	5.7	3
	239.8	5.0		1.00 – 1.09	5.2	2
	240.3	5.0		0.90 – 0.99	4.7	2
	240.8	5.0		0.80 – 0.89	4.2	2
	241.3	5.0		0.70 – 0.79	3.7	2
	241.8	5.0		0.60 – 0.69	3.2	2
	242.3	5.0		0.50 – 0.59	2.7	1
	242.8	5.0		0.40 – 0.49	2.2	1

[a] Normal saline (0.9% sodium chloride)

Use only polyolefin, PVC non-di-ethylhexylphthalate (non-DEHP), or ethyl vinyl acetate (EVA) infusion bags/pump cassettes and polyolefin, PVC non-DEHP, or EVA intravenous tubing with a sterile, non-pyrogenic, low protein-binding 0.2 micron in-line filter

Table 8. Steps to prepare BLINCYTO CASSETTE under aseptic conditions using aseptic techniques

Step 1	• Transfer appropriate amount of 0.9% sodium chloride solution to the cassette
Step 2	• Transfer appropriate amount of BLINCYTO IV solution stabiliser to the cassette • Gently mix the contents of the cassette to avoid foaming • Discard remaining BLINCYTO IV solution stabiliser vial if applicable
Step 3	• Reconstitute BLINCYTO lyophilised powder vial with 3 mL of Preservative Free Sterile Water for injection • Do not reconstitute BLINCYTO with BLINCYTO IV solution stabiliser • Do not shake • Gently swirl contents to avoid excess foaming • Reconstitute the required number of BLINCYTO vials (see table above) as needed • Visually inspect the reconstituted solution for particulate matter and to confirm colour, the solution should be clear to slightly opalescent, colourless to slightly yellow
Step 4	• Transfer appropriate amount of reconstituted BLINCYTO solution into the cassette • Gently mix the contents of the cassette to avoid foaming
Step 5	• Redraw approximately 10 mL of fluid from the cassette and inject back to ensure no BLINCYTO remains in the cassette line • Gently mix again
Step 6	• Remove air from the cassette
Step 7	• Attach the intravenous tubing with the sterile 0.2 micron in-line filter to the cassette
Step 8	• Prime the intravenous tubing with the prepared BLINCYTO solution for infusion • Do not prime the intravenous tubing with 0.9% sodium chloride solution for injection
Step 9	• Store at 2°C to 8°C for a maximum of 10 days if not used immediately • Clearly label the prepared IV infusion bag or cassette with the dose, infusion rate and duration of infusion

BLINCYTO Preparation Card for Pharmacists

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 Precautions and Dosage and Administration).*

Indication: treatment of relapsed or refractory (R/R) B-cell precursor acute lymphoblastic leukaemia (ALL); treatment of minimal residual disease (MRD) positive ALL in patients in complete haematological remission. **Contraindications:** hypersensitivity to blinatumomab, CHO-derived proteins or any excipient. **Precautions:** neurologic events; increased risk for serious infections; cytokine release syndrome; infusion reactions; tumour lysis syndrome, pancreatitis. Management of these adverse reactions may require interruption or discontinuation of treatment. Neutropenia and febrile neutropenia; elevated liver enzymes; leukoencephalopathy; medication errors – strictly follow preparation and administration instructions. Pregnancy Category: C. Use contraception during and for 48 hours after treatment. Discontinue breast-feeding during and for at least 48 hours after treatment. Do not use recommended adult fixed dose in paediatric patients. No data in patients aged less than 28 days. **Interactions:** low potential of clinically meaningful drug interaction with BLINCYTO-mediated cytokine elevation. Vaccination with live viral vaccines not recommended 2 weeks prior to or during treatment, and until recovery of B lymphocytes to normal range following last treatment cycle. **Adverse Reactions:** Common: infections, pyrexia, infusion-related reactions, headache, anaemia, febrile neutropenia, neutropenia, thrombocytopenia, oedema, increased liver enzymes, fatigue, nausea, tremor, hypokalaemia, diarrhoea, chills. See also Precautions for serious adverse reactions. **Dosage & Administration:** R/R ALL: Single cycle is 4 weeks continuous intravenous (cIV) infusion then 2 week treatment free interval. *For patients greater than or equal to 45 kg (fixed dose):* Cycle 1 - starting dose 9 micrograms/day for days 1-7, then 28 micrograms/day for days 8-28. All other cycles 28 micrograms/day for 4 weeks. *For patients less than 45 kg (body surface area based dose*): Cycle 1 - starting dose 5 micrograms/m^2/day for days 1-7 (do not exceed 9 micrograms/day), then 15 micrograms/m^2/day (do not exceed 28 micrograms/day);all other cycles, 15 micrograms/m^2/day (do not exceed 28 micrograms/day). For maintenance, 28 day cIV infusion, then 56 days treatment free. Hospitalise at least first 9 days of Cycle 1 and first 2 days of Cycle 2. Supervision or hospitalisation for other cycle starts and reinitiation. Adults: premedicate with 20 mg IV dexamethasone prior to initiation of each cycle. Intrathecal chemotherapy prophylaxis recommended before and during therapy. Treat with dexamethasone (≤ 24 mg/day) if high tumour burden. Paediatrics: premedicate with dexamethasone 10 mg/m^2 (not to exceed 20 mg) oral or IV 6 to 12 hours prior to start of BLINCYTO (Cycle 1 day 1), followed by premedication with dexamethasone 5 mg/m^2 oral or IV within 30 minutes of start of BLINCYTO (Cycle 1 day 1). MRD+ ALL: 28 day cIV infusion then 14 days treatment free, for up to 4 cycles; premedicate with prednisone 100 mg IV or equivalent 1 hour prior to start of BLINCYTO each cycle; hospitalise first 3 days Cycle 1 and first 2 days Cycle 2, supervise/hospital for subsequent cycle starts and reinitiation – see full PI. R/R & MRD+ ALL - Interrupt Blincyto if grade 3 neurological events, Cytokine Release Syndrome or other clinically relevant adverse reactions occur see full PI. Refer to full Product Information before prescribing; available from Amgen Australia Pty Ltd, Ph: 1800 803 638 or at www.amgen.com.au/Blincyto.PI

BLINCYTO® (blinatumomab)

Important Risk Minimisation Information for Patients and Caregivers

This educational brochure contains important information about BLINCYTO

This educational material is essential to ensure the safe and effective use of the medicine and appropriate management of the important selected adverse reactions. Please read it carefully before taking the medicine.

Please ensure you read the Consumer Medicine Information leaflet for further information on your treatment

If you have any questions about BLINCYTO, please speak to your doctor or nurse.

This information is not intended to replace discussions with your doctor or other health care professionals who are treating your acute lymphoblastic leukaemia. Read the BLINCYTO Consumer Medicine Information provided to you by your health care professional (HCP) before you start treatment. BLINCYTO Consumer Medicine Information is available at www.amgen.com.au/Blincyto.CMI

For more information on BLINCYTO or to report any adverse events or product complaints involving BLINCYTO please contact Australia Medical Information on 1800 803 638

Important things to know about BLINCYTO

Infusion pump and its accessories	• You will receive BLINCYTO solution through an infusion that delivers the medicine directly through a tube inserted into a vein.
	• You will have the pump connected to you 24 hours a day for 28 days.
	• Make sure the tubing stays connected to the pump at all times.
	• **Do not let the tubing become tangled or twisted at any time.**
	• **Do not lie on the tubing.**
	• **Do not change the pump settings on purpose**:
	  ○ If the pump alarm goes off at any time, get help from your doctor or nurse immediately.
	  ○ If the pump stops working unexpectedly or if the infusion bag empties too quickly, get help from your doctor or nurse immediately.
	• **Do not pull the tubing or unplug the pump at any time.**
	• **If you notice blood in the tubing, get help from your doctor or nurse immediately.**
	• Keep the pump, the tubing, and the covering at the site where it is inserted into your vein dry at all times.
	• If you have any concerns regarding how your pump is working, please contact your doctor or nurse.

Nervous system problems	• BLINCYTO may make you feel dizzy, confused, or cause shaky hands, fits or trouble with walking, speaking or writing. • Call your doctor or nurse immediately if you experience these or any other unusual symptoms. For more information, see the Consumer Medicine Information. • **Do not drive your car, use heavy machinery or engage in hazardous activities while receiving this medicine**
Cytokine Release Syndrome	• When receiving BLINCYTO treatment, you might experience an event called cytokine release syndrome that can be caused by the destruction of cancer cells. • You may experience the following symptoms: fever, tiredness or weakness, low blood pressure, nausea, vomiting, skin rash, swelling or chills, shortness of breath, headache and dizziness. If any of the symptoms become severe or you experience any other unusual symptoms, please contact your doctor immediately

Patient Card

Please show this card to all emergency and healthcare providers

Information about BLINCYTO® (blinatumomab)

My name is _____

I am being treated with BLINCYTO, a treatment for acute lymphoblastic leukaemia, which can lower my immune system.

I started treatment on _____

Before providing any treatment, please call my prescribing doctor at the number below. If any medical evaluations are undertaken, please provide copies of all medical records, including any treatments and/or test results, to the doctor(s) named below.

	Name	Hospital	City	Phone Number
Haematologist Oncologist				
Haematology Nurse				

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 Precautions and Dosage and Administration).*

Indication: treatment of relapsed or refractory (R/R) B-cell precursor acute lymphoblastic leukaemia (ALL); treatment of minimal residual disease (MRD) positive ALL in patients in complete haematological remission. **Contraindications:** hypersensitivity to blinatumomab, CHO-derived proteins or any excipient. **Precautions:** neurologic events; increased risk for serious infections; cytokine release syndrome; infusion reactions; tumour lysis syndrome, pancreatitis. Management of these adverse reactions may require interruption or discontinuation of treatment. Neutropenia and febrile neutropenia; elevated liver enzymes; leukoencephalopathy; medication errors – strictly follow preparation and administration instructions. Pregnancy Category: C. Use contraception during and for 48 hours after treatment. Discontinue breast-feeding during and for at least 48 hours after treatment. Do not use recommended adult fixed dose in paediatric patients. No data in patients aged less than 28 days. **Interactions:** low potential of clinically meaningful drug interaction with BLINCYTO-mediated cytokine elevation. Vaccination with live viral vaccines not recommended 2 weeks prior to or during treatment, and until recovery of B lymphocytes to normal range following last treatment cycle. **Adverse Reactions:** Common: infections, pyrexia, infusion-related reactions, headache, anaemia, febrile neutropenia, neutropenia, thrombocytopenia, oedema, increased liver enzymes, fatigue, nausea, tremor, hypokalaemia, diarrhoea, chills. See also Precautions for serious adverse reactions. **Dosage & Administration:** R/R ALL: Single cycle is 4 weeks continuous intravenous (cIV) infusion then 2 week treatment free interval. *For patients greater than or equal to 45 kg (fixed dose):* Cycle 1 - starting dose 9 micrograms/day for days 1-7, then 28 micrograms/day for days 8-28. All other cycles 28 micrograms/day for 4 weeks. *For patients less than 45 kg (body surface area based dose*): Cycle 1 - starting dose 5 micrograms/m^2/day for days 1-7 (do not exceed 9 micrograms/day), then 15 micrograms/m^2/day (do not exceed 28 micrograms/day);all other cycles, 15 micrograms/m^2/day (do not exceed 28 micrograms/day). For maintenance, 28 day cIV infusion, then 56 days treatment free. Hospitalise at least first 9 days of Cycle 1 and first 2 days of Cycle 2. Supervision or hospitalisation for other cycle starts and reinitiation. Adults: premedicate with 20 mg IV dexamethasone prior to initiation of each cycle. Intrathecal chemotherapy prophylaxis recommended before and during therapy. Treat with dexamethasone (≤ 24 mg/day) if high tumour burden. Paediatrics: premedicate with dexamethasone 10 mg/m^2 (not to exceed 20 mg) oral or IV 6 to 12 hours prior to start of BLINCYTO (Cycle 1 day 1), followed by premedication with dexamethasone 5 mg/m^2 oral or IV within 30 minutes of start of BLINCYTO (Cycle 1 day 1). MRD+ ALL: 28 day cIV infusion then 14 days treatment free, for up to 4 cycles; premedicate with prednisone 100 mg IV or equivalent 1 hour prior to start of BLINCYTO each cycle; hospitalise first 3 days Cycle 1 and first 2 days Cycle 2, supervise/hospital for subsequent cycle starts and reinitiation – see full PI. R/R & MRD+ ALL - Interrupt Blincyto if grade 3 neurological events, Cytokine Release Syndrome or other clinically relevant adverse reactions occur see full PI. Refer to full Product Information before prescribing; available from Amgen Australia Pty Ltd, Ph: 1800 803 638 or at www.amgen.com.au/Blincyto.PI

For more information on BLINCYTO® or to report any adverse events or product complaints involving BLINCYTO® please contact Australia Medical Information on 1800 803 638.

PBS Information: Section 100 listed. Authority required.
Refer to PBS Schedule for full Authority listing.

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).

REFER TO FULL PRODUCT INFORMATION BEFORE PRESCRIBING; AVAILABLE FROM AMGEN AUSTRALIA PTY LTD, PH: 1800 803 638 OR AT WWW.AMGEN.COM.AU/BLINCYTO.PI

BLINCYTO® Minimum Product Information: Indication: treatment of relapsed or refractory (R/R) B-cell precursor acute lymphoblastic leukaemia (ALL); treatment of minimal residual disease (MRD) positive ALL in patients in complete haematological remission. **Contraindications:** hypersensitivity to blinatumomab, CHO-derived proteins or any excipient. **Precautions:** neurologic events; increased risk for serious infections; cytokine release syndrome; infusion reactions; tumour lysis syndrome, pancreatitis. Management of these adverse reactions may require interruption or discontinuation of treatment. Neutropenia and febrile neutropenia; elevated liver enzymes; leukoencephalopathy; medication errors – strictly follow preparation and administration instructions. Pregnancy Category: C. Use contraception during and for 48 hours after treatment. Discontinue breast-feeding during and for at least 48 hours after treatment. Do not use recommended adult fixed dose in paediatric patients. No data in patients aged less than 28 days. **Interactions:** low potential of clinically meaningful drug interaction with BLINCYTO-mediated cytokine elevation. Vaccination with live viral vaccines not recommended 2 weeks prior to or during treatment, and until recovery of B lymphocytes to normal range following last treatment cycle. **Adverse Reactions:** Common: infections, pyrexia, infusion-related reactions, headache, anaemia, febrile neutropenia, neutropenia, thrombocytopenia, oedema, increased liver enzymes, fatigue, nausea, tremor, hypokalaemia, diarrhoea, chills. See also Precautions for serious adverse reactions. **Dosage & Administration:** R/R ALL: Single cycle is 4 weeks continuous intravenous (cIV) infusion then 2 week treatment free interval. *For patients greater than or equal to 45 kg (fixed dose):* Cycle 1 – starting dose 9 micrograms/day for days 1-7, then 28 micrograms/day for days 8-28. All other cycles 28 micrograms/day for 4 weeks. *For patients less than 45 kg (body surface area based dose):* Cycle 1 – starting dose 5 micrograms/m^2/day for days 1-7 (do not exceed 9 micrograms/day), then 15 micrograms/m^2/day (do not exceed 28 micrograms/day);all other cycles, 15 micrograms/m^2/day (do not exceed 28 micrograms/day). For maintenance, 28 day cIV infusion, then 56 days treatment free. Hospitalise at least first 9 days of Cycle 1 and first 2 days of Cycle 2. Supervision or hospitalisation for other cycle starts and reinitiation. Adults: premedicate with 20 mg IV dexamethasone prior to initiation of each cycle. Intrathecal chemotherapy prophylaxis recommended before and during therapy. Treat with dexamethasone (≤ 24 mg/day) if high tumour burden. Paediatrics: premedicate with dexamethasone 10 mg/m^2 (not to exceed 20 mg) oral or IV 6 to 12 hours prior to start of BLINCYTO® (Cycle 1 day 1), followed by premedication with dexamethasone 5 mg/m^2 oral or IV within 30 minutes of start of BLINCYTO® (Cycle 1 day 1). MRD+ ALL: 28 day cIV infusion then 14 days treatment free, for up to 4 cycles; premedicate with prednisone 100 mg IV or equivalent 1 hour prior to start of BLINCYTO® each cycle; hospitalise first 3 days Cycle 1 and first 2 days Cycle 2, supervise/hospital for subsequent cycle starts and reinitiation – see full PI. R/R & MRD+ ALL – Interrupt BLINCYTO® if grade 3 neurological events, Cytokine Release Syndrome or other clinically relevant adverse reactions occur see full PI.

BLINCYTO® (blinatumomab)

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