Systemic Anti-Cancer Treatment Protocol

Blinatumomab (Blincyto®)

B-Precursor Acute Lymphoblastic Leukaemia

REF: MPHABLIHA
(Version: 1.0)

Approved for use in:

1. Treatment of patients with B-precursor, CD19 positive, acute lymphoblastic leukaemia (ALL) post intensive first-line induction chemotherapy who are in first haematological complete remission and with minimal residual disease (MRD) ≥ 0.1% and have:

- Philadelphia negative ALL **or**
- Philadelphia positive ALL **(note this is an off-label indication)**

The following criteria must be met:

- Patient must have an ECOG performance status of 0-2
- Patient will be treated with 1 cycle of induction blinatumomab and the potential benefits and risks associated with continued treatment after the first cycle will be assessed
- A maximum of 4 cycles of blinatumomab will be given
- Blinatumomab will be used as monotherapy
- No planned treatment breaks or more than 4 weeks beyond the cycle length are allowed

Blueteq registration required

2. The treatment of relapsed/ refractory Philadelphia negative B precursor acute lymphoblastic leukaemia.

The following criteria must be met:

- Patient must have an ECOG performance status of 0—2

- A maximum of 5 cycles will be administered
- Blinatumomab will be given as monotherapy
- No planned treatment breaks of more than 6 weeks beyond the expected cycle length are allowed

Blueteq registration required

Dosage:

1. Minimal residual disease (MRD) positive after intensive first line chemotherapy

Patient weight	Cycles 1 to 4	
	Day 1 to 28	Days 29 to 42
≥45kg *(fixed dose)*	**28mcg/day** via continuous infusion	14 day treatment free interval
<45kg	Discuss with pharmacy	

- Hospitalisation is recommended for initiation, at a minimum for the first 3 days of cycle 1 (14 days if CNS disease) and the first 2 days of subsequent cycles. Caution should be exercised as cases of late occurrence of first neurological events in the second cycle have been observed.
- Patients who are in complete remission after the first cycle may receive a further 3 consolidation cycles, based on individual benefits-risks assessment

2. Philadelphia chromosome negative **relapsed or refractory** B-precursor ALL

Patient weight	Cycle 1			Cycle 2 to 5	
	Day 1 to 7	Day 8 to 28	Day 29 to 42	Days 1 to 28	Days 29 to 42
≥45kg *(fixed dose)*	**9mcg/day** via continuous infusion	**28mcg/day** via continuous infusion	14 day treatment free interval	**28mcg/day** via continuous infusion	14 day treatment free interval
<45kg *(BSA-based dose)*	**5mcg/m²/day** via continuous infusion *(not to exceed 9mcg/day)*	**15mcg/m²/day** via continuous infusion *(not to exceed 28mcg/day)*		**15mcg/m²/day** via continuous infusion *(not to exceed 28mcg/day)*	

- Hospitalisation is recommended for initiation, at a minimum for the first 9 days of cycle 1 (14 days if CNS disease) and the first 2 days (minimum) of cycle 2. Caution should be exercised as cases of late occurrence of first neurological events in the second cycle have been observed.
- Patients who are in complete remission after the first 2 cycles may receive a further 3 consolidation cycles, based on individual benefits-risks assessment.

Administration:

- See below for information on pre-hydration to reduce the risk of tumour lysis syndrome.
- Monitor for infusion reactions/delayed infusion reactions.
- Please ensure you are familiar with how to use the pump (bodyguard 323 device). Training can be provided if required **(See Appendix 1 of this protocol for further information)**

Supportive treatments:

- Consider use of dexamethasone as pre-phase treatment for patients with high tumour burden (not to exceed 24 mg/day) (≥50% leukaemic blast cells or >15,000/µL peripheral blood leukaemic counts)
- Intrathecal chemotherapy prophylaxis is recommended before and during Blinatumomab therapy, to prevent central nervous system ALL relapse. A suggested regimen would be;
    - Methotrexate 12.5mg at Day minus 2 (mandatory to exclude CNS disease)
    - Methotrexate 12.5mg on Day 15 and Day 28 of each cycle

Pre-medication Prior to each Blinatumomab cycle (Day 1 only):

- Dexamethasone IV 20mg STAT (1 hour prior to the initiation of each cycle.)
- Paracetamol PO 1g STAT.

Supportive medication

- Paracetamol 1g four times a day PRN for pyrexia (PO)
- Anti-uremic therapy as per Haemato-oncology directorate Tumour-lysis policy, including pre-hydration
- Mouth care as per Haemato-oncology directorate Antimicrobial Prophylaxis Policy
- Antimicrobial prophylaxis as per Haemato-oncology directorate Antimicrobial Prophylaxis Policy
- Norethisterone 5-10mg three times a day as clinically indicated (women of childbearing potential)

Cautions:

If the patient has involvement of CNS in their disease, treatment with blinatumomab must not be initiated until clearance of cerebrospinal blasts.

Caution if history of neurological disease (increased risk of toxicity).

Caution should be exercised with monitoring, as cases of late occurrence of first neurological events in the second cycle have been observed.

Women of childbearing potential have to use effective contraception during and for at least 48 hours after treatment with Blinatumomab.

Complications of treatment include cytokine release syndrome, neurotoxicity, tumour lysis syndrome and increased LFTs, see toxicities section for further information.

Blinatumomab has major influence on the ability to drive and use machines. Confusion and disorientation, coordination and balance disorders, risk of seizures and disturbances in consciousness can occur. Due to the potential for neurologic events, patients receiving blinatumomab should refrain from driving, engaging in hazardous

occupations or activities such as driving or operating heavy or potentially dangerous machinery while blinatumomab is being administered. Patients must be advised that they may experience neurologic events.

Emetogenicity

Low risk

Extravasation risk

Non-vesicant, minimal risk

Treatment Schedule:

1. Minimal residual disease positive after intensive first line chemotherapy

All cycles				
Day	**Drug**	**Dosage**	**Route**	**Diluent and Rate**
Cycle 1 to 4 Day 1 Pre-meds	Dexamethasone	20mg	IV	Give ONE HOUR before blinatumomab infusion
	Paracetamol	1g	PO	STAT at least 30 mins before starting
Cycle 1 to 4 Days 1 to 28	**Blinatumomab**	≥45kg 28mcg/day	**Continuous IV infusion**	250ml sodium chloride 0.9%. Infused over 72 or 96 hours • Duration depends on day of bag change. • Rate depends on duration of bag • Administer via non-pyrogenic line with 0.2micron filter
		<45kg Discuss with pharmacy		

Important notes:

1. Do not flush the BLINCYTO® infusion line or intravenous catheter, especially when changing infusion bags. Flushing when changing bags or at completion of infusion can result in excess dosage and complications thereof.

2. Discard appropriately any remaining solution in the bag at the end of the infusion. Not all the solution in the bag will be administered to the patient (only 240ml will be administered). This extra amount is to account for intravenous infusion line loss.

3. When administering via a multi-lumen venous catheter, BLINCYTO should be infused through a dedicated lumen

2. Philadelphia chromosome negative relapsed or refractory B-precursor ALL

All cycles				
Day	**Drug**	**Dosage**	**Route**	**Diluent and Rate**
Cycle 1 Day 1 Pre-meds	Dexamethasone	20mg	IV	Give ONE HOUR before blinatumomab infusion
	Paracetamol	1g	PO	STAT at least 30 mins before starting
Cycle 1 Days 1 to 7	**Blinatumomab**	≥45kg 9mcg/day	**Continuous IV infusion**	250ml sodium chloride 0.9%. Infused over 72 or 96 hours • Duration depends on day of bag change. • Rate depends on duration of bag • Administer via non-pyrogenic line with 0.2micron filter
		<45kg 5mcg/m^2/day		
Cycle 1 Days 8 to 28	**Blinatumomab**	≥45kg 28mcg/day	**Continuous IV infusion**	250ml sodium chloride 0.9%. Infused over 72 or 96 hours • Duration depends on day of bag change. • Rate depends on duration of bag • Administer via non-pyrogenic line with 0.2micron filter
		<45kg 15mcg/m^2/day		
Cycle 2 to 5 Day 1 Pre-meds	Dexamethasone	20mg	IV	Give by slow IV bolus injection Give ONE HOUR before blinatumomab infusion
	Paracetamol	1g	PO	Four times daily for 48 hours
Cycle 2 to 5 Days 1 to 28	**Blinatumomab**	≥45kg 28mcg/day	**Continuous IV infusion**	250ml sodium chloride 0.9%. Infused over 72 or 96 hours • Duration depends on day of bag change. • Rate depends on duration of bag • Administer via non-pyrogenic line with 0.2micron filter
		<45kg 15mcg/m^2/day		

Important notes:

1. Do not flush the BLINCYTO® infusion line or intravenous catheter, especially when changing infusion bags. Flushing when changing bags or at completion of infusion can result in excess dosage and complications thereof.

2. Discard appropriately any remaining solution in the bag at the end of the infusion. Not all the solution in the bag will be administered to the patient (only 240ml will be administered). This extra amount is to account for intravenous infusion line loss.

3. When administering via a multi-lumen venous catheter, BLINCYTO should be infused through a dedicated lumen**.**

Scheduling

1. Starting a cycle

- Treatment can only start on a **Monday, Thursday or Friday**
- Ensure the schedule prescribed matches the booked dates for bag changes outlined below. **Pay particular attention to bank holidays**.
- Patients should be scheduled for starting treatment and for subsequent bag changes in the mornings (from 11am onwards)
- Patients should stick with the same schedule for the duration of their treatment. If a schedule change is required please ensure the new corresponding schedule is prescribed correctly ensuring the prescription is set at the correct cycle number and correct dose.

The patient will have a bag running for 4 days, have a bag change, then the next bag will run for 3 days and then repeat.

Cycle No.	Day	Duration of bag (days)	Blinatumomab Dose, infusion duration and Rate
Cycle 1 to 4 (or 5, depending on indication)	**Day 1**	4	250ml sodium chloride 0.9% infused over **96 hours** at a rate of **2.5ml/hr**
	Day 5	3	250ml sodium chloride 0.9% infused over **72 hours** at a rate of **3.3 mL/hr**
	Day 8	4	250ml sodium chloride 0.9% infused over **96 hours** at a rate of **2.5ml/hr**
	Day 12	3	250ml sodium chloride 0.9% infused over **72 hours** at a rate of **3.3 mL/hr**
	Day 15	4	250ml sodium chloride 0.9% infused over **96 hours** at a rate of **2.5ml/hr**
	Day 19	3	250ml sodium chloride 0.9% infused over **72 hours** at a rate of **3.3 mL/hr**
	Day 22	4	250ml sodium chloride 0.9% infused over **96 hours** at a rate of **2.5ml/hr**
	Day 26	3	250ml sodium chloride 0.9% infused over **72 hours** at a rate of **3.3 mL/hr**

2. Bag changes during cycle

BAG CHANGE days		
Cycle start DAY	**Bag change Days**	**Notes**
MONDAY	MONDAYS & FRIDAYS	Schedule bag change at the same time of the day for each change. The bag change must occur within 4 hours of the designated time regardless of the remaining volume in the existing infusion bag. .
THURSDAY	THURSDAYS & MONDAYS	
FRIDAY	FRIDAYS & TUESDAYS	

Drug Interactions

No formal drug interaction studies have been performed to date. In vitro studies suggest that blinatumomab did not affect CYP450.

Initiation of blinatumomab treatment causes transient release of cytokines during the first days of treatment that may suppress CYP450 enzymes. Therefore patients who are taking CYP450 and transporter substrates with a narrow therapeutic index e.g. warfarin, ciclosporin, tacrolimus etc. should be closely monitored for adverse effects or fluctuating drug concentrations during this time. The dose of the concomitant medicinal product should be adjusted as needed to prevent toxicity.

Main toxicities

Consider discontinuing blinatumomab temporarily or permanently as appropriate for the following severe (grade 3) and life-threatening (grade 4) toxicities. Based on the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Managing active infections may require either temporary interruption or permanent discontinuation of Blinatumomab.

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

interruption in that cycle. If an interruption due to an adverse event is longer than 7 days, start a new cycle. If the toxicity takes more than 14 days to resolve, discontinue BLINCYTO permanently, except if described differently in the table below.

Toxicity	Grade	Action for patients ≥45kg	Action for patients <45kg
Cytokine release syndrome, tumour lysis syndrome	Grade 3	Interrupt treatment until resolved, and then restart at 9mcg/day. Can escalate to 28mcg/day after 7 days if the toxicity does not recur. Liaise with pharmacist if this happens, for manufacturing purposes	Interrupt treatment until resolved, and then restart at 5mcg/m^2/day. Can escalate to 15mcg/m^2/day after 7 days if the toxicity does not recur. Liaise with pharmacist if this happens, for manufacturing purposes
	Grade 4	Discontinue treatment permanently.	Discontinue treatment permanently.
Neurological toxicity	Convulsion	Discontinue treatment permanently if more than one convulsion occurs.	Discontinue treatment permanently if more than one convulsion occurs.
	Grade 3	Interrupt treatment until no more than grade 1 (mild) and for at least 3 days, then restart treatment at 9mcg/day. Can escalate to 28mcg/day after 7days if the toxicity does not recur. Liaise with pharmacist for manufacturing purposes For reinitiating, premedicate with 24mg of dexamethasone. Then reduce dexamethasone step-wise over 4days. If the toxicity occurred at 9mcg/day, or if the toxicity takes more than 7days to resolve, permanently discontinue.	Interrupt treatment until no more than grade 1 (mild) and for at least 3 days, then restart treatment at 5mcg/m^2/day, (Liaise with pharmacist if this happens, for manufacturing purposes) If the toxicity takes more than 7 days to resolve, discontinue treatment permanently.
	Grade 4	Discontinue treatment permanently.	Discontinue treatment permanently.
Elevated liver enzymes	Grade 3	If clinically relevant, interrupt treatment until no more than grade 1 (mild), and then restart treatment at 9mcg/day. Can escalate to 28mcg/day after 7 days if the toxicity does not recur. Liaise with pharmacist for manufacturing purposes	If clinically relevant, interrupt treatment until no more than grade 1 (mild), and then restart treatment at 5mcg/m^2/day. Escalate to 15mcg/m^2/day after 7 days if the toxicity does not recur. Liaise with pharmacist for manufacturing purposes
	Grade 4	Consider discontinuing treatment permanently.	Consider discontinuing treatment permanently.
Other clinically relevant (as determined by treating physician) adverse reactions	Grade 3	Interrupt treatment until no more than grade 1 (mild), then restart treatment at 9mcg/day. Escalate to 28mcg/day after 7 days if the toxicity does not recur. Liaise with pharmacist for manufacturing purposes	Interrupt treatment until no more than grade 1 (mild), then restart treatment at 5mcg/m^2/day. Escalate to 15mcg/m^2/day after 7 days if the toxicity does not recur. Liaise with pharmacist for manufacturing purposes
	Grade 4	Consider discontinuing treatment permanently.	Consider discontinuing treatment permanently.

Investigations and treatment plan

	Pre	Cycle 1	Mid cycle bag changes	Cycle 2	Cycle 3	Cycle 4+	Ongoing
Clinical review	X	X		X	X	X	Every cycle
SACT Assessment (including PS and toxicity assessment)	X	X		X	X	X	Every cycle
ANP review			X				Review and neurological examination
Neurological Examination	X	X	X	X	X	X	Repeat at regular intervals during therapy (daily while an in-patient and then each time bag changed thereafter). **See appendix 2 for further information**
Blood pressure/ Pulse/ Temperature/ Respiratory rate		X	X	X	X	X	Monitor regularly for 48 hours cycles 1 and 2. Monitor for the first hour subsequent cycles.
Bone Marrow Assessment	X						Repeat as clinically indicated
FBC	X	X	X	X	X	X	
Magnesium, DAT, ESR, Immunoglobulins, β2 microglobulin	X						Repeat as clinically indicated
Hepatitis B core antibody and surface antigen, Hep C antibody, EBV, CMV, VZV, HIV 1+2 (after consent)	X						
U&E, LFT, Uric Acid, LDH, Bone profile	X	X	X	X	X	X	Every cycle
CrCl	X						As clinically indicated thereafter
Informed Consent	X						
Weight recorded	X	X		X	X	X	Every cycle
Height	X						
Pregnancy test	X						Where appropriate

Dose Modifications and Toxicity Management:

If treatment is interrupted by **≥4 hours**, supervision by a healthcare professional or hospitalisation is recommended on re-initiation.

Treatment interruption **< 7 days**: Continue the same cycle to a total 28 days of infusion, inclusive of days before and after the interruption in that cycle.

Treatment interruption **> 7 days**: Start a new cycle

Treatment interruption **> 14days**: Discontinue Blinatumomab permanently, except if described differently in the table below.

Haematological toxicity:

Proceed on day 1 if all apply:-

ANC ≥ 1.0 x 10^9/L	Platelets ≥ 100 x 10^9/L
Hb ≤80g/L	

Delay 1 week on day 1 if any apply:-

ANC <1.0 x 10^9/L	Platelets <100 x 10^9/L
Hb >80g/L	

Non-Haematological toxicity:

Renal	No dose adjustments required in mild to moderate renal impairment Safety and efficacy has not been studied in severe renal impairment
Hepatic	No dose adjustments required. No safety and efficacy has been studied in severe hepatic impairment Note that significantly impaired hepatic function might be a sign of disease progression and require cessation or change of treatment. **Always discuss deteriorating organ function with consultant**

Drug specific management:

Cytokine release storm and infusion reactions	Cytokine release syndrome (CRS) which may be life-threatening or fatal (grade ≥ 4) has been reported in patients receiving BLINCYTO (see section 4.8). Serious adverse events that may be signs and symptoms of CRS included pyrexia, asthenia, headache, hypotension, total bilirubin increased, and nausea; uncommonly, these events led to BLINCYTO discontinuation. The median time to onset of a CRS event was 2 days. Patients should be closely monitored for signs or symptoms of these events. Disseminated intravascular coagulation (DIC) and capillary leak syndrome (CLS, e.g. hypotension, hypoalbuminaemia, oedema and haemoconcentration) have been commonly associated with CRS. Patients experiencing capillary leak syndrome should be managed promptly. Haemophagocytic histiocytosis/macrophage activation syndrome (MAS) has been uncommonly reported in the setting of CRS. Infusion reactions may be clinically indistinguishable from manifestations of CRS. The infusion reactions were generally rapid, occurring within 48 hours after initiating infusion. However some patients reported delayed onset of infusion reactions or in later cycles. Patients should be observed closely for infusion reactions, especially during the initiation of the first and second treatment cycles and treated appropriately. Anti-pyretic use (e.g. paracetamol) is recommended to help reduce pyrexia during the first 48 hours of each cycle. To mitigate the risk of CRS, it is important to initiate BLINCYTO (cycle 1, days 1-7) at the recommended starting dose. Management of these events may require either temporary interruption or discontinuation of BLINCYTO.
Tumour lysis syndrome	Tumour lysis syndrome (TLS), which may be life-threatening or fatal (grade ≥ 4) has been observed in patients receiving BLINCYTO. Appropriate prophylactic measures including aggressive hydration and anti-hyperuricaemic therapy (such as allopurinol or rasburicase) should be used for the prevention and treatment of TLS during BLINCYTO treatment, especially in patients with higher leukocytosis or a high tumour burden. Patients should be closely monitored for signs or symptoms of TLS, including renal function and fluid balance in the first 48 hours after the first infusion. In clinical studies, patients with moderate renal impairment showed an increased incidence of TLS compared with patients with mild renal impairment or normal renal function. Management of these events may require either temporary interruption or discontinuation of BLINCYTO.

Medication errors:

Medication errors have been observed with the use of Blinatumomab as it is quite a complex regimen. It is very important that the instructions for preparation and administration are strictly followed to minimise medication errors.

Ensure that you are confident/ competent in setting the appropriate pump for use. Training and guidance can be provided (see Appendix 1 for further information)

References:

1. Summary of Product Characteristics Blinatumomab (Blincyto®) last updated 25 January 2019 Accessed via https://www.medicines.org.uk/emc/product/5064
2. National Institute of Health, National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) version v4.03: June 14, 2010. Available online from https://www.eortc.be/services/doc/ctc/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf
3. NICE TA450. Blinatumomab for previously treated Philadelphia-chromosome-negative acute lymphoblastic leukaemia. The National Institute for Health and Care Excellence (2017).
4. Haemato-Oncology Policy: Prophylaxis of Infection in Neutropenic/Immunocompromised Haemato-Oncology Patients (currently only available via Sharepoint)
5. RLUH Tumour Lysis Policy

Appendix one – Administration information and advice

- Follow the instructions in the attached manual to test, set up, prime and run the Blinatumomab infusion via the Bodyguard 323 pump.
- Note once the line has been primed the volume to be infused from each bag is 240ml
- The infusion rate will depend on whether you are giving 72 hour or 96 hour infusion – refer to the protocol for correct rate
- If further assistance is required and for technical issues, the company can be contacted on the number below
- The pump and lines can be found on the haematology day ward

Pump instruction manual:

https://infusystem.com/images/manuals/Bodyguard%20323.pdf

Pump Company Contact Details:

Tel: 01253 894 646

Website: www.cmemedical.co.uk

Drug company contact details:

Contact pharmacy if specific drug information or training is required (e.g. management of toxicities) who can contact a pharmaceutical representative

Appendix 2 – Neurotoxicity examination

- Neurological examination should only be carried out by a suitably competent doctor or Associate Nurse Practitioner (ANP).

Neurological examination should include:

1. Mental status

https://www.msdmanuals.com/professional/neurologic-disorders/neurologic-examination/how-to-assess-mental-status

2. Cranial nerve assessment

https://www.msdmanuals.com/en-gb/professional/neurologic-disorders/neurologic-examination/how-to-assess-the-cranial-nerves

3. Motor system

https://www.msdmanuals.com/en-gb/professional/neurologic-disorders/neurologic-examination/how-to-assess-the-motor-system

4. Sensory system

https://www.msdmanuals.com/en-sg/professional/neurologic-disorders/neurologic-examination/how-to-assess-sensation

5. Coordination and gait.

https://www.msdmanuals.com/professional/neurologic-disorders/neurologic-examination/how-to-assess-gait,-stance,-and-coordination