Blinatumomab for Relapsed Paediatric ALL - Consolidation Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved reimbursement status*
As monotherapy for the treatment of paediatric patients aged 1 year or older with high-risk first relapsed Philadelphia chromosome negative CD19 positive B-precursor acute lymphoblastic leukaemia (ALL) as part of the consolidation therapy.	C91	P00707a	ODMS 01/05/2022

*For post 2012 indications

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.

The requirement for INTRATHECAL prophylaxis should be considered before and during therapy to prevent central nervous system ALL relapse. Please refer to the relevant protocol for INTRATHECAL prophylaxis.

Patients may receive 1 cycle of blinatumomab after induction. A single cycle of treatment is 28 days (4 weeks) of continuous infusion.

- Hospitalisation is recommended at a minimum for the first 9 days of the cycle.
    - In patients with a history or presence of clinically relevant CNS pathology, hospitalisation is recommended at a minimum for the first 14 days of the cycle. Caution should be exercised as cases of late occurrence of first neurological events have been observed.
    - For re-initiation (e.g. if treatment is interrupted for 4 or more hours), supervision by a healthcare professional or hospitalisation is recommended.

Facilities to treat anaphylaxis MUST be present when systemic anti-cancer therapy (SACT) is administered.

Day	Drug	Dose for patients greater than or equal to 45 kg (fixed-dose)	Dose for patients less than 45 kg (BSA-based dose)	Route
1-7	Blinatumomab	[a]9 mcg/day	[a]5 mcg/m^2/day *(not to exceed 9 mcg/day)*	[b]Continuous IV infusion
8-28	Blinatumomab	28 mcg/day	15 mcg/m^2/day *(not to exceed 28 mcg/day)*	[b]Continuous IV infusion

[a]Starting dose may be increased at the discretion of the prescribing Consultant.

Prescribing note: mcg ≡ micrograms ≡ µg

[b]Blinatumomab is administered as a continuous intravenous infusion delivered at constant flow rate using an infusion pump. **The infusion pump should be programmable, lockable and have an alarm. Elastomeric pumps should not be used.** The infusion bag must be changed at least every 96 hours for sterility reasons. **Prepared doses of blinatumomab once removed from the refrigerator or attached to the patient, it has an expiry of ONLY 96 hours.**

It must be administered using intravenous tubing that contains an in-line, sterile, non-pyrogenic, low-protein binding 0.2 micrometre in-line filter. Blinatumomab should be infused through a dedicated lumen.

Important note: The giving set must be primed with blinatumomab and not with NaCl 0.9% (may be carried out in Aseptic Compounding Unit (ACU)- liaise with pharmacy). Do not flush the blinatumomab 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. Nursing staff must record the time and date of removal from refrigerator on the Blinatumomab label or on administration record on the space provided.

PRE-PHASE STEROIDS:

For patients with high tumour burden i.e. for patients with ≥ 50% leukaemic blasts or > 15,000/microlitre peripheral blood leukaemic blast counts, treat with pre-phase dexAMETHasone (10mg/m^2/day up to a maximum of 24 mg/day) for 5 days

ELIGIBILITY:

- Indications as above
- Patients with Philadelphia chromosome negative (Ph-) high-risk (HR) first relapse B-precursor ALL
- Patients with bone marrow blast percentage < 5% (M1) by flow cytometry on day 15 of induction treatment OR bone marrow blast percentage < 1% on day 29 of induction therapy OR blast percentage in line with indications for blinatumomab as per the guideline for HR relapse
- Age ≥1 and <18 years
- Adequate organ function

EXCLUSIONS:

- Hypersensitivity to blinatumomab or to any of the excipients
- Clinically relevant central nervous system (CNS) pathology requiring treatment (e.g. unstable epilepsy)
- Breast-feeding
- Pregnancy

- Known infection with human immunodeficiency virus (HIV) or chronic infection with hepatitis B virus (HBsAg positive) or hepatitis C virus (anti-HCV positive)

PRESCRIPTIVE AUTHORITY:

- The treatment plan must be initiated by a Consultant Haematologist working in the area of paediatric haematological malignancies

TESTS:

Baseline tests:

- FBC, renal and liver profile
- Coagulation screen
- Ferritin
- IgG, IgA, IgM
- HSV PCR (serum) if history of HSV +ve stomatitis
- Uric acid
- Urinalysis via dipstick
- Neurological assessment
- CSF examination
- Virology screen: All patients should be tested for both HBsAg and HBcAb as per local policy and Hepatitis C
- Pregnancy test in female post-menarchal adolescents

Regular tests:

- FBC, renal and liver profile on day 1, 2, 8 and 15 of cycle
- Uric acid
- Coagulation Screen
- Clinical age-specific monitoring for signs and symptoms of neurologic events
- 6 hourly neurological observations on days 1, 2, 8 and 9

Disease monitoring:

Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant.

Renal and Hepatic Impairment:

Table 1: Dose modification of blinatumomab in renal and hepatic impairment

Renal Impairment	Hepatic Impairment
Based on pharmacokinetic analyses, dose adjustment is not necessary in patients with mild to moderate renal dysfunction. The safety and efficacy of blinatumomab have not been studied in patients with severe renal impairment.	Based on pharmacokinetic analyses, no effect of baseline liver function on blinatumomab exposure is expected and adjustment of the initial dose is not necessary. The safety and efficacy of blinatumomab have not been studied in patients with severe hepatic impairment.
Dose modifications from SmPC	

Management of adverse events:

- Consideration to discontinue blinatumomab temporarily or permanently as appropriate should be made in the case of the following severe (grade 3) or life-threatening (grade 4) toxicities:
  - cytokine release syndrome
  - tumour lysis syndrome
  - neurological toxicity
  - Elevated liver enzymes and any other clinically relevant toxicities
- **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 blinatumomab permanently, except if described differently in Table 2 below:

Table 2: Dose modifications of blinatumomab for adverse events

Toxicity	Grade*	Action for patients greater than or equal to 45 kg	Action for patients less than 45 kg
All	1-2	Refer to local policy	
Cytokine release syndrome, tumour lysis syndrome	3	Stop blinatumomab and treat with dexAMETHasone 0.4mg/kg/day (maximum 24mg/day) IV, in 3 divided doses until resolved. Give IV tocilizumab[i] 8mg/kg. Do not re-start blinatumomab unless discussed and agreed with a Haematology Consultant.	Stop blinatumomab and treat with dexAMETHasone 0.4mg/kg/day (maximum 24mg/day) IV, in 3 divided doses until resolved. Wean over 4 days Give IV tocilizumab[i] 12mg/kg if <30kg, or 8mg/kg IV if ≥ 30kg. Do not restart blinatumomab unless discussed and agreed with a Haematology Consultant.
	4	As for grade 3. Discontinue blinatumomab permanently.	
Neurological toxicity	Convulsion	Discontinue blinatumomab permanently if more than one convulsion occurs.	
	3	Stop blinatumomab. Give dexAMETHasone 0.4mg/kg/day (max 24mg/day) in 3 divided doses until symptoms resolve.	Stop blinatumomab. Give dexAMETHasone 0.4mg/kg/day until symptoms subside or until no more than grade 1 (mild) and for at least 3 days then restart blinatumomab at 5 micrograms/m^2/day (or 3.75micrograms/m^2/day if on 5micrograms/m^2/day when event occurred). Wean dexAMETHasone over 4 days. If the toxicity takes more than 7 days to resolve, discontinue blinatumomab permanently.
	4	As for grade 3. Discontinue blinatumomab permanently.	

Elevated Liver Enzymes	3	If clinically relevant, interrupt blinatumomab until no more than grade 1 (mild) then restart blinatumomab at 9 mcg/day. Escalate to 28 mcg/day after 7 days if the toxicity does not recur.	If clinically relevant, interrupt blinatumomab until no more than grade 1 (mild) then restart blinatumomab at 5 mcg/m^2/day. Escalate to 15 mcg/m^2/day after 7 days if the toxicity does not recur.
	4	Consider discontinuing blinatumomab permanently.	
Other clinically relevant (as determined by treating physician) adverse reactions	3	Interrupt blinatumomab until no more than grade 1 (mild) then restart blinatumomab at 9 mcg/day. Escalate to 28 mcg/day after 7 days if the toxicity does not recur	Interrupt blinatumomab until no more than grade 1 (mild) then restart blinatumomab at 5mcg/m^2/day. Escalate to 15 mcg/m^2/day after 7 days if the toxicity does not recur
	4	Consider discontinuing blinatumomab permanently.	
Death	5		
*Based on the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Grade 3 is severe, and grade 4 is life threatening.			

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

- As outlined in NCCP Classification Document for Systemic Anti Cancer Therapy (SACT) Induced Nausea and Vomiting Available on the NCCP website

Blinatumomab: Low **(Refer to local policy).**

For information:

Within NCIS regimens, anti-emetics have been standardised by the Medical Oncologists and Haemato-oncologists and information is available in the following document:

- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Medical Oncology) - Available on the NCCP website
- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Haemato-oncology) - Available on the NCCP website

PREMEDICATIONS:

In paediatric patients, dexAMETHasone 10 mg/m^2 (not to exceed 20mg) should be administered orally or intravenously 6-12 hours prior to the start of blinatumomab (day 1). This should be

followed by dexAMETHasone 5mg/m^2 (orally or Intravenously) within 30 minutes PRIOR TO the start of blinatumomab (day 1). This may be omitted if disease burden <5%.
If blinatumomab infusion is stopped for four hours or more in children with a high disease burden, repeat intravenous dexAMETHasone pre-med 5mg/m^2 30 minutes prior to re-starting the infusion.

- Prior to dose escalations or re-initiation after an interruption (e.g. from 5 micrograms/m^2/day to 15 micrograms/m^2/day) repeat dexAMETHasone 5mg/m^2 pre-medication x 1 dose

OTHER SUPPORTIVE CARE:

- Anti-pyretic use (e.g. paracetamol) is recommended to reduce pyrexia during the first 48 hours of each treatment cycle
- INTRATHECAL prophylaxis should be considered before and during therapy to prevent central nervous system ALL relapse
- PJP prophylaxis (**Refer to local policy)**
- Cytokine Release Syndrome treatment (see Table 2 above and **refer to local policy**)
- **Strict fluid balance and weight:**
  - 4 hourly fluid balance. Give furosemide if clinically indicated after discussion with consultant.
  - Daily weight and girth, may need to be twice daily if signs of CRS/ascites.
- **Observations:** During the first 24 hours of infusion, temperature pulse and respirations should be monitored to detect signs of infusion reaction and/or CRS. BP and neuro-observations should be taken every 4 hours during the first 24 hours, or more frequently if clinical concerns. If the child remains stable after 24 hours, observations can be taken every 4 hours (including neuro-observations) until the first 72 hours of infusion are complete. If unstable discuss with clinician.
- **Neurological examination:** Clinical team must complete a neurological examination daily for at least the first 72 hours of infusion.
- **Antifungal Prophylaxis:** Not routinely indicated unless the child has a history of fungal infection or they have been neutropenic for a significant period of time.

ADVERSE EFFECTS

- ***Blinatumomab* is subject to additional monitoring. Healthcare professionals are asked to report any suspected adverse reactions.**

- Please refer to the relevant Summary of Product Characteristics (SmPC) for details.

DRUG INTERACTIONS:

- Current SmPC and drug interaction databases should be consulted for more information.

COMPANY SUPPORT RESOURCES/Useful Links:

Please note that this is for information only and does not constitute endorsement by the NCCP

Healthcare professional educational resources:

Physicians:
https://www.hpra.ie/img/uploaded/swedocuments/db50722b-c274-4090-98f1-187aa2ca2a06.pdf
Nurses:
https://www.hpra.ie/img/uploaded/swedocuments/83ef7f9a-252c-49e9-8880-25382ad02d83.pdf
Pharmacists:
https://www.hpra.ie/img/uploaded/swedocuments/56262718-93af-4a41-a4f8-ec413a974494.pdf

Patient educational resources:

Patient alert card:
https://www.hpra.ie/img/uploaded/swedocuments/1b89ca15-1888-41dd-9680-8479ab91da22.pdf
Guide for Patients/Caregivers:
https://www.hpra.ie/img/uploaded/swedocuments/5ec91c7d-6c38-424c-8c57-0db39d24a86d.pdf

REFERENCES:

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2. O'Connor et al, Relapsed ALL UK Guideline v.1 January 2021
3. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V6 2025. Available at: https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/nccp-classification-document-for-systemic-anti-cancer-therapy-sact-induced-nausea-and-vomiting.pdf
4. Blinatumomab (BLINCYTO®) Summary of Product characteristics. Accessed January 2024. Available at: https://www.ema.europa.eu/en/documents/product-information/blincyto-epar-product-information_en.pdf

Version	Date	Amendment	Approved By
1	06/05/2022		Dr Andrea Malone
2	20/06/2024	Reviewed. Updated Table 2 and footnote. Added black triangle status. Updated premedication section.	Dr Andrea Malone

		Updated other supportive care section.	
2a	20/06/2024	Updated in line with NCCP Standardisation	NCCP
2b	25/03/2025	Additional note added to treatment table regarding dosage units.	NCCP

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] This is an unlicensed indication for the use of Tocilizumab (Table 2) in Ireland. Patient's should be informed of this and consented to treatment in line with the hospital's policy on the use of unlicensed medication and unlicensed or "off label" indications. Prescribers should be fully aware of their responsibility in communicating any relevant information to the patient and also ensuring that the unlicensed or "off label" indication has been acknowledged by the hospital's Drugs and Therapeutics Committee, or equivalent, in line with hospital policy.