Blinatumomab Paediatric 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 Philadelphia chromosome negative CD19 positive B-cell precursor ALL which is refractory or in relapse after receiving at least two prior therapies or in relapse after receiving prior allogeneic hematopoietic stem cell transplantation.	C91	P00567a	ODMS 01/05/2019

*For post 2012 indications only

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.

A single cycle of treatment is 42 days (6 weeks). This includes 28 days (4 weeks) of continuous infusion and 14 days (2 week) treatment-free interval.

- Patients receive 2 cycles of treatment as a bridge to transplant.

- Hospitalisation is recommended for initiation at a minimum for:
  - the first 9 days of the first cycle
  - the first 2 days of the second cycle

- In patients with a history or presence of clinically relevant central nervous system (CNS) pathology, hospitalisation is recommended at a minimum for the first 14 days of the first cycle.
  - In the second cycle, hospitalisation is recommended at a minimum for 2 days (or as per clinician). Caution should be exercised as cases of late occurrence of first neurological events in the second cycle have been observed.

- For all subsequent cycle starts and 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	Cycle
1-7	Blinatumomab	[a]9 mcg/day	5 mcg/m^2/day *(not to exceed 9 mcg/day)*	[b]Continuous IV infusion	1 (42 day cycle)
8-28	Blinatumomab	28 mcg/day	15 mcg/m^2/day *(not to exceed 28 mcg/day)*	[b]Continuous IV infusion	
1-28	Blinatumomab	28 mcg/day	15 mcg/m^2/day *(not to exceed 28 mcg/day)*	[b]Continuous IV infusion	2 (42 day cycle)

[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 of 2.5mL/hr 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. **Prepared doses of blinatumomab has an expiry of 10 days, however 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 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. ACU prepare an infusion containing 250mL plus overage to allow for priming of line and for not flushing the line between administrations.
Once the patient is stabilised (after initial 4 days), blinatumomab can be made in CADD cassettes to be infused via a CADD Legacy® Ambulatory pumps (or equivalent approved ambulatory pump). The cassette will contain 250mL of which 240mL should be infused. Prepared doses of blinatumomab have an expiry of 10 days when stored at 2-8°C, however, it has an expiry of ONLY 96 hours once removed from refrigerator/ once attached to the patient. Nursing staff must record the time and date of removal from refrigerator on the Blinatumomab label 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
- Greater than 25% blasts in marrow or MRD > 1 x 10^{-3} pre HSCT
- Karnofsky performance status ≥ 50% for patients ≥ 16 years and Lansky Performance Status (LPS) of ≥ 50% for patients < 16 years

EXCLUSIONS:

- Hypersensitivity to the blinatumomab or to any of the excipients
- Breast-feeding
- Pregnancy
- Isolated extramedullary disease
- Prior anti-CD19 therapy
- 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 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 each 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: Management of adverse events

Toxicity	Grade*	Action for patients greater than or equal to 45 kg	Action for patients less than 45 kg
Cytokine release syndrome, Tumour lysis syndrome. See also local policy.	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. 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 1 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) 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 micrograms/day. Escalate to 28 micrograms/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 micrograms/ m^2/day. Escalate to 15 micrograms/m^2/day after 7 days if the toxicity does not recur.
	4	Consider discontinuing blinatumomab permanently.	
	5	Death	
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 micrograms/day. Escalate to 28 micrograms/day after 7 days if the toxicity does not recur.	Interrupt blinatumomab until no more than grade 1 (mild), then restart blinatumomab at 5micrograms/m^2/day. Escalate to 15 micrograms/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.**			

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

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

Blinatumumab: 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 (cycle 1, day 1). This should be followed by dexAMETHasone 5mg/m^2 (orally or Intravenously) within 30 minutes PRIOR TO the start of blinatumomab (cycle 1, day 1).
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 intravenous dexAMETHasone 5mg/m^2

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. Gore et al. Survival after blinatumomab treatment in pediatric patients with relapse/refractory B-Cell precursor acute lymphoblastic leukemia. Blood Cancer Journal (2018) 8:80
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®) – Clarification of premedication with dexAMETHasone in paediatric patients Safety update. Available at: https://www.hpra.ie/docs/default-source/default-document-library/important-safety-information---blincyto-(blinatumomab)fd5b0c2697826eee9b55ff00008c97d0.pdf?sfvrsn=0
5. Blinatumomab (Blincyto®) Summary of product characteristics. Accessed Jan 2024. Available at: https://www.ema.europa.eu/en/documents/product-information/blincyto-epar-product-information_en.pdf

Version	Date	Amendment	Approved By
1			Dr Andrea Malone
2	06/09/2019	Clarification regarding administration of dexAMETHasone as premedication in line with safety update	Dr Andrea Malone
3	31/12/2021	Regimen reviewed.	Dr Andrea Malone
4	20/06/2024	Reviewed. Updated Table 2 and footer. Updated Other Supportive Care Section.	Dr Andrea Malone
4a	20/06/2024	Updated in line with NCCP standardisation.	NCCP
4b	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.