Blinatumomab for Relapsed Paediatric ALL: Consolidation Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	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

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 proophylaxis.

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 the blinatumomab is administered.

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

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

[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 sodium chloride 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. 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.

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

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).

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**)

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS:

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

- **Neurologic events**: Neurologic events including events with a fatal outcome have been observed. Grade 3 (CTCAE version 4.0) or higher (severe or life-threatening) neurologic events following initiation of blinatumomab administration included encephalopathy, seizures, speech disorders, disturbances in consciousness, confusion and disorientation, and coordination and balance disorders. Among patients that experienced a neurologic event, the median time to the first event was within the first two weeks of treatment and the majority of events resolved after treatment interruption and infrequently led to blinatumomab treatment discontinuation. It is recommended that a neurological examination be performed in patients prior to starting blinatumomab therapy and that patients be clinically monitored for signs and symptoms of neurologic events (e.g. writing test). Management of these signs and symptoms to resolution may require either temporary interruption or permanent discontinuation of blinatumomab. In the event of a seizure, secondary prophylaxis with appropriate anticonvulsant medicinal products (e.g. levetiracetam) is recommended.

- **Infections:** Patients receiving blinatumomab should be clinically monitored for signs and symptoms of infection and treated appropriately. Management of infections may require either temporary interruption or discontinuation of blinatumomab.
- **Cytokine release syndrome and infusion reactions:** Cases of potentially life-threatening cytokine release syndrome (CRS) have been reported in patients receiving blinatumomab. Serious adverse events included pyrexia, asthenia, headache, hypotension, elevated liver enzymes, total bilirubin increased, and nausea. In some cases, disseminated intravascular coagulation (DIC) and capillary leak syndrome and haemophagocytic lymphohistiocytosis/macrophage activation syndrome have been 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. 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 treatment. To mitigate the risk of CRS, it is important to initiate blinatumomab at the recommended starting dose. Management of these events may require either temporary interruption or discontinuation to blinatumomab therapy.
- **Tumour lysis syndrome**: Tumour lysis syndrome (TLS), which may be life-threatening or fatal (grade ≥ 4) has been observed in patients receiving blinatumomab. 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 blinatumomab 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 blinatumomab.
- **Neutropenia and febrile neutropenia**: Neutropenia and febrile neutropenia, including life-threatening cases, have been observed in patients receiving blinatumomab. Laboratory parameters (including, but not limited to white blood cell count and absolute neutrophil count) should be monitored routinely during blinatumomab infusion, especially during the first 9 days of treatment, and treated appropriately.
- **Elevated liver enzymes:** Treatment with blinatumomab was associated with transient elevations in liver enzymes. The majority of the events were observed within the first week of treatment initiation and did not require interruption or discontinuation of blinatumomab. Monitoring of alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), and total blood bilirubin prior to the start of and during blinatumomab treatment (especially during the first 48 hours of treatment) should be performed. Management of these events may require either temporary interruption or discontinuation of blinatumomab.
- **Pancreatitis:** Pancreatitis, life threatening or fatal, has been reported in patients receiving blinatumomab in clinical trials and the post-marketing setting. High-dose steroid therapy may have contributed, in some cases, to the pancreatitis. Patients should be closely monitored for signs and symptoms of pancreatitis. Patient evaluation may include physical examination, laboratory evaluation for serum amylase and serum lipase, and abdominal imaging, such as ultrasound and

other appropriate diagnostic measures. Management of pancreatitis may require either temporary interruption or discontinuation of blinatumomab.

- **Leukoencephalopathy including progressive multifocal leukoencephalopathy**: Cranial magnetic resonance imaging (MRI) changes showing leukoencephalopathy have been observed in patients receiving blinatumomab, 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. Due to the potential for progressive multifocal leukoencephalopathy (PML), patients should be monitored for signs and symptoms. In case of suspicious events consider consultation with a neurologist, brain MRI and examination of cerebral spinal fluid (CSF).
- **Immunisations**: The safety of immunisation with live viral vaccines during or following blinatumomab therapy has not been studied. Vaccination with live virus vaccines is not recommended for at least 2 weeks prior to the start of treatment, during treatment, and until recovery of B lymphocytes to normal ranges following last treatment cycle. Due to the potential depletion of B-cells in newborns following exposure to blinatumomab during pregnancy, newborns should be monitored for B-cell depletion and vaccinations with live virus vaccines should be postponed until the infant's B-cell count has recovered.
- **Contraception**: For female post-menarchal adolescents, effective contraception should be used during and for at least 48 hours, after treatment with blinatumomab.

DRUG INTERACTIONS:

- Current drug interaction databases should be consulted for more information.
- No formal drug interaction studies have been performed.
- Initiation of blinatumomab treatment causes transient release of cytokines during the first days of treatment that may suppress CYP450 enzymes. Patients who are receiving medicinal products that are CYP450 and transporter substrates with a narrow therapeutic index should be monitored for adverse effects (e.g. warfarin) or drug concentrations (e.g. cyclosporine) during this time. The dose of the concomitant medicinal product should be adjusted as needed.

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:

1. Locatelli F, et al. Effect of Blinatumomab vs Chemotherapy on Event-Free Survival Among Children with High-risk First-relapse B-Cell Acute Lymphoblastic Leukaemia: A Randomised Clinical Trial. JAMA 2021; 325(9): 843-854. Available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7926287/
2. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V3 2021. 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
3. BLINCYTO® (blinatumomab) Summary of Product characteristics. Accessed April 2022. 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

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] This is an unlicensed indication for the use of Blinatumomab 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.