Blinatumomab Paediatric Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	*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	P0567a	ODMS 01/05/2019

**If the reimbursement status is not defined[1], the indication has yet to be assessed through the formal HSE reimbursement process.*

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

Day	Drug	Dose for patients greater than or equal to 45KG (fixed-dose)	Dose for patients less than 45 kg (BSA-based dose)	Route	Cycle
1-7	Blinatumomab	[a]9 micrograms/day	5 micrograms/m^2/day *(not to exceed 9 micrograms/day)*	[b]Continuous IV infusion	1 (42 day cycle)
8-28	Blinatumomab	28 micrograms/day	15 micrograms/m^2/day *(not to exceed 28 micrograms/day)*	[b]Continuous IV infusion	
1-28	Blinatumomab	28 micrograms/day	15 micrograms/m^2/day *(not to exceed 28 micrograms/day)*	[ab]Continuous IV infusion	2 (42 day cycle)

[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 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 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. 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 250mls of which 240mls 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

ELIGIBILTY:

- 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.

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 3 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[ii] 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[ii] 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 three divided dosed 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/kg/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	
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.	

*** Based on the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.**

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 (cycle 1, day 1) This should be followed by dexamethasone 5mg/m^2 (orally or Intravenously) within 30 minutes of 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 3 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.

This medicinal product is subject to additional monitoring. Healthcare professionals are asked to report any suspected adverse reactions.

- **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
- **Infusion reactions** are very common within the first few hours of the blinatumomab infusion commencing. It is usually in the form of fever +/- flu-like symptoms. If convinced this is an infusion reaction (and not cytokine release syndrome), it can be managed symptomatically using

paracetamol and chlorphenamine and hydrocortisone. There is no need to stop the infusion, unless there are other signs of cytokine release syndrome. Blood cultures and CRP should be taken, and consider antibiotic cover as per supportive care protocol if there is clinical concern or patient is neutropenic.

- **Cytokine release syndrome and infusion reactions:** Potentially life-threatening cytokine release syndromes (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, capillary leak syndrome, and haemophagocytic lymphohistiocytosis/macrophage activation syndrome have been reported in the setting of CRS. Patients should be closely monitored for signs or symptoms of these events. 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 blinatumomab (cycle 1, days 1-7) 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 the first cycle, 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 the first 2 cycles 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 v 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

DRUG INTERACTIONS:

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

ATC CODE:

Blinatumomab - L01XC19

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/0b9576a7-7f72-49b7-8f5d-3cb8335c8d42.pdf
Nurses:
https://www.hpra.ie/img/uploaded/swedocuments/991ee8b4-58ae-4767-96a6-ae03f5ce0254.pdf
Pharmacists:
https://www.hpra.ie/img/uploaded/swedocuments/88ff3d35-7b9a-473d-a0cb-aa9abacfaa8b.pdf

REFERENCES:

1. Stackelberg, A et al. Phase I/Phase II Study of Blinatumomab in Pediatric Patients With Relapsed/Refractory Acute Lymphoblastic Leukemia. J Clin Oncol 2016;34:4381-4389

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. Blincyto® Summary of product characteristics accessed May2019. 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

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] ODMS – Oncology Drug Management System
CDS – Community Drug Schemes (CDS) including the High Tech arrangements of the PCRS community drug schemes
Further details on the Cancer Drug Management Programme is available at;
http://www.hse.ie/eng/services/list/5/cancer/profinfo/medonc/cdmp/

[ii] This is an unlicensed indication for the use of tocilizumab 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