Blinatumomab Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	*Reimbursement Status
Treatment of adult patients with relapsed or refractory B cell precursor (BCP) Philadelphia chromosome negative acute lymphoblastic leukaemia (ALL) who have received no prior salvage treatment for relapsed/refractory (R/R) disease and are considered eligible for transplant (i.e. as a bridge-to-transplant).	C91	00538a	ODMS 01/05/2019

**If the reimbursement status is not defined [i], 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	Route	Cycle
1-7	Blinatumomab	9mcg/day	[a]Continuous IV infusion	1 (42 day cycle)
8-28	Blinatumomab	28mcg/day	[a]Continuous IV infusion	
1-28	Blinatumomab	28mcg/day	[a]Continuous IV infusion	2 (42 day cycle)

[a] 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. There is a choice of bag change frequency (Table 1). However, the target therapeutic dose of blinatumomab delivered does not change.
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: 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.
Please refer to the Summary of Product Characteristics for detailed information on the preparation and administration of blinatumomab.

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

Table 1: Planned bag change frequency and infusion rate

Planned bag change frequency	Infusion rate
Every 24 hours	10ml/hour
Every 48 hours	5ml/hour
Every 72 hours	3.3ml/hour
Every 96 hours	2.5ml/hour

ELIGIBILTY:

- Indications as above
- ECOG 0-2

EXCLUSIONS:

- Hypersensitivity to the blinatumomab or to any of the excipients
- Breast-feeding
- Pregnancy
- Isolated extramedullary disease
- Active ALL in the CNS (confirmed by CSF analysis) or testes (ensure no clinical sign thereof)
- 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
- Uric acid
- Urinalysis via dipstick
- Neurological assessment
- Virology screen: All patients should be tested for both HBsAg and HBcAb as per local policy and Hepatitis C
- Pregnancy test
- CSF immunophenotyping to exclude CNS involvement
- IgG, IgA, IgM

Regular tests:

- FBC, Renal and liver profile on day 1, 2, 8 and 15 of each cycle
- Uric acid
- Coagulation Screen
- Clinical monitoring for signs and symptoms of neurologic events. This should include a weekly "writing test" where patient writes a simple sentence in their medical records
- Monthly GAMs

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 2: 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 3: Management of adverse events

Toxicity	Grade	Action
Cytokine release syndrome, tumour lysis syndrome	3	Interrupt blinatumomab until resolved, then restart blinatumomab at 9 mcg/day. Escalate to 28 mcg/day after 7 days if the toxicity does not recur
	4	Discontinue blinatumomab permanently
Neurological toxicity	Convulsion	Discontinue blinatumomab permanently if more than 1 convulsion occurs
	3	Interrupt blinatumomab until no more than grade 1 (mild) and for at least 3 days, then restart blinatumomab at 9 mcg/day. Escalate to 28 mcg/day after 7 days if the toxicity does not recur. For reinitiation, premedicate with a 24 mg dose of dexamethasone. Then reduce dexamethasone step-wise over 4 days. If the toxicity occurred at 9 mcg/day, or if the toxicity takes more than 7 days to resolve, discontinue blinatumomab permanently
	4	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
	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
	4	Consider discontinuing blinatumomab permanently.

SUPPORTIVE CARE:

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

PREMEDICATIONS:

Dexamethasone 20 mg intravenous should be administered 1 hour prior to initiation of each cycle of blinatumomab therapy.

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
- Proton pump Inhibitor (**Refer to local policy).**

- PJP prophylaxis (**Refer to local policy).**
- Anti-viral prophylaxis (**Refer to local policy).**
- Anti-fungal prophylaxis (**Refer to local policy).**
- Oral hygiene (**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. The median time from initiation of blinatumomab to onset of a neurologic event was 9 days. The majority of events resolved after treatment interruption. Elderly patients experienced a higher rate of neurological toxicities, including cognitive disorder, encephalopathy, and confusion. Patients with a medical history of neurologic signs and symptoms (such as dizziness, hypoaesthesia, hyporeflexia, tremor, dysaesthesia, paraesthesia, memory impairment) demonstrated a higher rate of neurologic events (such as tremor, dizziness, confusional state, encephalopathy and ataxia). The median time to onset of a neurologic event in these patients was 12 days.
  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:** Potentially life-threatening cytokine release syndrome (CRS) have been reported in patients receiving blinatumomab. Infusion reactions have also occurred and may be clinically indistinguishable from manifestations of CRS.
  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. Management of CRS events may require either temporary interruption or discontinuation of blinatumomab.
- **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 BLINCYTO 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.

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:

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2. Dombret H, Topps MS et al. Blinatumomab vs SOC Chemotherapy in First Salvage Compared with second or greater salvage in a Phase 3 Study. Presented at 22nd Congress of the European hematology . Association;June22-25, 2017; Abstract S478
3. BLINCYTO Summary of Product Characteristics. Accessed October 2018. Available at https://www.ema.europa.eu/documents/product-information/blincyto-epar-product-information_en.pdf

Version	Date	Amendment	Approved By
1	01/05/2019		Dr Larry Bacon

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/