Blinatumomab Therapy (ALL with MRD ≥ 0.1%)

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
As monotherapy for the treatment of adults with Philadelphia chromosome negative CD19 positive B-precursor acute lymphoblastic leukaemia (ALL) in first or second complete remission with minimal residual disease (MRD) greater than or equal to 0.1%	C91	00590	ODMS 01/02/2021

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 may receive 1 cycle of induction treatment followed by up to 3 additional cycles of blinatumomab consolidation treatment.

- The majority of patients who respond to blinatumomab achieve a response after 1 cycle Therefore, the potential benefit and risks associated with continued therapy in patients who do not show haematological and/or clinical improvement after 1 treatment cycle should be assessed by the treating physician.

- Hospitalisation is recommended for initiation at a minimum for:
  - the first 3 days of the first cycle
  - the first 2 days of subsequent cycles.

- 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

  Recommended dose (for patients at least 45 kg in weight)

Day	Drug	Dose	Route	Cycle
1-28	Blinatumomab	28 micrograms/day	[a]Continuous IV infusion	**Induction cycle 1** (42 day cycle)
29-42	TREATMENT FREE INTERVAL			
1-28	Blinatumomab	28 micrograms/day	[a]Continuous IV infusion	**Consolidation cycle 2-4** (42 day cycle)
29-42	TREATMENT FREE INTERVAL			

[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.

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

ELIGIBILITY:

- Indications as above
- ECOG 0-1
- Patients with B-precursor acute lymphoblastic leukemia (ALL) in complete hematologic remission (CR) defined as less than 5% blasts in bone marrow after at least 3 intense chemotherapy blocks.
- Presence of minimal residual disease (MRD)
    - at a level of $\geq 10^{-3}$ (molecular failure or molecular relapse) in an assay with a minimum sensitivity of 10^{-4} documented after an interval of at least 2 weeks from last systemic chemotherapy
      or
    - at a level of $\geq 10^{-4}$ by multiparamater flow cytometry in an assay with a minimum sensitivity of 10^{-4} documented after an interval of at least 2 weeks from last systemic chemotherapy
- Haematologic criteria for remission as defined below:
    - <5% blasts
    - Absolute neutrophil count ≥1,000/µL
    - Platelets ≥50,000/µL (transfusion permitted)
    - Haemoglobin level ≥9 g/dL (transfusion permitted)

- Adequate renal and hepatic function

EXCLUSIONS:

- Hypersensitivity to blinatumomab or to any of the excipients
- Pregnancy or breast feeding
- Presence of circulating blasts or current extramedullary involvement by ALL
- History of or active relevant autoimmune disease
- Current CNS leukaemia (confirmed by CSF analysis)
- 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:

- Clinical testing of MRD using a validated assay with minimum sensitivity of 10^{-4}
- 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 IgG, IgA, IgM

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	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
	Convulsion	Discontinue blinatumomab permanently if more than 1 convulsion occurs
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.
*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 : Minimal (Refer to local policy).

PREMEDICATIONS:

Prednisone 100 mg intravenously or dexamethasone 16 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*. Blinatumomab is subject to additional monitoring. Healthcare professionals are asked to report any suspected adverse reactions.**

- **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.
- **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.
- **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.
- **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.
- **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.

- **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.
- **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.
- **Women of childbearing potential/contraception in females**: Blinatumomab should not be used during pregnancy unless the potential benefit outweighs the potential risk to the foetus. Women of childbearing potential have to use effective contraception during and for at least 48 hours after treatment with 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.

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/44849cf5-26a1-4998-9b2a-9a7cf6ab8fdf.pdf

Nurses:
https://www.hpra.ie/img/uploaded/swedocuments/3d587bd2-4db1-43bf-a72f-e6bbe8b21118.pdf

Pharmacists:
https://www.hpra.ie/img/uploaded/swedocuments/ffb0071a-3d78-4fcb-bc8e-fe9a5d3f1837.pdf

Patient educational resources:

Patient alert card:
https://www.hpra.ie/img/uploaded/swedocuments/149fa061-10fd-4371-8a2f-f47eb2333cde.pdf

Patient and carer brochure:

https://www.hpra.ie/img/uploaded/swedocuments/c99920e0-5146-41b6-a3e3-1c043e9c0c6b.pdf

REFERENCES:

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2. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V4 2022. 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® SmPC. Last updated: 05/11/2019. Accessed October 2022. Available at: https://www.ema.europa.eu/en/documents/product-information/blincyto-epar-product-information_en.pdf

Version	Date	Amendment	Approved By
1	01/02/2021		NCCP Lymphoid Clinical Advisory Group
2	04/10/2022	Reviewed. Updated adverse events	Dr Larry Bacon

Comments and feedback welcome at oncologydrugs@cancercontrol.ie