BLINCYTO®▼ (blinatumomab)

Important Risk Minimisation Information for Physicians

This educational brochure contains important information regarding the administration of BLINCYTO and the risks of medication errors and neurologic events

This educational material is essential to ensure the safe and effective use of the product and appropriate management of the important selected risks and therefore it is advised to be read carefully before prescribing and administering the medicinal product

If you have any questions about the administration and the adverse events of BLINCYTO, refer to the Summary of Product Characteristics (SmPC), on the European Medicines Agency website under following link: https://www.ema.europa.eu/en/medicines/human/EPAR/blincyto#product-information-section.

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions to the Medicines Authority by post or e-mail: ADR reporting/ Sir Temi Zammit Building, Malta Life Sciences Park, San Gwann or on www.medicinesauthority.gov.mt/adrportal

BLINCYTO® (blinatumomab)

This guide has been developed as part of a Risk Management Plan (RMP) for prescribers involved in the care of patients treated with BLINCYTO, to provide you with further information about some of the risks (neurologic events and medication errors) associated with the use of BLINCYTO.

What is BLINCYTO®?

BLINCYTO is a bispecific T-cell engager antibody construct that binds specifically to CD19 expressed on the surface of cells of B-lineage origin and CD3 expressed on the surface of T-cells. Blincyto is indicated as:

- monotherapy for the treatment of adults with Philadelphia chromosome negative CD19 positive relapsed or refractory B-precursor acute lymphoblastic leukaemia (ALL)
- monotherapy for the treatment of adults with Philadelphia chromosome negative CD19 positive B-precursor ALL in first or second complete remission with minimal residual disease (MRD) greater than or equal to 0.1%
- monotherapy for the treatment of paediatric patients aged 1 year or older with Philadelphia chromosome negative CD19 positive B 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

Overview of BLINCYTO treatment

Patients will receive BLINCYTO by continuous intravenous infusion.

- For the treatment of Philadelphia chromosome negative relapsed or refractory B-precursor ALL, 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

- For the treatment of Philadelphia chromosome negative MRD positive B-precursor ALL, hospitalisation is recommended at a minimum for
  - the first 3 days of the first cycle
  - the first 2 days of subsequent cycles
- Supervision by healthcare professional or hospitalisation is recommended for all subsequent cycle starts and reinitiation (eg, if treatment is interrupted for 4 or more hours)
- In patients with a history or presence of clinically relevant central nervous system (CNS) pathology (see section 4.4 of the SmPC), 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, and clinical judgment should be based on tolerance to blinatumomab in the first cycle. Caution should be exercised as cases of late occurrence of first neurological events have been observed.

Posology for Philadelphia chromosome negative relapsed or refractory B-precursor ALL

A single treatment cycle consists of 28 days (4 weeks) of continuous BLINCYTO infusion. Each cycle of treatment is separated by a 14 day (2-week) treatment-free interval. Patients may receive 2 cycles of treatment. Patients who have achieved complete remission (CR/CRh) after 2 treatment cycles may receive up to 3 additional cycles of BLINCYTO for consolidation treatment, based on an individual benefit-risk assessment.

Recommended daily dose is by patient weight. Patients greater than or equal to 45 kg receive a fixed-dose and for patients less than 45 kg, the dose is calculated using the patient's body surface area (BSA). In adult patients, dexamethasone 20 mg intravenous should be administered 1 hour prior to initiation of each cycle of BLINCYTO therapy.

In paediatric patients, dexamethasone 10 mg/m^2 (not to exceed 20 mg) should be administered orally or intravenously 6 to 12 hours prior to the start of BLINCYTO (cycle 1, day 1). This should be followed by dexamethasone 5 mg/m^2 orally or intravenously within 30 minutes prior to the start of BLINCYTO (cycle 1, day 1).

Recommended dose (for patients greater than or equal to 45 kg or less than 45 kg in weight) is provided below in Table 1.

Table 1. Recommended dose for Philadelphia chromosome negative relapsed or refractory B-precursor ALL

Patient weight	Cycle 1			Subsequent cycles	
	Days 1-7	Days 8-28	Days 29-42	Days 1-28	Days 29-42
Greater than or equal to 45 kg *(fixed-dose)*	9 mcg/day via continuous infusion	28 mcg/day via continuous infusion	14 day treatment free interval	28 mcg/day via continuous infusion	14 day treatment free interval
Less than 45 kg *(BSA-based dose)*	5 mcg/m^2/day via continuous infusion *(not to exceed 9 mcg/day)*	15 mcg/m^2/day via continuous infusion *(not to exceed 28 mcg/day)*		15 mcg/m^2/day via continuous infusion *(not to exceed 28 mcg/day)*	

Posology for MRD positive B-precursor ALL (for patients at least 45 kg in weight)

A single cycle of treatment of BLINCYTO induction or consolidation is 28 days (4 weeks) of continuous intravenous infusion followed by a 14 day (2 week) treatment-free interval (total 42 days). Patients may receive 1 cycle of induction treatment followed by up to 3 additional cycles of BLINCYTO consolidation treatment. The majority of patients who respond to blinatumomab achieve a response after 1 cycle (see section 5.1 of the SmPC). 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.

Recommended dose (for patients at least 45 kg in weight) is provided below in Table 2. Prednisone 100 mg intravenously or equivalent (eg, dexamethasone 16 mg) should be administered 1 hour prior to initiation of each cycle of BLINCYTO therapy.

Table 2. Recommended dose (for patients at least 45 kg in weight) for MRD positive B-precursor ALL

Treatment cycle(s)	
Induction Cycle 1	
Days 1-28	Days 29-42
28 mcg/day	14-day treatment-free interval
Consolidation Cycles 2-4	
Days 1-28	Days 29-42
28 mcg/day	14-day treatment-free interval

Method of administration

Patients will receive continuous intravenous infusion of BLINCYTO. Discuss the infusion duration with your patients as there is a choice of bag change frequency. However, the target therapeutic dose of BLINCYTO delivered does not change.

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

Dose adjustment

In the case of toxicities, consideration can be made to interrupt or discontinue the infusion of BLINCYTO. Please refer to Dose adjustment under section 4.2 Posology and method of administration of the SmPC for further detail instruction.
If the interruption of treatment after an adverse event is no longer than 7 days, re-start BLINCYTO to 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 does not resolve within 14 days, discontinue BLINCYTO permanently, except in those circumstances as described in the SmPC (Please refer to Dose adjustment under Section 4.2 Posology and method of administration).

Risks of Medication Errors and Neurologic Events

The following actions should be taken to prevent or minimise the risk of medication errors and neurological events.

Medication errors

Medication errors are unintended errors in the prescribing, dispensing, or administration of a medicinal product while in the control of the healthcare professional or patient.

In the phase III clinical study in adult patients with relapsed/refractory ALL treated with BLINCYTO (N = 267), medication errors were observed in 4.5% of subjects.

To minimise the potential for medication errors, please counsel your patients on the following:

- Not to unlock the pump
- Not to try to fix the pump if the pump does not appear to perform properly (for example: alarm goes off) at any time, and to contact you or the nurse immediately
- Not to change any pump settings on purpose (with the exception of stopping the pump in case of emergency)

In addition, you can help by reporting any medication errors that you or your patients have encountered or experienced to <##>.

Neurologic events

In the phase III clinical study (N = 267) and the single-arm phase II clinical study (N = 189) in adult patients with relapsed/refractory ALL treated with BLINCYTO, neurologic events ocurred approximately in 66% of subjects. The most common neurologic adverse reactions (≥10% of patients) reported were headache and tremor. Some other common neurologic adverse reactions (≥ 1% to < 10%) included dizziness, somnolence, hypoaesthesia, encephalopathy, aphasia, paresthesia, seizure, cognitive disorder, ataxia, and memory impairment. Serious and grade ≥ 3 neurologic events occurred in approximately 11.6% and 12.1% of subjects, respectively, of which the most common serious adverse reactions were encephalopathy, tremor, aphasia, and confusional state. The majority of neurologic events (80.5%) were clinically reversible and resolved following interruption of BLINCYTO. The median time to the first event was within the first 2 weeks of treatment. One case of fatal encephalopathy has been reported in an earlier phase II clinical single-arm study. Neurologic events were reported for 71.5% of adult patients with MRD positive B precursor ALL treated with BLINCYTO (N = 137) of which 22.6% were considered serious. Grade ≥ 3 and grade ≥ 4 events, respectively, were reported for 16.1% and 2.2% of adult patients with MRD positive B precursor ALL.
For clinical management of neurologic events, please refer to Neurologic events under Section 4.4 Special warnings and precautions of the SmPC.

Elderly patients may be more susceptible to serious neurologic events such as cognitive disorder, encephalopathy, and confusion. Patients with a medical history of neurologic signs and symptoms may experience a higher rate of neurologic events (such as tremor, dizziness, confusional state, encephalopathy and ataxia) when receiving BLINCYTO. Among these patients, the median time to the first neurologic event was within the first cycle of treatment.

There is limited experience with BLINCYTO in patients with documented active ALL in the CNS or cerebrospinal fluid (CSF). Consider treating these patients after clearance of CSF blasts with CNS directed therapy (such as intrathecal chemotherapy).

There is also limited experience in patients with a history or presence of clinically relevant CNS pathology. In particular, caution should be exercised as they may be at higher risk of neurological events (ie, tremor, dizziness, confusional state, encephalopathy and ataxia).

Assess patients for signs and symptoms of neurological events (eg, confusion, disorientation, dizziness, tremor, seizure) prior to and throughout the treatment cycle. Consider using a

writing test periodically to assist with monitoring for neurological events during BLINCYTO treatment.

In case of seizure, consider using an appropriate anticonvulsant.

Consider to interrupt or discontinue the infusion of BLINCYTO temporarily as appropriate in case of grade 3 or 4 neurological toxicity. Please see table below.

Neurological toxicity	**Action for patients greater than or equal to 45 kg**	**Action for patients less than 45 kg**
Convulsion	Discontinue BLINCYTO permanently if more than one convulsion occurs.	Discontinue BLINCYTO permanently if more than one convulsion occurs.
Grade 3	Interrupt BLINCYTO until no more than grade 1 (mild) and for at least 3 days, then restart BLINCYTO at 9 mcg/day. Escalate to 28 mcg/day after 7 days if the toxicity does not recur. For re-initiation, pre-medicate 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 BLINCYTO permanently.	Interrupt BLINCYTO until no more than grade 1 (mild) and for at least 3 days, then restart BLINCYTO at 5 mcg/m^2/day. Escalate to 15 mcg/m^2/day after 7 days if the toxicity does not recur. If the toxicity occurred at 5 mcg/m^2/day, or if the toxicity takes more than 7 days to resolve, discontinue BLINCYTO permanently.
Grade 4	Discontinue BLINCYTO permanently.	Discontinue BLINCYTO permanently.

It is essential to counsel patients regarding the potential neurologic effects:

- Not to drive, operate heavy machines or engage in hazardous activities while receiving BLINCYTO
- To contact you if they experience neurological symptoms

An observational study is being conducted in selected countries within the European region/zone, to gather data on the real-world use of BLINCYTO. The primary objective of this study is to characterize the safety profile of BLINCYTO in routine clinical practice including medication errors. In addition, a patient survey is being conducted to assess, in patients or caregivers, knowledge of the potential for neurologic events and medication errors and to enquire of their awareness of the BLINCYTO patient educational materials.

Please inform your patients of these studies and encourage their participation.

In the clinical studies of adult ALL patients treated with BLINCYTO, less than 3% tested positive for anti-blinatumomab antibodies. Six of those patients had anti-blinatumomab antibodies with in-vitro neutralizing activity. No anti-blinatumomab antibodies were detected in clinical studies of paediatric patients with relapsed or refractory ALL treated with blinatumomab.

If formation of anti-blinatumomab antibodies with a clinically significant effect is suspected, contact the Marketing Authorisation Holder to discuss antibody testing. Contact details are provided in section 6 of the package leaflet.