BLINCYTO® ▼ (blinatumomab)

Educational Brochure for Physicians

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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

▼ 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. See below for how to report adverse reactions.

This document has been reviewed and approved by The Saudi Food and Drug Authority (SFDA).

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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 for the treatment of Philadelphia chromosome-negative relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL)

Overview of BLINCYTO treatment

Patients will receive BLINCYTO by continuous intravenous infusion.

- For the treatment of 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
- 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.

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Posology for 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). For adult patients, premedicate with 20 mg dexamethasone 1 hour prior to the first dose of BLINCYTO of each cycle, prior to a step dose (such as Cycle 1 day 8), and when restarting an infusion after an interruption of 4 or more hours.

For pediatric patients, premedicate with 5 mg/m2 of dexamethasone, to a maximum dose of 20 mg prior to the first dose of BLINCYTO in the first cycle, prior to a step dose (such as Cycle 1 day 8), and when restarting an infusion after an interruption of 4 or more hours in the first cycle.

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

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Table 1. Recommended dose for 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)*	

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

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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 <##>.

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Neurologic events

In the phase III clinical study (N = 267) and the single-arm phase II clinical study (N = 189) in adult patients with Philadelphia chromosome negative relapsed/refractory B-precursor 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 62.2% of adult patients with Philadelphia chromosome positive relapsed or refractory B-precursor ALL (N = 45). Serious and grade ≥ 3 neurologic events were reported at 13.3% each in adult patients with Philadelphia chromosome positive relapsed or refractory B-precursor ALL. Neurologic events were reported for 71.5% of adult patients with MRD positive B-precursor ALL treated with BLINCYTO (N = 137), 22.6% of patients experienced serious events. 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).

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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.

Please inform your patients of this study 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.

Contact details for adverse event reporting or to request further information. Any suspected adverse reactions should be reported immediately to local Amgen safety contacts or the National Pharmacovigilance and Drug Safety Center

Amgen Local Safety Contacts
Tel: +966 112 799328
E-mail: Safety-MEA@amgen.com

The National Pharmacovigilance Centre (NPC)
Saudi Food and Drug Authority (SFDA)
SFDA call center 19999
Toll free phone: 8002490000
Fax: +966-11-2057662
E-mail: npc.drug@sfda.gov.sa Online: http://ade.sfda.gov.sa/

Should you have any questions or require additional information regarding the use of Blincyto, please contact Medical Information on +966 112 799366 or by e-mail at: meamedinfo@amgen.com

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