EDUCATIONAL BROCHURE FOR PHYSICIANS

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), provided with this brochure.

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. It is indicated for the treatment of adults with Philadelphia chromosome negative relapsed or refractory B-precursor acute lymphoblastic leukaemia (ALL).

Overview of BLINCYTO® treatment

Patients will receive BLINCYTO® by continuous intravenous infusion .

- 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 (e.g. 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 in the second cycle have been observed.

A single treatment cycle consists of 4 weeks of continuous BLINCYTO® infusion. Each cycle of treatment is separated by a 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.

Table 1. Recommended dose (for patients at least 45 kg in weight)

Cycle 1		2 week-treatment free interval (days 29-42)	Cycle 2 and subsequent cycles (days 1-28)
Starting dose (days 1-7)	Subsequent dose (days 8-28)		
9 mcg/day via continuous infusion	28 mcg/day via continuous infusion		28 mcg/day via continuous infusion

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 minimize 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 pivotal clinical study (n = 189), medication errors were observed in 3.2% of subjects. The majority of these errors were reported as overdoses and occurred primarily due to infusion pump errors and BLINCYTO® preparation errors. Most errors of overdose did not result in an adverse event.
Of the ones associated with adverse events, most events were consistent with the known safety profile, mild in severity, and resolved.

To minimize 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)

Neurologic events

In the pivotal clinical study (n=189), neurologic events ocurred approximately in 52% of subjects. The most common neurologic adverse reactions (≥10% of patients) reported were dizziness and tremor . Some other common neurologic adverse reactions (≥1% and <10%) included encephalopathy, aphasia, paresthesia, convulsion, cognitive disorder, confusional state, disorientation, and memory impairment. Serious neurologic events occurred in approximately 16% of subjects. Elderly patients experienced a higher rate of neurologic events. Patients with a medical history of neurologic signs and symptoms may experience a higher rate of neurologic events when receiving BLINCYTO®.

There is limited experience with BLINCYTO® in patients with documented active ALL in the central nervous system (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 central nervous system CNS pathology. In particular, caution should be exercised as they may be at higher risk of neurological events (i.e. tremor, dizziness, confusional state, encephalopathy and ataxia). The median time to onset of a neurologic event in this population was 12 days.

Assess patients for signs and symptoms of neurological events (e.g. 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	Convulsion	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.
	Grade 4	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 will be 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.

You can find more on whether any of the aforementioned studies are carried out in Malta, by contacting the Marketing Authorization Holder, through its Local Representative, Amgen S.r.l. Via Tazzoli 6, 20154 Milan. Phone number: +39 02 6241121; e-mail: eu-it-farmacovigilanza@amgen.com

If it is conducted, please inform your patients of these studies and encourage their participation.

In the pivotal clinical study (n=189), less than 1.4% of patients treated with BLINCYTO® tested positive for binding and neutralizing anti-blinatumomab antibodies. 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.

▼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