BLINCYTO® ▼ (blinatumomab)

Important Risk Minimisation Information for Nurses

The information in this guide is not intended as a replacement for the Summary of Product Characteristics (SmPC).

Please read the BLINCTYO SmPC, in conjunction with this guide.

The BLINCYTO SmPC is available, on the European Medicines Agency website under following link: https://www.ema.europa.eu/en/medicines/human/EPAR/blincyto#product-information-section.

As part of the BLINCYTO Marketing Authorisation in European Union (EU), this guide has been developed for nurses involved in the care of patients treated with BLINCYTO to provide further information about **how to minimise or prevent Neurologic events including Immune effector cell-associated neurotoxicity syndrome (ICANS) associated with the use of BLINCYTO**

To obtain additional copies of the BLINCYTO SmPC, Package Leaflet, this Guide for Nurses, Guide for Patients and Patient Card, please contact Cherubino Ltd, Delf Building, Sliema Road, Gzira or via email on: pharmacovigilance@cherubino.com.mt

▼ 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 Malta Medicines Authority, Sir Temi Zammit Buildings, Malta Life Science Park, San Gwann SGN 300 Malta or at http:/www.medicinesauthority.gov.mt/adrportal. Adverse reactions should also be reported to Cherubino Ltd on 21343270 or pharmacovigilance@cherubino.com.mt

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1 Overview

In order to minimise the risk of neurologic events including immune effector cell-associated neurotoxicity (ICANS), ensure the patient has been counselled at initiation of treatment (see section 2 of this Guide for further details) and has received and understands the content of the following:

- Guide for Patients and Caregivers
- Patient Card
- Package Leaflet

Please report any suspected adverse reactions that your patients have encountered or experienced (refer to page 1 for instructions).

2 Important Information on Neurologic Events including ICANS

- Neurologic events including ICANS, including events with a fatal outcome, have been observed during treatment with BLINCYTO. Events have included encephalopathy, seizures, speech disorders, disturbances in consciousness, confusion and disorientation, and coordination and balance disorders.
- Prior to, and throughout the treatment cycles, assess patients for signs and symptoms of neurologic events including ICANS (see Section 4.4 of the BLINCYTO SmPC for further information)
    - Signs and symptoms may include:
        - Aphasia
        - Seizure
        - Cognitive disorder
        - Memory impairment
        - Somnolence
        - Depressed level of consciousness
        - Motor findings/weakness
        - Elevated intracranial pressure (ICP)
        - Cerebral edema
        - Dysgraphia

- It is recommended that a neurological examination, including Immune Cell-Associated Encephalopathy (ICE)/Cornell Assessment Paediatric Delirium (CAPD) Assessment, be performed in patients prior to starting BLINCYTO therapy and that patients be clinically monitored for signs and symptoms of neurologic events (e.g. writing test).

3 ICANS Grading and Toxicity Management

Assessment of the severity of ICANS reported during blinatumomab treatment is based on the American Society for Transplantation and Cellular Therapy (ASTCT) 2019 grading criteria (Lee et al 2019).

Follow steps 1 to 3 below to determine the ICANS grade and recommended management:

1. Assess Immune Cell-Associated Encephalopathy (ICE)/ Cornell Assessment Paediatric Delirium (CAPD) score based on the age of the patient, as follows:
    a. Use ICE assessment (table 1) for patients ≥12 years of age
    b. Use CAPD assessment (table 2) for patients <12 years of age, or for patients ≥12 years of age with baseline developmental delay
2. Determine ICANS Grade:
    a. Once the ICE/CAPD score is calculated, use table 3 to determine the overall ICANS severity (grade)
    b. If a patient is unarousable and unable to perform the ICE or CAPD assessment, this would be associated to an ICANS grade 4
    c. Grading is determined by the most severe event, not attributable to any other cause
3. Consult Prescribing Physician on ICANS Management:
    a. Once the ICANS grade is determined, immediately consult the prescribing physician to decide on appropriate BLINCYTO management measures. Please refer to table 4 in this Guide or table 6 in section 4.2 of the BLINCYTO SmPC for recommendation for management of ICANS.

Table 1. Encephalopathy Assessment for Patients Aged 12 Years and Older Using ICE[1]

ICE score
• Orientation: orientation to year, month, city, hospital: 4 points • Naming: ability to name 3 objects (eg, point to clock, pen, button): 3 points • Following commands: ability to follow simple commands (eg, “Show me 2 fingers” or “Close your eyes and stick out your tongue”): 1 point • Writing: ability to write a standard sentence: 1 point • Attention: ability to count backwards from 100 by 10: 1 point

[1] Reproduced with permission from Elsevier

Table 2. Encephalopathy Assessment for Children <12 Years Using CAPD[2]

Answer the following based on interactions with the child over the course of the shift *Note: For patients 1-2 years old, text in italics serve as guidance to the corresponding question; for patients under 1 year old, refer to Figure. 2 of the Delirium screening anchored in child development: The Cornell Assessment for Pediatric Delirium publication[3]*					
	Never, 4	Rarely, 3	Sometimes, 2	Often, 1	Always, 0
1. Does the child make eye contact with the caregiver? *Holds gaze, prefers primary parent, looks at speaker*					
2. Are the child's actions purposeful? *Reaches and manipulates objects, tries to change position, if mobile may try to get up*					
3. Is the child aware of his/her surroundings? *Prefers primary parent, upset when separated from preferred caregivers. Comforted by familiar objects (ie, blanket or stuffed animal)*					
4. Does the child communicate needs and wants? *Uses single words or signs*					
	Never, 0	Rarely, 1	Sometimes, 2	Often, 3	Always, 4
5. Is the child restless? *No sustained calm state*					
6. Is the child inconsolable? *Not soothed by usual comforting actions, eg, singing, holding, talking, and reading*					
7. Is the child underactive; very little movement while awake? *Little if any play, efforts to sit up, pull up, and if mobile crawl or walk around*					
8. Does it take the child a long time to respond to interactions? *Not following simple directions. If verbal, not engaging in simple dialog with words or jargon*					

[2] Reproduced with permission from Cornell University and Elsevier

[3] Delirium screening anchored in child development: The Cornell Assessment for Pediatric Delirium publication (https://pmc.ncbi.nlm.nih.gov/articles/PMC5031084/)

Table 3. ASTCT ICANS Consensus Grading[4]

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score for patients age ≥12 years*	7-9	3-6	0-2	0 (patient is unarousable and unable to perform ICE)
CAPD score for patients age <12 years	1-8	1-8	≥9	Unable to perform CAPD
Depressed level of consciousness[+]	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma
Seizure (at any age)	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5 min); or Repetitive clinical or electrical seizures without return to baseline in between
Motor findings[z]	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated ICP/ cerebral oedema	N/A	N/A	Focal/local edema on neuroimaging[x]	Decerebrate or decorticate posturing, cranial nerve VI palsy, papilledema, Cushing's triad, or signs of diffuse cerebral edema on neuroimaging

[4] Reproduced with permission from Elsevier

CAPD= Cornell Assessment of Pediatric Delirium

ICANS grade is determined by the most severe event (ICE or CAPD score, level of consciousness, seizure, motor findings, raised ICP/cerebral edema) not attributable to any other cause. Baseline CAPD score should be considered before attributing to ICANS.

[*] A patient with an ICE score of 0 may be classified as grade 3 ICANS if awake with global aphasia, but a patient with an ICE score of 0 may be classified as grade 4 ICANS if unarousable.

[+] Depressed level of consciousness should be attributable to no other cause (eg, no sedating medication).

[z] Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE v5.0, but they do not influence ICANS grading.

[x] Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE v5.0.

Table 4. Recommendation for Management of ICANS

Extracted from Section 4.2 (table 6) of the Blincyto SmPC.

Grade	Presenting symptoms	Actions (to be discussed with physician)
Grade 1	ICE score 7-9 *CAPD score 1-8** or depressed level of consciousness[a]: awakens spontaneously.	Interrupt blinatumomab until ICANS resolves. Monitor neurologic symptoms and consider consultation with a neurologist for further evaluation and management. Consider non-sedating, antiseizure medicinal products (e.g. levetiracetam) for seizure prophylaxis. *Action for patients ≥ 45 kg:* Consider treatment with dexamethasone[b] up to 8 mg/dose up to 3 doses administered over 24 hours. For reinitiation, premedicate with up to 20 mg dexamethasone 1-3 hours before BLINCYTO restart. *Action for patients < 45 kg:* Consider treatment with dexamethasone[b] at a total daily dose up to 0.2-0.4 mg/kg/day (up to a maximum 24 mg/day). For reinitiation, premedicate with 5 mg/m^2 dexamethasone (maximum 20 mg dose) 1-3 hours before BLINCYTO restart.

Grade	Presenting symptoms	Actions (to be discussed with physician)
Grade 2	ICE score 3-6 *CAPD score 1-8** or depressed level of consciousness[a]: awakens to voice.	Interrupt BLINCYTO Administer dexamethasone[b]: *For patients ≥ 45 kg:* Administer dexamethasone 8 mg/dose up to 3 doses/day (24 mg/day maximum) for up to 2 days or until event resolution, whichever is sooner. *For patients < 45 kg:* Administer dexamethasone at a total daily dose of at least 0.2-0.4 mg/kg/day (maximum 24 mg per day) administered over 3 doses for up to 2 days or until event resolution, whichever is sooner. Monitor neurologic symptoms and consider consultation with a neurologist and other specialists for further evaluation and management. Consider non-sedating, antiseizure medicinal products (e.g. levetiracetam) for seizure prophylaxis. *Action for patients ≥ 45 kg:* Interrupt BLINCYTO until ICANS resolves, then restart BLINCYTO at 9 mcg/day. Escalate to 28 mcg/day after 7 days if the toxicity does not recur. For reinitiation, premedicate with up to 20 mg dexamethasone[b] 1-3 hours before BLINCYTO restart. *Action for patients < 45 kg:* Interrupt BLINCYTO until ICANS resolve, 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. For reinitiation, premedicate with 5 mg/m^2 dexamethasone[b] (maximum 20 mg dose) 1-3 hours before BLINCYTO restart.

Grade	Presenting symptoms	Actions (to be discussed with physician)
Grade 3	ICE score 0-2 *CAPD ≥ 9* or depressed level of consciousness[a]: • awakens only to tactile stimulus, or seizures[a], either: • any clinical seizure, focal or generalised, that resolves rapidly, or • non-convulsive seizures on electroencephalogram (EEG) that resolve with intervention, or raised intracranial pressure: • focal/local oedema on neuroimaging[a]	Interrupt BLINCYTO Administer dexamethasone[b]: *For patients ≥ 45 kg:* Administer dexamethasone 8 mg/dose 3 doses/day (24 mg/day maximum) until event resolution to grade 1 or less and then taper as clinically indicated. *For patients < 45 kg:* Administer dexamethasone at a total daily dose of at least 0.2-0.4 mg/kg/day (maximum 24 mg per day) until event resolution to grade 1 or less and then taper as clinically indicated. Monitor neurologic symptoms and consider consultation with a neurologist and other specialists for further evaluation and management. Consider non-sedating, antiseizure medicinal products (e.g. levetiracetam) for seizure prophylaxis. Provide supportive therapy, which may include intensive care. *Action for patients ≥ 45 kg:* Interrupt BLINCYTO until ICANS resolves, then restart BLINCYTO at 9 mcg/day. Escalate to 28 mcg/day after 7 days if the toxicity does not recur. For reinitiation, premedicate with up to 20 mg dexamethasone[b] 1-3 hours before BLINCYTO restart. If the toxicity occurred at 9 mcg/day, or if the toxicity takes more than 7 days to resolve, discontinue BLINCYTO permanently. *Action for patients < 45 kg:* Interrupt BLINCYTO until ICANS resolves, 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. For reinitiation, premedicate with 5 mg/m^2 dexamethasone[b] (maximum 20 mg/dose) 1-3 hours before BLINCYTO restart. If the toxicity occurred at 5 mcg/m^2/day, or if the toxicity takes more than 7 days to resolve, discontinue BLINCYTO permanently. *Action for all patients:* Permanently discontinue BLINCYTO if more than one seizure occurs.

Grade	Presenting symptoms	Actions (to be discussed with physician)
Grade 4	ICE score 0 *Unable to perform CAPD** or, depressed level of consciousness[a] either: • patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse, or • stupor or coma, or seizures[a], either: • life-threatening prolonged seizure (> 5 minutes), or • repetitive clinical or electrical seizures without return to baseline in between, or motor findings[a]: • deep focal motor weakness such as hemiparesis or paraparesis, or raised intracranial pressure/cerebral oedema[a], with signs/symptoms such as: • diffuse cerebral oedema on neuroimaging, or • decerebrate or decorticate posturing, or • cranial nerve VI palsy, or • papilledema, or • Cushing's triad	Permanently discontinue BLINCYTO Administer dexamethasone[b]: *For patients ≥ 45 kg:* Administer dexamethasone 8 mg/dose 3 doses/day until event resolution to grade 1 or less and then taper as clinically indicated. Alternatively, consider administration of methylprednisolone 1000 mg per day intravenously for 3 days; taper as clinically indicated. *For patients < 45 kg:* Administer dexamethasone at a total daily dose of at least 0.2-0.4 mg/kg/day until event resolution to grade 1 or less and then taper as clinically indicated. Alternatively, consider administration of methylprednisolone 30 mg/kg/day (maximum 1000 mg/day) in divided doses intravenously for 3 days; taper as clinically indicated. Monitor neurologic symptoms and consider consultation with a neurologist and other specialists for further evaluation and management. Consider non-sedating, antiseizure medicinal products (e.g. levetiracetam) for seizure prophylaxis. Provide supportive therapy, which may include intensive care.

[a] Not attributable to any other cause.
[b] All references to dexamethasone administration are dexamethasone or equivalent medicinal products.
* Scores between 1-8 may represent no impairment, grade 1 or grade 2 ICANS and must be combined with clinical assessment.

4 Counselling the Patient

It is essential to counsel your patients on Neurologic Events including ICANS during BLINCYTO treatment.

4.1 Description of Neurologic Events including ICANS

- Advise patients to call their healthcare provider to ask for emergency medical help immediately if they experience any of the following neurologic events:
    - uncontrolled shaking (or tremor)
    - confusion
    - disturbances of brain function (encephalopathy)
    - difficulty communicating (aphasia) and/or writing (dysgraphia)
    - seizure (convulsion)
- Advise patients not drive or operate moving vehicles/heavy machinery or engage in hazardous activities whilst receiving BLINCYTO.

4.2 Check the Patient has Received Educational Materials

- Ensure patients have received a copy of the documents listed below and check with the patients to see if they have any questions about their content:
    - Guide for Patients and Caregivers
    - Patient Card
    - Package Leaflet

[This Guide for Nurses fulfills the conditions of the marketing authorisation and has been approved by the competent authority.]