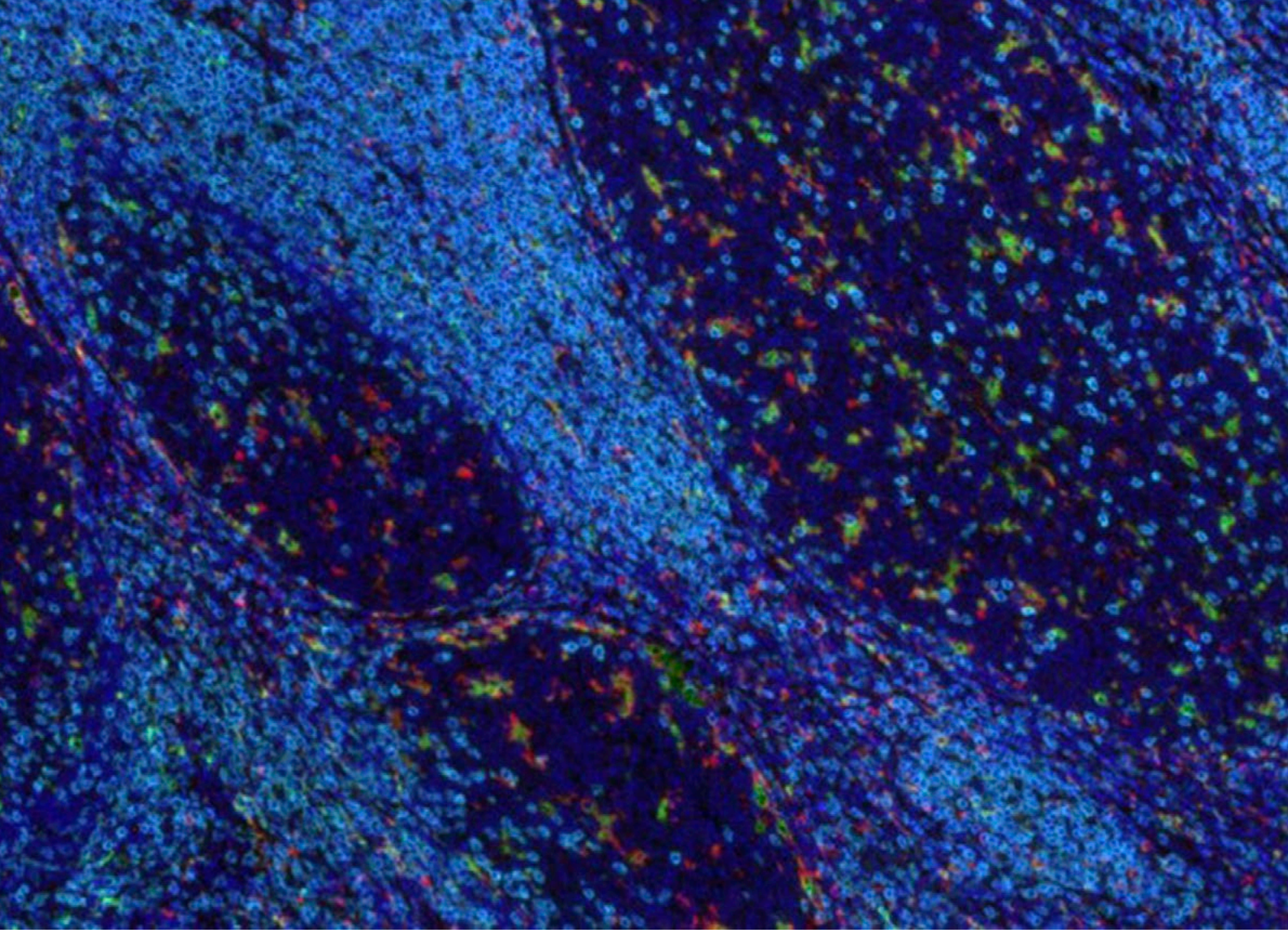

TALVEY®▼ (talquetamab)

HCP Educational Guide on the Identification, Management and Monitoring of Neurologic Toxicity

Johnson&Johnson

▼ 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 events via HPRA Pharmacovigilance, Website www.hpra.ie. Adverse events should also be reported to Janssen Sciences Ireland UC, a Johnson and Johnson Company, on +44 1494 567 447 or email dsafety@its.jnj.com.

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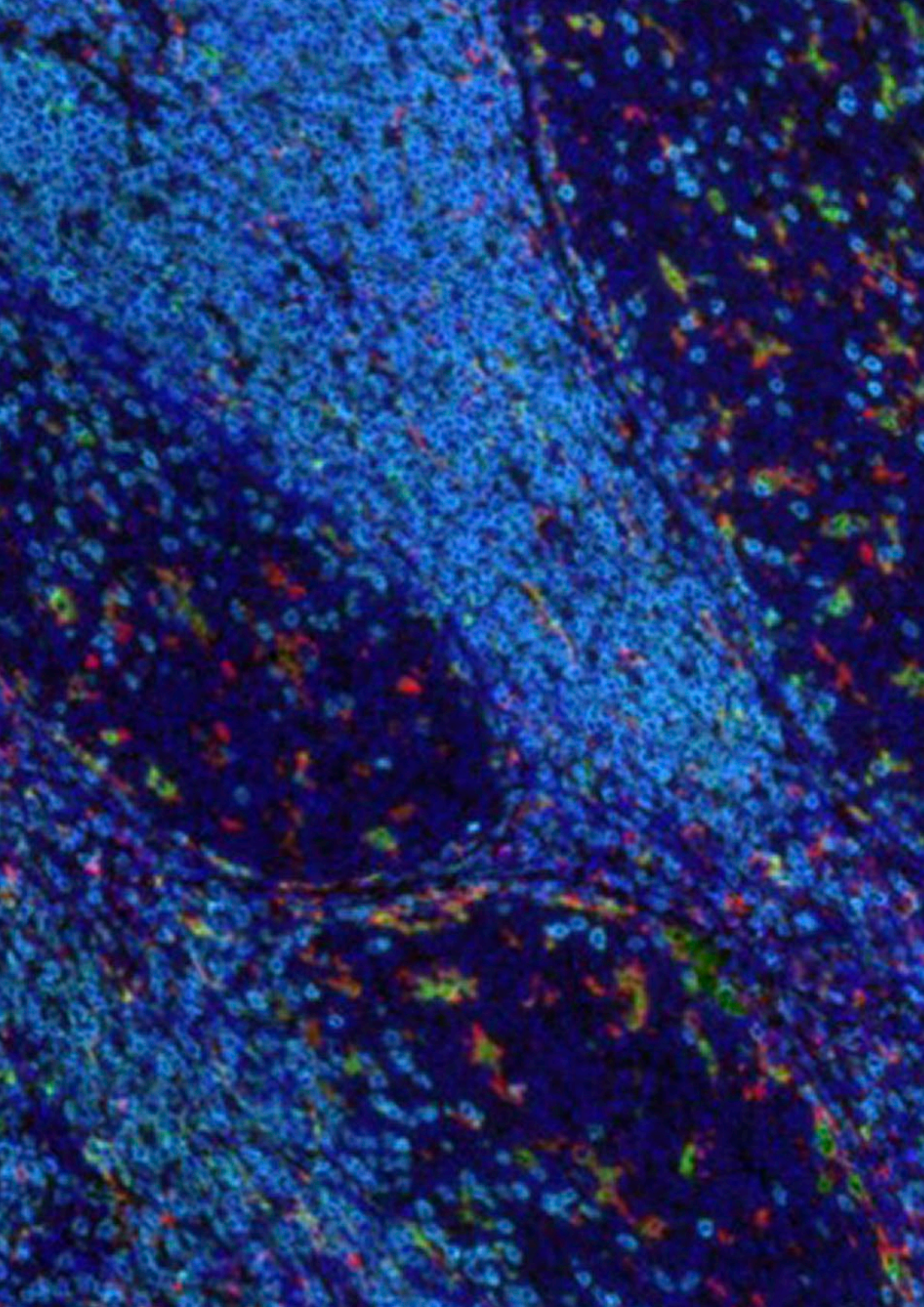

Contents

Objectives of the educational material

This educational material is aimed at all healthcare professionals who are expected to prescribe or administer talquetamab.

Key objectives

- Facilitate identification of neurologic toxicity, including ICANS
- Ensure awareness of the risk of neurologic toxicity, including ICANS, and provide recommendations to minimise the risk*
- Facilitate management of neurologic toxicity, including ICANS
- Facilitate monitoring of neurologic toxicity, including ICANS
- Ensure that adverse reactions are adequately and appropriately reported

*Including information on frequency, severity, and time to onset observed in patients who received treatment with talquetamab.

Identification of neurologic toxicity, including ICANS

Clinical **signs and symptoms of ICANS** may include, but are not limited to:

Confusional state	**Depressed level of consciousness**	**Disorientation**
Somnolence	**Lethargy**	**Bradyphrenia**

The onset of ICANS can be concurrent with CRS, following resolution of CRS, or in the absence of CRS.

1. TALVEY Summary of Product Characteristics

The risk of neurologic toxicity, including ICANS

ICANS, including fatal reactions, have occurred following treatment with TALVEY.

Reported outcomes in MonumenTAL-1:

Serious or life-threatening neurologic toxicities, including ICANS, have occurred following treatment with talquetamab.

In MonumenTAL-1 (N=339), neurologic toxicity events were reported in **29% of patients** receiving talquetamab

- The most frequently reported neurologic toxicity event was **headache** (9%)
- ICANS data were only collected in Phase 2 of MonumenTAL-1; of the 265 patients in Phase 2, **ICANS occurred in 9.8%** (n=26) of patients

There are no data on the use of talquetamab in **patients with CNS involvement** of myeloma or other clinically relevant CNS pathologies*

Table 1 and **Table 2** outline the **key reported outcomes** for neurologic toxicities, including ICANS, and ICANS in the MonumenTAL-1 study.

Table 1: Reported neurologic toxicity, including ICANS, in MonumenTAL-1 (N=339)

	MonumenTAL-1 (N=339)
Incidence of neurologic toxicity events, %	
Grade 1	17
Grade 2	11
Grade 3	2.3
Grade 4	0.3

*Patients with CNS involvement of myeloma or other clinically relevant CNS pathologies were not eligible for MonumenTAL-1 due to the potential risk of ICANS.
1. TALVEY Summary of Product Characteristics

Table 2: Reported ICANS in Phase 2 of MonumenTAL-1 (n=265)

	Phase 2 MonumenTAL-1 (N=265)
Incidence of ICANS	
All grades, %	9.8
Grade 3/4, %	2.3
More than one event, %	3
Concurrent with CRS*, %	68
Fatal events, n	1
Most frequent clinical manifestations of ICANS, %	
Confusional state	3.8
Disorientation	1.9
Somnolence	1.9
Depressed level of consciousness	1.9
Median time to onset of ICANS, hours	28
ICANS events within 48 hours from last dose, %	68
ICANS events after 48 hours from last dose, %	32
Median duration of ICANS, hours	9

Most patients experienced ICANS during the step-up phase following the 0.01 mg/kg dose, the 0.06 mg/kg dose, or the initial 0.4 mg/kg and 0.8 mg/kg treatment dose (3% each).

*During or within 7 days of CRS resolution.
1. TALVEY Summary of Product Characteristics

Management of neurologic toxicity, including ICANS

At the first sign of neurologic toxicity, including ICANS, **neurology evaluation** should be considered and other causes of neurologic symptoms should be ruled out.

For ICANS and other neurologic toxicities, talquetamab should be **withheld or discontinued** based on severity and management recommendations outlined in **Table 3** and **Table 4** should be followed.

Intensive care and supportive therapy should be provided for severe or life-threatening neurologic toxicities, including ICANS.

Talquetamab should be administered by an HCP with adequately-trained medical personnel and appropriate medical equipment to manage severe reactions, including CRS and neurologic toxicity, including ICANS.

1. TALVEY Summary of Product Characteristics

Table 3: Recommendations for management of ICANS[1]

ICANS Grade*‡	Concurrent CRS	No concurrent CRS
Grade 1 ICE¶ score 7–9 or depressed level of consciousness:§ awakens spontaneously	• Management of CRS per **Appendix I** • Monitor neurologic symptoms and consider neurology consultation and evaluation, per physician discretion.	• Monitor neurologic symptoms and consider neurology consultation and evaluation, per physician discretion.
	• Withhold talquetamab until ICANS resolves. • Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis.	
Grade 2 ICE¶ score 3–6 or depressed level of consciousness:§ awakens to voice	• Administer tocilizumab per **Appendix I** for management of CRS. • If no improvement after starting tocilizumab, administer dexamethasone** 10 mg intravenously every 6 hours if not already taking other corticosteroids. Continue dexamethasone use until resolution to Grade 1 or less, then taper.	• Administer dexamethasone** 10 mg intravenously every 6 hours. Continue dexamethasone use until resolution to Grade 1 or less, then taper.
	• Withhold talquetamab until ICANS resolves • Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis. Consider neurology consultation and other specialists for further evaluation, as needed. • Monitor patient for 48 hours following the next dose of talquetamab. Instruct patients to remain within proximity of a healthcare facility during monitoring.	

*Management is determined by the most severe event, not attributable to any other cause. ‡Based on ASTCT grading for ICANS.2 ¶If patient is arousable and able to perform Immune Effector Cell-Associated Encephalopathy (ICE) Assessment, assess: **Orientation** (oriented to year, month, city, hospital = 4 points); **Naming** (name 3 objects, e.g., point to clock, pen, button = 3 points); **Following Commands** (e.g., "show me 2 fingers" or "close your eyes and stick out your tongue" = 1 point); **Writing** (ability to write a standard sentence = 1 point); and **Attention** (count backwards from 100 by ten = 1 point). If patient is unarousable and unable to perform ICE Assessment (Grade 4 ICANS) = 0 points. §Attributable to no other cause.
**All references to dexamethasone administration are dexamethasone or equivalent.
1. TALVEY Summary of Product Characteristics. 2. Lee DW, et al. Biol Blood Marrow Transplant 2019;25:625–638.

ICANS Grade*‡	Concurrent CRS	No concurrent CRS
Grade 3 ICE¶ score 0–2 (if ICE score is 0, but the patient is arousable [e.g., awake with global aphasia] and able to perform assessment) or depressed level of consciousness:§ awakens only to tactile stimulus or seizures,§ either: • any clinical seizure, focal or generalised, that resolves rapidly, or • non-convulsive seizures on EEG that resolve with intervention or raised intracranial pressure: focal/local oedema on neuroimaging§	• Administer tocilizumab per **Appendix I** for management of CRS • Administer dexamethasone** 10 mg intravenously with the first dose of tocilizumab and repeat dose every 6 hours. Continue dexamethasone use until resolution to Grade 1 or less, then taper	• Administer dexamethasone** 10 mg intravenously every 6 hours. Continue dexamethasone use until resolution to Grade 1 or less, then taper
	• Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis. Consider neurology consultation and other specialists for further evaluation, as needed **First occurrence:** • Withhold talquetamab until ICANS resolves • Monitor patient for 48 hours following the next dose of talquetamab. Instruct patients to remain within proximity of a healthcare facility during monitoring **Recurrent:** • Permanently discontinue talquetamab	

*Management is determined by the most severe event, not attributable to any other cause. ‡Based on ASTCT grading for ICANS.2 ¶If patient is arousable and able to perform Immune Effector Cell-Associated Encephalopathy (ICE) Assessment, assess: **Orientation** (oriented to year, month, city, hospital = 4 points); **Naming** (name 3 objects, e.g., point to clock, pen, button = 3 points); **Following Commands** (e.g., "show me 2 fingers" or "close your eyes and stick out your tongue" = 1 point); **Writing** (ability to write a standard sentence = 1 point); and **Attention** (count backwards from 100 by ten = 1 point). If patient is unarousable and unable to perform ICE Assessment (Grade 4 ICANS) = 0 points. §Attributable to no other cause.
**All references to dexamethasone administration are dexamethasone or equivalent.
1. TALVEY Summary of Product Characteristics. 2. Lee DW, et al. Biol Blood Marrow Transplant 2019;25:625–638.

ICANS Grade*‡	Concurrent CRS	No concurrent CRS
Grade 4 ICE¶ score 0 (patient is unarousable and unable to perform ICE assessment) or depressed level of consciousness,§ either: • patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse, or • stupor or coma, or seizures,§ either: • life-threatening prolonged seizure (>5 minutes), or • repetitive clinical or electrical seizures without return to baseline in between, or motor findings:§ • deep focal motor weakness such as hemiparesis or paraparesis, or raised intracranial pressure/cerebral oedema,§ with signs/symptoms such as: • diffuse cerebral oedema on neuroimaging, or • decerebrate or decorticate posturing, or • cranial nerve VI palsy, or • papilloedema, or • Cushing's triad	• Administer tocilizumab per **Appendix I** for management of CRS • Administer dexamethasone** 10 mg intravenously and repeat dose every 6 hours. Continue dexamethasone use until resolution to Grade 1 or less, then taper • Alternatively, consider administration of methylprednisolone 1,000 mg per day intravenously with first dose of tocilizumab, and continue methylprednisolone 1,000 mg per day intravenously for 2 or more days	• Administer dexamethasone** 10 mg intravenously and repeat dose every 6 hours. Continue dexamethasone use until resolution to Grade 1 or less, then taper • Alternatively, consider administration of methylprednisolone 1,000 mg per day intravenously for 3 days; if improves, then manage as above
	• Permanently discontinue talquetamab • Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis. Consider neurology consultation and other specialists for further evaluation, as needed • In case of raised intracranial pressure/cerebral oedema, refer to local institutional guidelines for management	

*Management is determined by the most severe event, not attributable to any other cause. ‡Based on ASTCT grading for ICANS.2 ¶If patient is arousable and able to perform Immune Effector Cell-Associated Encephalopathy (ICE) Assessment, assess: **Orientation** (oriented to year, month, city, hospital = 4 points); **Naming** (name 3 objects, e.g., point to clock, pen, button = 3 points); **Following Commands** (e.g., "show me 2 fingers" or "close your eyes and stick out your tongue" = 1 point); **Writing** (ability to write a standard sentence = 1 point); and **Attention** (count backwards from 100 by ten = 1 point). If patient is unarousable and unable to perform ICE Assessment (Grade 4 ICANS) = 0 points. §Attributable to no other cause.
**All references to dexamethasone administration are dexamethasone or equivalent.
1. TALVEY Summary of Product Characteristics. 2. Lee DW, et al. Biol Blood Marrow Transplant 2019;25:625–638.

Management of neurologic toxicity, excluding ICANS

Table 4: Recommendations for management of neurologic toxicity, excluding ICANS

Severity*	Actions
Grade 1	• Withhold talquetamab until neurologic toxicity symptoms resolve or stabilise‡
Grade 2	• Withhold talquetamab until neurologic toxicity symptoms improve to Grade 1 or less‡ • Provide supportive therapy
Grade 3	**First occurrence:** • Withhold talquetamab until neurologic toxicity symptoms improve to Grade 1 or less‡ • Provide supportive therapy **Recurrent:** • Permanently discontinue talquetamab • Provide supportive therapy, which may include intensive care
Grade 4	• Permanently discontinue talquetamab • Provide supportive therapy, which may include intensive care

*Based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03. ‡Please refer to the talquetamab Summary of Product Characteristics for recommendations on restarting talquetamab after dose delays.

1. TALVEY Summary of Product Characteristics

Monitoring of neurologic toxicity, including ICANS

Patients should be monitored for signs and symptoms of neurologic toxicities and treated promptly

Patients should be counselled to seek medical attention should signs or symptoms of neurologic toxicities, including ICANS, occur

At the first sign of neurologic toxicities including ICANS, the patient should be **immediately evaluated** and supportive care should be provided based on severity.

Patients who experience Grade 2 or higher ICANS should be instructed to remain **within proximity of a healthcare facility** and monitored for signs and symptoms for 48 hours following the next dose of talquetamab.

Due to the potential for ICANS, patients should be instructed to **avoid driving or operating machines** during the step-up phase and for 48 hours after completion of the step-up phase, and in the event of new onset of any neurological symptoms, until symptoms resolve.

1. TALVEY Summary of Product Characteristics

Reporting of suspected adverse reactions

▼ **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.**

Reporting suspected adverse reactions after authorisation of the medicinal product is important as it allows continued monitoring of the benefit/risk balance of the medicinal product.

When reporting a suspected adverse reaction, please provide as much information as possible, including information about medical history, any concomitant medication, onset and treatment date.

Reporting of Adverse Events

Healthcare professionals are asked to report any suspected adverse events via HPRA Pharmacovigilance: Website www.hpra.ie. Adverse events should also be reported to Janssen Sciences Ireland UC, a Johnson and Johnson Company, on +44 1494 567 447 or at dsafety@its.jnj.com.

In order to improve the traceability of TALVEY, the tradename and the batch number of the administered product should be clearly recorded in the patient file and when reporting an Adverse Event.

Glossary

ASTCT	American Society for Transplantation and Cellular Therapy
CNS	Central nervous system
CRS	Cytokine release syndrome
EEG	Electroencephalogram
HCP	Healthcare professional
ICANS	Immune effector cell-associated neurotoxicity syndrome
ICE	Immune effector-cell associated encephalopathy

Appendix 1: Management of CRS

Table 5: Recommendations for management of CRS[1]

CRS Grade*	Talquetamab actions	Tocilizumab‡	Corticosteroids¶
Grade 1 Temperature ≥38°C§	• Withhold talquetamab until CRS resolves • Administer pre-treatment medicinal products prior to next dose of talquetamab	• May be considered	• Not applicable
Grade 2 Temperature ≥38°C§ with either: • Hypotension responsive to fluids and not requiring vasopressors, or • Oxygen requirement of low-flow nasal cannula** or blow-by	• Withhold talquetamab until CRS resolves • Administer pre-treatment medicinal product prior to next dose of talquetamab • Monitor patient for 48 hours following the next dose of talquetamab. Instruct patients to remain within proximity of a healthcare facility during monitoring	• Administer tocilizumab¶ 8 mg/kg intravenously over 1 hour (not to exceed 800 mg) • Repeat tocilizumab every 8 hours as needed, if not responsive to intravenous fluids or increasing supplemental oxygen • Limit to a maximum of 3 doses in a 24-hour period; maximum total of 4 doses	• If no improvement within 24 hours of starting tocilizumab, administer methylprednisolone 1 mg/kg intravenously twice daily, or dexamethasone 10 mg intravenously every 6 hours • Continue corticosteroid use until the event is Grade 1 or less, then taper over 3 days

*Based on ASTCT grading for CRS.2 ‡Refer to tocilizumab prescribing information for details. ¶Treat unresponsive CRS per institutional guidelines. §Attributed to CRS. Fever may not always be present concurrently with hypotension or hypoxia as it may be masked by interventions such as antipyretics or anticytokine therapy (e.g., tocilizumab or corticosteroids). **Low-flow nasal cannula is ≤6 L/min, and high-flow nasal cannula is >6 L/min.

1. TALVEY Summary of Product Characteristics. 2. Lee DW, et al. Biol Blood Marrow Transplant 2019;25:625–638.

CRS Grade*	Talquetamab actions	Tocilizumab‡	Corticosteroids¶
Grade 3 Temperature ≥38°C§ with either: • Hypotension requiring one vasopressor, with or without vasopressin, or • Oxygen requirement of high-flow nasal cannula**, facemask, non-rebreather mask, or Venturi mask	**Duration <48 hours:** • As per Grade 2 CRS **Recurrent or duration ≥48 hours:** • Permanently discontinue talquetamab	• Administer tocilizumab 8 mg/kg intravenously over 1 hour (not to exceed 800 mg) • Repeat tocilizumab every 8 hours as needed, if not responsive to intravenous fluids or increasing supplemental oxygen • Limit to a maximum of 3 doses in a 24-hour period; maximum total of 4 doses	• If no improvement, administer methylprednisolone 1 mg/kg intravenously twice daily or dexamethasone (e.g., 10 mg intravenously every 6 hours) • Continue corticosteroid use until the event is Grade 1 or less, then taper over 3 days
Grade 4 Temperature ≥38°C§ with either: • Hypotension requiring multiple vasopressors (excluding vasopressin), or • Oxygen requirement of positive pressure (e.g., continuous positive airway pressure [CPAP], bilevel positive airway pressure [BiPAP], intubation, and mechanical ventilation)	• Permanently discontinue talquetamab	• Administer tocilizumab 8 mg/kg intravenously over 1 hour (not to exceed 800 mg) • Repeat tocilizumab every 8 hours as needed, if not responsive to intravenous fluids or increasing supplemental oxygen • Limit to a maximum of 3 doses in a 24-hour period; maximum total of 4 doses	• As above or administer methylprednisolone 1,000 mg intravenously per day for 3 days, per physician discretion • If no improvement or if condition worsens, consider alternate immunosuppressants¶

*Based on ASTCT grading for CRS.2 ‡Refer to tocilizumab prescribing information for details. ¶Treat unresponsive CRS per institutional guidelines. §Attributed to CRS. Fever may not always be present concurrently with hypotension or hypoxia as it may be masked by interventions such as antipyretics or anticytokine therapy (e.g., tocilizumab or corticosteroids). **Low-flow nasal cannula is ≤6 L/min, and high-flow nasal cannula is >6 L/min.

1. TALVEY Summary of Product Characteristics. 2. Lee DW, et al. Biol Blood Marrow Transplant 2019;25:625–638.

Notes