

GUIDE FOR HEALTHCARE PROVIDERS

# Management of CRS and neurotoxicity, including ICANS

 **IMDELLTRA™**  
tarlatamab for injection

IMDELLTRA™ (tarlatamab) is a bispecific delta-like ligand 3 (DLL3)-directed cluster of differentiation 3 (CD3) T-cell engager molecule indicated for the treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC) with disease progression on or after at least two prior lines of therapy including platinum-based chemotherapy.

IMDELLTRA has been issued market authorization with conditions, pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization. For further information on IMDELLTRA, refer to Health Canada's Notice of Compliance with conditions – drug products website: <https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/notice-compliance/conditions.html>.

Cytokine release syndrome (CRS) and neurologic toxicity, including immune effector cell-associated neurotoxicity syndrome (ICANS), may be severe or life-threatening. This guidance document supplements the information found in the Product Monograph.

Please consult the Product Monograph at [www.amgen.ca/Imdelltra\\_PM\\_EN](http://www.amgen.ca/Imdelltra_PM_EN).

Report any serious adverse events suggestive of CRS or neurologic toxicity, including ICANS:

- To Amgen Canada Inc. at 1-866-502-6436, or
- To Health Canada at 1-866-234-2345 or visit the web page on adverse reactions (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html>) for information on how to report online, by mail, or by fax.

**DISCLAIMER:**

This material was developed by Amgen as part of the risk minimization plan for IMDELLTRA.  
This material is not intended for promotional use.

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## Overview

1. Please refer to the Product Monograph for the full safety profile, and recommendations on step-up dosing and patient monitoring.
2. Inform the patient/caregiver that IMDELLTRA may cause side effects that may be severe or life-threatening.

CRS and neurologic toxicity, including ICANS, are important risks associated with treatment of IMDELLTRA with possible signs and symptoms as follows:

CRS: Pyrexia, hypotension, tachycardia, headache, hypoxia, nausea, vomiting, and elevated liver enzymes.

Neurologic toxicity, including ICANS: Headache, peripheral neuropathy, taste disorder, dizziness, insomnia, muscular weakness, balance disorder, amnesia, delirium, confusional state, depressed level of consciousness, disorientation, somnolence, lethargy, and bradyphrenia.

3. Monitor patients from the start of the IMDELLTRA infusion for 24 hours on Cycle 1 Day 1 and Cycle 1 Day 8 in an appropriate healthcare setting.

## Guidance on managing cytokine release syndrome (CRS)

- To reduce the risk of CRS: Follow the recommended step-up dosing schedule and administer concomitant medications before and after Cycle 1 IMDELLTRA infusions. Administer IMDELLTRA in a healthcare facility equipped to monitor and manage CRS. Ensure patients are well hydrated prior to initiating IMDELLTRA.
- Clinical signs and symptoms of CRS may include, but are not limited to, pyrexia, hypotension, tachycardia, headache, hypoxia, nausea, vomiting, and elevated liver enzymes.
- Diagnose CRS based on clinical presentation. Evaluate for and treat other causes of fever, hypoxia, and hypotension.
  - o If CRS is suspected, manage according to the recommendations in **Table 1** and consider further management per current practice guidelines.
  - o For severe or life-threatening CRS, recommend anti-IL-6 therapy, for example, tocilizumab or equivalent, and intensive monitoring (e.g. ICU) for supportive therapy. Perform laboratory testing to monitor for disseminated intravascular coagulation (DIC), hematology parameters, as well as pulmonary, cardiac, renal, and hepatic function.

**Table 1: Guidelines for grading and management of CRS**

CRS Grade*	Defining symptoms	IMDELLTRA dosage modification	Management*
<b>Grade 1</b>	Symptoms require symptomatic treatment only (e.g. fever $\geq 38^{\circ}\text{C}$ without hypotension or hypoxia).	Withhold IMDELLTRA until event resolves, then resume IMDELLTRA at the next scheduled dose.†	• Administer symptomatic treatment (e.g. acetaminophen) for fever.
<b>Grade 2</b>	Symptoms require and respond to moderate intervention. <ul style="list-style-type: none"> <li>• Fever: <math>\geq 38^{\circ}\text{C}</math>,</li> <li>• Hypotension responsive to fluids not requiring vasopressors, and/or</li> <li>• Hypoxia requiring low-flow nasal cannula or blow-by.</li> </ul>	Withhold IMDELLTRA until event resolves, then resume IMDELLTRA at the next scheduled dose.†	<ul style="list-style-type: none"> <li>• Recommend hospitalization for a minimum of 24 hours with cardiac telemetry and pulse oximetry.</li> <li>• Administer symptomatic treatment (e.g. acetaminophen) for fever.</li> <li>• Administer supplemental oxygen and intravenous (IV) fluids when indicated.</li> <li>• Consider dexamethasone‡ (or equivalent) 8 mg IV.</li> <li>• Consider tocilizumab (or equivalent).</li> <li>• When resuming treatment at the next planned dose, monitor patients from the start of the IMDELLTRA infusion for 24 hours in an appropriate healthcare setting.</li> </ul>
<b>Grade 3</b>	Severe symptoms defined as temperature $\geq 38^{\circ}\text{C}$ with: <ul style="list-style-type: none"> <li>• Hemodynamic instability requiring a vasopressor (with or without vasopressin) or</li> <li>• Worsening hypoxia or respiratory distress requiring high-flow nasal cannula (<math>&gt; 6\text{ L/min}</math> oxygen) or face mask.</li> </ul>	Withhold IMDELLTRA until the event resolves, then resume IMDELLTRA at the next scheduled dose.†  For recurrent Grade 3 events, permanently discontinue IMDELLTRA.	In addition to Grade 2 treatment: <ul style="list-style-type: none"> <li>• Recommend intensive monitoring, e.g. ICU care.</li> <li>• Administer dexamethasone‡ (or equivalent) 8 mg IV every 8 hours up to 3 doses.</li> <li>• Vasopressor support as needed.</li> <li>• High-flow oxygen support as needed.</li> <li>• Recommend tocilizumab (or equivalent).</li> <li>• Prior to the next dose, administer concomitant medications as recommended in <b>Table 4</b> of this guide. When resuming treatment at the next planned dose, monitor patients from the start of the IMDELLTRA infusion for 24 hours in an appropriate healthcare setting.</li> </ul>
<b>Grade 4</b>	Life-threatening symptoms defined as temperature $\geq 38^{\circ}\text{C}$ with: <ul style="list-style-type: none"> <li>• Hemodynamic instability requiring multiple vasopressors (excluding vasopressin).</li> <li>• Worsening hypoxia or respiratory distress despite oxygen administration requiring positive pressure.</li> </ul>	Permanently discontinue IMDELLTRA.	<ul style="list-style-type: none"> <li>• ICU care.</li> <li>• Per Grade 3 treatment.</li> <li>• Recommend tocilizumab (or equivalent).</li> </ul>

\*Based on American Society for Transplantation and Cellular Therapy (ASTCT) Consensus Grading (2019).

†See **Table 3** in this guide for recommendations on restarting IMDELLTRA after dose delays.

‡Taper steroids per standard of care guidelines.

4. On Cycle 1 Day 1 and Cycle 1 Day 8, advise patients to remain within 1 hour of an appropriate healthcare setting for a total of 48 hours from the start of the infusion with IMDELLTRA, accompanied by a caregiver.
5. Following IMDELLTRA infusion, advise patients to refrain from driving, operating heavy or potentially dangerous machinery, and engaging in hazardous occupations or activities in the event of any neurologic symptoms until they resolve.
6. Ensure the **Patient Wallet Card** is completed with the HCP contact information.
7. When providing the **Patient Wallet Card** to the patient and caregiver:
  - Explain the content of the card.
  - Remind them to always keep the card with them and show it to any HCP who may treat them.
8. Counsel the patient/caregiver to call or see their treating HCP IMMEDIATELY or go to the ER if they notice or experience any signs and symptoms of CRS or neurologic problems at any time during treatment with IMDELLTRA.

## Guidance on managing neurologic toxicity, including immune effector cell-associated neurotoxicity syndrome (ICANS)

- ICANS can occur several weeks following administration of IMDELLTRA. The onset of ICANS can be concurrent with CRS, following resolution of CRS, or in the absence of CRS.
- Clinical signs and symptoms of ICANS may include, but are not limited to, confusional state, depressed level of consciousness, disorientation, somnolence, lethargy, and bradyphrenia.
- At the first sign of neurologic toxicity, including ICANS, withhold IMDELLTRA and consider neurology evaluation.
  - o Rule out other causes of neurologic symptoms.
  - o Provide supportive therapy, which may include intensive care for severe or life-threatening neurologic toxicities.
  - o Manage ICANS and neurologic toxicity according to the recommendations in **Table 2** and consider further management per current practice guidelines.

**Table 2: Guidelines for management of neurologic toxicity, including ICANS**

ICANS Grade*	Defining symptoms	IMDELLTRA dosage modification	Management
<b>Grade 1</b>	ICE score 7–9 <sup>†</sup> with no depressed level of consciousness.	• Withhold IMDELLTRA until ICANS resolves, then resume IMDELLTRA at the next scheduled dose. <sup>‡</sup>	• Administer supportive care.
<b>Grade 2</b>	ICE score 3–6 <sup>†</sup> and/or mild somnolence awaking to voice.	• Withhold IMDELLTRA until ICANS resolves, then resume IMDELLTRA at the next scheduled dose. <sup>‡</sup>	• Administer supportive care. • Administer dexamethasone <sup>§</sup> (or equivalent) 10 mg IV. Can repeat every 6 hours or methylprednisolone 1 mg/kg IV every 12 hours if symptoms worsen. • Monitor neurologic symptoms and consider consultation with neurologist and other specialists for further evaluation and management per current practice guidelines. • Monitor patients for 24 hours following the next dose of IMDELLTRA.
<b>Grade 3</b>	ICE score 0–2 <sup>†</sup> and/or depressed level of consciousness awakening only to tactile stimulus and/or any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention and/or focal or local edema on neuroimaging.	• Withhold IMDELLTRA until ICANS resolves, then resume IMDELLTRA at the next scheduled dose. <sup>‡</sup> • If there is no improvement to Grade ≤ 1 within 7 days or Grade 3 toxicity reoccurs within 7 days of reinitiation, permanently discontinue IMDELLTRA. • For recurrent Grade 3 events, permanently discontinue.	• Recommend intensive monitoring e.g. ICU care. • Consider mechanical ventilation for airway protection. • Dexamethasone <sup>§</sup> (or equivalent) 10 mg IV every 6 hours or methylprednisolone 1 mg/kg IV every 12 hours. • Consider repeat neuroimaging (CT or MRI) every 2–3 days if patient has persistent Grade ≥ 3 neurotoxicity. • Monitor patients for 24 hours following the next dose of IMDELLTRA.
<b>Grade 4</b>	ICE score 0 <sup>†</sup> (patient is unarousable and unable to perform ICE) and/or stupor or coma and/or life-threatening prolonged seizure (> 5 minutes) or repetitive clinical or electrical seizures without return to baseline in between and/or diffuse cerebral edema on neuroimaging, decerebrate or decorticate posturing or papilledema, cranial nerve VI palsy, or Cushing’s triad.	• Permanently discontinue IMDELLTRA.	• ICU care. • Consider mechanical ventilation for airway protection. • High-dose corticosteroids. <sup>§</sup> • Consider repeat neuroimaging (CT or MRI) every 2–3 days if patient has persistent Grade ≥ 3 neurotoxicity. • Treat convulsive status epilepticus per institutional guidelines.

HCP: healthcare provider; ER: emergency room; ICU: intensive care unit; IV: intravenous; EEG: electroencephalogram; anti-IL-6: anti-interleukin-6; CT: computed tomography; MRI: magnetic resonance imaging

\*Based on ASTCT Consensus Grading (2019).

<sup>†</sup>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 (names three objects, e.g. point to clock, pen, button = 3 points); Following commands (e.g. “show me two 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 10 = 1 point). If patient is unarousable and unable to perform ICE Assessment (Grade 4 ICANS) = 0 points.

<sup>‡</sup>See **Table 3** in this guide for recommendations on restarting IMDELLTRA after dose delays.

<sup>§</sup>Taper steroids per standard of care guidelines.

## Guidance on restarting therapy after dosage delay

Table 3: Recommendations for restarting therapy with IMDELLTRA after dosage delay

Last dose administered	Time since the last dose	Action*†
1 mg on Cycle 1 Day 1	2 weeks or less ( $\leq 14$ days)	Administer IMDELLTRA 10 mg, then resume with the planned dosage schedule.
	Greater than 2 weeks ( $> 14$ days)	Administer IMDELLTRA step-up dose 1 mg. If tolerated, increase to 10 mg 1 week later. Then resume with the planned dosage schedule.
10 mg on Cycle 1 Day 8	3 weeks or less ( $\leq 21$ days)	Administer IMDELLTRA 10 mg, then resume with the planned dosage schedule.
	Greater than 3 weeks ( $> 21$ days)	Administer IMDELLTRA step-up dose 1 mg. If tolerated, increase to 10 mg 1 week later. Then resume with the planned dosage schedule.
10 mg on Cycle 1 Day 15 and subsequent cycles every 2 weeks thereafter	4 weeks or less ( $\leq 28$ days)	Administer IMDELLTRA 10 mg, then resume with the planned dosage schedule.
	Greater than 4 weeks ( $> 28$ days)	Administer IMDELLTRA step-up dose 1 mg. If tolerated, increase to 10 mg 1 week later. Then resume with the planned dosage schedule.

\*Administer recommended concomitant medications as described in [Table 4](#).

†Refer to the Product Monograph (Section 4.2, [Table 1](#)) for recommended dosage schedule and monitoring.

## Guidance on concomitant medications

Table 4: Recommended concomitant medications for IMDELLTRA administration

Treatment day	Medication	Administration
Day 1 and Day 8	Administer 8 mg of dexamethasone intravenously (or equivalent).	Within 1 hour prior to IMDELLTRA administration.
Day 1, Day 8, and Day 15	Administer 1 L of normal saline intravenously over 4–5 hours.	Immediately after completion of IMDELLTRA infusion.

Reference: 1. IMDELLTRA™ Product Monograph. Amgen Canada.