IMDELLTRA (AMG757)- tarlatamab-dlle
Amgen Inc

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use IMDELLTRA™ safely and effectively. See full prescribing information for IMDELLTRA.

IMDELLTRA™ (tarlatamab-dlle) for injection, for intravenous use
Initial U.S. Approval: 2024

WARNING: CYTOKINE RELEASE SYNDROME and NEUROLOGIC TOXICITY including IMMUNE EFFECTOR CELL-ASSOCIATED NEUROTOXICITY SYNDROME

See full prescribing information for complete boxed warning.

Cytokine release syndrome (CRS), including serious or life-threatening reactions, can occur in patients receiving IMDELLTRA. Initiate treatment with the IMDELLTRA using step-up dosing schedule to reduce the incidence and severity of CRS. Withhold IMDELLTRA until CRS resolves or permanently discontinue based on severity. (2.5, 5.1)
Neurologic toxicity including Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS), including serious or life-threatening reactions, can occur in patients receiving IMDELLTRA. Monitor patients for signs or symptoms of neurologic toxicity, including ICANS, during treatment and treat promptly. Withhold IMDELLTRA until ICANS resolves or permanently discontinue based on severity. (2.5, 5.2)

INDICATIONS AND USAGE

IMDELLTRA is a bispecific delta-like ligand 3 (DLL3)-directed CD3 T-cell engager indicated for the treatment of adult patients with extensive stage small cell lung cancer (ES-SCLC) with disease progression on or after platinum-based chemotherapy. (1)
This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s). (1)

DOSAGE AND ADMINISTRATION

- Administer as an intravenous infusion over 1-hour. (2.2)
- Administer IMDELLTRA according to the step-up dosing schedule in Table 1 to reduce the risk of cytokine release syndrome. (2.2)
- Administer concomitant medications as recommended. (2.3)
- Monitor patients from the start of the IMDELLTRA infusion for 22 to 24 hours on Cycle 1 Day 1 and Cycle 1 Day 8 in an appropriate healthcare setting.
- Recommend 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 following Cycle 1 Day 1 and Cycle 1 Day 8 doses, accompanied by a caregiver. (2.2)
- See Full Prescribing Information for instructions on preparation and administration. (2.2, 2.6)

DOSAGE FORMS AND STRENGTHS

For injection: 1 mg of lyophilized powder in a single-dose vial for reconstitution and further dilution. (3)
For injection: 10 mg of lyophilized powder in a single-dose vial for reconstitution and further dilution. (3)

CONTRAINDICATIONS

- None. (4)

WARNINGS AND PRECAUTIONS

- Cytopenias: Monitor complete blood counts prior to treatment with IMDELLTRA, before each dose, and as clinically indicated. Withhold or permanently discontinue based on severity. (5.3)
- Infections: Monitor for signs and symptoms of infection; treat appropriately. Withhold or permanently discontinue based on severity. (5.4)
- Hepatotoxicity: Monitor liver enzymes and bilirubin prior to treatment with IMDELLTRA, before each dose, and as clinically indicated. Withhold or permanently discontinue based on severity. (5.5)
- Hypersensitivity: Monitor for signs and symptoms of hypersensitivity and treat accordingly. Withhold or permanently discontinue based on severity. (5.6)

- Embryo-Fetal Toxicity: May cause fetal harm. Advise females of reproductive potential of the potential risk to the fetus and to use effective contraception (5.7, 8.1, 8.3)

ADVERSE REACTIONS

The most common adverse reactions (≥20%) were cytokine release syndrome, fatigue, pyrexia, dysgeusia, decreased appetite, musculoskeletal pain, constipation, anemia and nausea. (6)
The most common Grade 3 or 4 laboratory abnormalities (≥2%) were decreased lymphocytes, decreased sodium, increased uric acid, decreased total neutrophils, decreased hemoglobin, increased activated partial thromboplastin time, decreased potassium, increased aspartate aminotransferase, decreased white blood cells, decreased platelets, and increased alanine aminotransferase. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Amgen Inc. at 1-800-77-AMGEN (1-800-772-6436) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. (6)

USE IN SPECIFIC POPULATIONS

Lactation: Advise not to breastfeed. (8.2)
See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 5/2024

FULL PRESCRIBING INFORMATION: CONTENTS*

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FULL PRESCRIBING INFORMATION

WARNING: CYTOKINE RELEASE SYNDROME AND NEUROLOGIC TOXICITY including IMMUNE EFFECTOR CELL-ASSOCIATED NEUROTOXICITY SYNDROME

Cytokine release syndrome (CRS), including serious or life-threatening reactions, can occur in patients receiving IMDELLTRA. Initiate treatment with IMDELLTRA using the step-up dosing schedule to reduce the incidence and severity of CRS. Withhold IMDELLTRA until CRS resolves or permanently discontinue based on severity *[see Dosage and Administration (2.5) and Warnings and Precautions (5.1)].*

Neurologic toxicity, including immune effector cell-associated neurotoxicity syndrome (ICANS), including serious or life-threatening reactions, can occur in patients receiving IMDELLTRA. Monitor patients for signs and symptoms of neurologic toxicity, including ICANS, during treatment and treat promptly. Withhold IMDELLTRA until ICANS resolves or permanently discontinue based on severity *[see Dosage and Administration (2.5) and Warnings and Precautions (5.2)].*

1 INDICATIONS AND USAGE

IMDELLTRA is indicated for the treatment of adult patients with extensive stage small cell lung cancer (ES-SCLC) with disease progression on or after platinum-based chemotherapy.

This indication is approved under accelerated approval based on overall response rate and duration of response *[see Clinical Studies (14)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosing Information

- Administer IMDELLTRA according to the step-up dosing schedule in Table 1 to reduce the incidence and severity of cytokine release syndrome (CRS) *[see Dosage and Administration (2.2)].*
- For Cycle 1, administer recommended concomitant medications in Table 3 before and after Cycle 1 IMDELLTRA infusions to reduce the risk of CRS reactions *[see Dosage and Administration (2.3)].*
- IMDELLTRA should only be administered by a qualified healthcare professional with appropriate medical support to manage severe reactions such as CRS and neurologic toxicity including immune effector cell-associated neurotoxicity syndrome (ICANS) *[see Warnings and Precautions (5.1, 5.2)].*
- Due to the risk of CRS and neurologic toxicity, including ICANS, monitor patients from the start of the IMDELLTRA infusion for 22 to 24 hours on Cycle 1 Day 1 and Cycle 1 Day 8 in an appropriate healthcare setting *[see Dosage and Administration (2.5) and Warnings and Precautions (5.1, 5.2)].*
- Recommend that patients remain within 1-hour of an appropriate healthcare setting for a total of 48 hours from start of the infusion with IMDELLTRA following Cycle 1 Day 1 and Cycle 1 Day 8 doses, accompanied by a caregiver.
- Prior to administration of IMDELLTRA evaluate complete blood count, liver enzymes and bilirubin before each dose, and as clinically indicated *[see Warnings and Precautions (5.3, 5.5)].*
- Ensure patients are well hydrated prior to administration of IMDELLTRA *[see Warnings and Precautions (5.1)].*

2.2 Recommended Dosage and Administration

- Administer IMDELLTRA as an intravenous infusion over one hour.
- The recommended step-up dosage schedule for IMDELLTRA is provided in Table 1. Administer following step-up dosing to reduce the incidence and severity of CRS.
- After step-up dosing schedule, administer IMDELLTRA biweekly (every 2 weeks) until disease progression or unacceptable toxicity.

Table 1. Recommended Dosage and Schedule of IMDELLTRA

Dosing Schedule	Day	Dose of IMDELLTRA	Administration Instructions	Recommended Monitoring
Step-up Dosing Schedule Cycle 1	Day 1*	Step-up dose* 1 mg	Administer	Monitor patients from the start of the IMDELLTRA infusion for 22 to 24 hours on Cycle 1 Day 1 and Cycle 1 Day 8 in an appropriate healthcare setting. Recommend that patients remain within 1-hour of an appropriate healthcare setting for a total of 48 hours from start of the
	Day 8*	10 mg*		

			IMDELLTRA as a 1-hour intravenous infusion in an appropriate healthcare setting.	infusion with IMDELLTRA, accompanied by a caregiver.
	Day 15	10 mg		Observe patients for 6-8 hours post IMDELLTRA infusion†.
Cycle 2	Day 1 and 15	10 mg		Observe patients for 6-8 hours post IMDELLTRA infusion†.
Cycles 3 and 4	Day 1 and 15	10 mg		Observe patients for 3-4 hours post IMDELLTRA infusion †.
Cycle 5 and subsequent infusions	Day 1 and 15	10 mg		Observe patients for 2 hours post IMDELLTRA infusion †.

Note: see Table 4 for recommendation on restarting IMDELLTRA after dose delays.

* Administer recommended concomitant medications before and after Cycle 1 IMDELLTRA infusions as described in Table 3

† Extended monitoring in a healthcare setting is not required unless the patient experiences Grade ≥2 CRS, ICANS or neurological toxicity during prior treatments. See Tables 5 and 6 for monitoring recommendations.

Administration

- The intravenous (IV) catheter for concomitant medications administration can be used to administer the IMDELLTRA infusion.
- To ensure patency, flush the IV catheter over 3-5 mins using 0.9% Sodium Chloride for Injection.
- Administer the reconstituted and diluted IMDELLTRA as an intravenous infusion at a constant flow rate using an infusion pump. The pump should be programmable, lockable, non-elastomeric, and have an alarm.
- Table 2 provides the infusion duration and rate.

Table 2. IMDELLTRA Infusion Duration and Rate

Infusion Duration for 250 mL IV Preparation	Infusion Rate
1-hour	250 mL/hour

2.3 Recommended Concomitant Medications for IMDELLTRA Administration for Cycle 1

Administer recommended concomitant medications for IMDELLTRA administration during Cycle 1 as presented in Table 3 to reduce the risk of cytokine release syndrome *[see Warnings and Precautions (5.1)].*

Table 3. Recommended Concomitant Medications for IMDELLTRA Administration for Cycle 1

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 liter of normal saline intravenously over 4-5 hours	Immediately after completion of IMDELLTRA infusion

2.4 Restarting IMDELLTRA After Dosage Delay

If a dose of IMDELLTRA is delayed, restart therapy based on the recommendation as listed in Table 4 and resume the dosing schedule accordingly *[see Dosage and Administration (2.2)].* Administer recommended concomitant medications as indicated in section 2.3.

Table 4. Recommendations for Restarting Therapy with IMDELLTRA After Dosage Delay

Last Dose Administered	Time Since the Last Dose Administered	Action*
1 mg on Cycle 1 Day 1	2 weeks or less (≤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 (≤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 (≤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 before and after Cycle 1 IMDELLTRA infusions and monitor patients accordingly *[see Dosage and Administration (2.1, 2.2 and 2.3)].*

2.5 IMDELLTRA Dosage Modifications and Adverse Reaction Management

No dose reduction for IMDELLTRA is recommended. See Table 5 and Table 6 for recommended actions for the management of CRS, neurologic toxicity including ICANS

respectively and Table 7 for cytopenias, infections and other adverse reactions.

Cytokine Release Syndrome (CRS)

Diagnose CRS based on clinical presentation *[see Warnings and Precautions (5.1)]*. Evaluate for and treat other causes of fever, hypoxia, and hypotension.

If CRS is suspected, manage according to the recommendations in Table 5. Monitor patients who experience Grade 2 or higher CRS (e.g., hypotension not responsive to fluids, or hypoxia requiring supplemental oxygen) with continuous cardiac telemetry and pulse oximetry.

For severe or life-threatening CRS, recommend administering tocilizumab or equivalent therapy 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 5 provides the guidelines for grading and dosage modification and management of cytokine release syndrome.

Table 5. Guidelines for Grading and Dosage Modification and Management of Cytokine Release Syndrome*

CRS Grade	Defining Symptoms	IMDELLTRA Dosage Modification	Management
Grade 1	Symptoms require symptomatic treatment only (e.g., fever ≥ 100.4°F 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.
Grade 2	Symptoms require and respond to moderate intervention. • Fever ≥ 100.4°F, • Hypotension responsive to fluids not requiring vasopressors, and/or • Hypoxia requiring low flow nasal cannula or blow-by.	Withhold IMDELLTRA until event resolves, then resume IMDELLTRA at the next scheduled dose†.	• Recommend hospitalization for a minimum of 24 hours with cardiac telemetry and pulse oximetry. • Administer symptomatic treatment (e.g., acetaminophen) for fever. • Administer supplemental oxygen and intravenous fluids when indicated. • Consider dexamethasone[c] (or equivalent) 8 mg IV. • Consider tocilizumab (or equivalent). When resuming treatment at the next planned dose, monitor patients from the start of the IMDELLTRA infusion for 22 to 24 hours in an appropriate healthcare setting.

Grade 3	Severe symptoms defined as temperature ≥ 38°C with: • Hemodynamic instability requiring a vasopressor (with or without vasopressin) or • Worsening hypoxia or respiratory distress requiring high flow nasal canula (> 6 L/min oxygen) or face mask.	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: • Recommend intensive monitoring, e.g., ICU care. • Administer dexamethasone‡ (or equivalent) 8 mg IV every 8 hours up to 3 doses. • Vasopressor support as needed. • High flow oxygen support as needed. • Recommend tocilizumab (or equivalent) • Prior to the next dose, administer concomitant medications as recommended for Cycle 1 (see Table 3). When resuming treatment at the next planned dose, monitor patients from the start of the IMDELLTRA infusion for 22 to 24 hours in an appropriate healthcare setting.
Grade 4	Life-threatening symptoms defined as temperature ≥100.4°F with: • Hemodynamic instability requiring multiple vasopressors (excluding vasopressin). • Worsening hypoxia or respiratory distress despite oxygen administration requiring positive pressure.	Permanently discontinue IMDELLTRA.	• ICU care. • Per Grade 3 treatment. • Recommend tocilizumab (or equivalent).

* CRS based on American Society for Transplantation and Cellular Therapy (ASTCT) Consensus Grading (2019).
† See Table 4 for recommendations on restarting IMDELLTRA after dose delays *[see Dosage and Administration (2.4)]*
‡ Taper steroids per standard of care guidelines.

Neurologic Toxicity including ICANS

At the first sign of neurologic toxicity, including ICANS, withhold IMDELLTRA and consider neurology evaluation. Rule out other causes of neurologic symptoms. Provide supportive therapy, which may include intensive care, for severe or life-threatening neurologic toxicities, including ICANS *[see Warnings and Precautions (5.2)]*. Manage ICANS and neurologic toxicity according to the recommendations in Table 6 and consider further management per current practice guidelines.

Table 6. Guidelines for Management of Neurologic Toxicity including Immune Effector Cell-Associated Neurotoxicity Syndrome*

ICANS Grade*	Defining Symptoms	IMDELLTRA Dosage Modifications	Management
Grade 1*	ICE score 7-9† with no depressed level of consciousness.	• Withhold IMDELLTRA until ICANS resolves, then resume IMDELLTRA at the next scheduled dose‡.	• Supportive care.
Grade 2*	ICE score 3-6† and/or mild somnolence awaking to voice.	• Withhold IMDELLTRA until ICANS resolves, then resume IMDELLTRA at the next scheduled dose‡.	• Supportive care. • Dexamethasone§ (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. • Monitor patients for 22 to 24 hours following the next dose of IMDELLTRA.
	ICE score 0-2† and/or depressed level of consciousness	• Withhold IMDELLTRA until the ICANS resolves, then resume IMDELLTRA at the next scheduled dose‡	• Recommend intensive monitoring, e.g., ICU care. • Consider mechanical ventilation for airway protection. Dexamethasone§ (or

	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.	scheduled dose‡. • 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.	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 22 to 24 hours following the next dose of IMDELLTRA.
Grade 4*	ICE score 0† (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§. • Consider repeat neuroimaging (CT or MRI) every 2-3 days if patient has persistent Grade ≥ 3 neurotoxicity. • Treat convulsive status epilepticus per institutional guidelines.

* ICANS based on American Society for Transplantation and Cellular Therapy (ASTCT) Consensus Grading (2019)

† 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 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.

‡ See Table 4 for recommendations on restarting IMDELLTRA after dose delays *[see Dosage and Administration (2.4)]*

§ Taper steroids per standard of care guidelines

Table 7. Recommended Treatment Interruptions of IMDELLTRA for the Management of Cytopenias, Infections, and Other Adverse Reactions

Adverse Reactions	Severity*	Dosage Modification†
Cytopenias *[see Warnings and Precautions (5.3)]*	Grade 3 or Grade 4 Neutropenia	Withhold IMDELLTRA until recovery to ≤Grade 2. Consider administration of granulocyte colony stimulating factor (G-CSF). Permanently discontinue if recovery to ≤Grade 2 does not occur within 3 weeks.
	Recurrent Grade 4 Neutropenia	Permanently discontinue IMDELLTRA
	Febrile neutropenia	Withhold IMDELLTRA until neutropenia recovers to ≤Grade 2 and fever resolves.
	Hemoglobin <8 g/dL	Withhold IMDELLTRA until hemoglobin is ≥8 g/dL.
	Grade 3 or Grade 4 Decreased platelet count	Withhold IMDELLTRA until platelet count is ≤Grade 2 and no evidence of bleeding. Permanently discontinue if recovery to ≤Grade 2 does not occur within 3 weeks.
	Recurrent Grade 4 Decreased platelet count	Permanently discontinue IMDELLTRA.
Infections *[see Warnings and Precautions (5.4)]*	All Grades	Withhold IMDELLTRA in the step-up phase in patients until infection resolves.
	Grade 3	Withhold IMDELLTRA during the treatment phase until infection improves to ≤Grade 1†.
	Grade 4	Permanently discontinue IMDELLTRA.
Hepatotoxicity *[see Warnings and Precautions (5.5)]*	Grade 3 Increased ALT or AST or bilirubin	Withhold IMDELLTRA until adverse events improve to ≤ Grade 1.
	Grade 4 Increased ALT or AST or bilirubin	Permanently discontinue IMDELLTRA.
	AST or ALT > 3 × ULN with total bilirubin > 2 × ULN in the absence of alternative causes	Permanently discontinue IMDELLTRA.
		Withhold IMDELLTRA until recovery to ≤Grade 1 or

Other Adverse Reactions *[see Adverse Reactions (6.1)]*	Grade 3 or 4	baseline. Consider permanently discontinuing if adverse reaction does not resolve within 28 days. Consider permanent discontinuation for Grade 4 events.

* Severity based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 5.0.
† Refer to Table 4 for dose restarting guidance.

2.6 Preparation

Material Compatibility Information

- IV bags composed of ethyl vinyl acetate (EVA), polyolefin, and polyvinyl chloride, (PVC) have been shown to be compatible with IMDELLTRA at the specified administration conditions.
- IV line and catheter materials composed of polyolefin, PVC, and polyurethane have been shown to be compatible with IMDELLTRA at the specified administration conditions.
- The use of Closed System Transfer Device (CSTD) is not recommended due to potential wrong dose medication error risk. Amgen has not performed compatibility testing of vial adaptor CSTDs with IMDELLTRA.

Step 1: Reconstitute IMDELLTRA with Sterile Water for Injection

- Table 8 provides the required amount of sterile water for injection required to reconstitute IMDELLTRA 1 mg and 10 mg vials.

Do not use IV Solution Stabilizer (IVSS) to reconstitute IMDELLTRA.

The IV Solution Stabilizer (IVSS) is used to coat the intravenous bag prior to addition of reconstituted IMDELLTRA to prevent adsorption of IMDELLTRA to IV bags and IV tubing.

Table 8. Required Amount of Sterile Water for Injection to Reconstitute IMDELLTRA*

IMDELLTRA Vial Strength	Amount of Sterile Water for Injection Needed to Reconstitute IMDELLTRA	Resulting Concentration
1 mg	1.3 mL	0.9 mg/mL
10 mg	4.4 mL	2.4 mg/mL

* Each vial contains overfill to allow for withdrawal of 1.1 mL (1 mg vial) or 4.2 mL (10 mg vial) after reconstitution to ensure delivery at the stated concentration of labeled vial strength.

- Using a needle and syringe filled with the required amount of sterile water, inject the sterile water against the glass vial. Avoid injecting the water directly onto the powder to prevent foaming.
- Gently swirl the contents to mix. Do not shake.
- Inspect parenteral drug products for particulate matter and discoloration prior to

administration. Inspect that the solution is clear to opalescent, colorless to slightly yellow. Do not use if the solution is cloudy or has particulates.
- Further dilute reconstituted IMDELLTRA.
- The reconstituted IMDELLTRA must be further diluted within 4 hours of reconstitution or discarded.

Prepare the infusion bag: Steps 2 to 5

Step 2 : Withdraw 0.9% Sodium Chloride for Injection
- Using a 250 mL prefilled bag of 0.9% Sodium Chloride for Injection, withdraw the amount of sodium chloride specified in Table 9 and discard.

Table 9. Required Amount of 0.9% Sodium Chloride to Withdraw from 250 mL IV Bag

IMDELLTRA Vial Strength	IMDELLTRA Dose	Volume of 0.9% Sodium Chloride to Withdraw From 250 mL IV Bag
1 mg	1 mg	14 mL
10 mg	10 mg	17 mL

Step 3: Add IV Solution Stabilizer to the infusion bag
- Inject 13 mL of IV Solution Stabilizer (IVSS) into the 250 mL 0.9% Sodium Chloride infusion bag, see Table 10.
- Gently mix the contents of the infusion bag to avoid foaming. Do not shake.

Table 10. Required Amount of IV Solution Stabilizer (IVSS) to Add to IV Bag

IMDELLTRA Vial Strength	IMDELLTRA Dose	Volume of IV Solution Stabilizer (IVSS) to Add to IV Bag
1 mg	1 mg	13 mL
10 mg	10 mg	13 mL

Step 4: Dilute the reconstituted IMDELLTRA into the infusion bag
- Transfer the required volume of reconstituted IMDELLTRA listed in Table 11 to the infusion bag *(containing IV Solution Stabilizer).*

NOTE: the final concentrations for the different strength vials are NOT the same following reconstitution and further dilution.

Table 11. Required Amount of Reconstituted IMDELLTRA to Add to 250 mL IV Bag

IMDELLTRA Vial Strength	IMDELLTRA Dose	Volume of Reconstituted IMDELLTRA to Add

		to 250 mL IV Bag
1 mg	1 mg	1.1 mL
10 mg	10 mg	4.2 mL

- Gently mix the contents of the bag. Do not shake.

Step 5: Remove air from IV bag

Remove air from the prepared IV bag using an empty syringe to avoid foaming.

Step 6: Prime IV tubing

- Prime intravenous tubing with either 0.9% Sodium Chloride for Injection or with the final prepared product.
- See Table 12 for maximum storage time of prepared IMDELLTRA infusion.

Prepared IMDELLTRA Infusion Bag Storage Requirements

- Administer reconstituted and diluted IMDELLTRA immediately.
- Table 12 displays the maximum storage time for the prepared IMDELLTRA infusion bag.
- Maximum storage time includes total duration from the time of reconstitution of the vial of IMDELLTRA to the end of the infusion.

Table 12. Maximum Storage Time

	Room Temperature 20°C to 25°C (68°F to 77°F)	**Refrigerated 2°C to 8°C (36°F to 46°F)**
Prepared IMDELLTRA Infusion Bag	8 hours	7 days
• Discard IMDELLTRA infusion after maximum storage time (from time of reconstitution). • Do not re-refrigerate prepared infusion bag.		

3 DOSAGE FORMS AND STRENGTHS

For injection: 1 mg of white to slightly yellow lyophilized powder in a single-dose vial for reconstitution and further dilution.

For injection: 10 mg of white to slightly yellow lyophilized powder in a single-dose vial for reconstitution and further dilution.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Cytokine Release Syndrome

IMDELLTRA can cause cytokine release syndrome (CRS) including serious or life-threatening reactions.

In the pooled safety population *[see Adverse Reactions (6.1)],* CRS occurred in 55% of patients who received IMDELLTRA, including 34% Grade 1, 19% Grade 2, 1.1% Grade 3 and 0.5% Grade 4. Recurrent CRS occurred in 24% of IMDELLTRA-treated patients including 18% Grade 1 and 6% Grade 2.

Most events (43%) of CRS occurred after the first dose with 29% of patients experiencing any grade CRS after the second dose and 9% of patients experiencing CRS following the third dose or later. Following the Day 1, Day 8, Day 15 infusions, 16%, 4.3%, and 2.1% of patients experienced ≥ Grade 2 CRS, respectively. The median time to onset of all grade CRS from most recent dose of IMDELLTRA was 13.5 hours (range: 1 to 268 hours). The median time to onset of ≥ Grade 2 CRS from most recent dose of IMDELLTRA was 14.6 hours (range: 2 to 566 hours).

Clinical signs and symptoms of CRS included pyrexia, hypotension, fatigue, tachycardia, headache, hypoxia, nausea and vomiting. Potentially life-threatening complications of CRS may include cardiac dysfunction, acute respiratory distress syndrome, neurologic toxicity, renal and/or hepatic failure, and disseminated intravascular coagulation (DIC).

Administer IMDELLTRA following the recommended step-up dosing and administer concomitant medications before and after Cycle 1 IMDELLTRA infusions as described in Table 3 to reduce the risk of CRS *[see Dosage and Administration (2.3)].* Administer IMDELLTRA in an appropriate health care facility equipped to monitor and manage CRS. Ensure patients are well hydrated prior to administration of IMDELLTRA.

Closely monitor patients for signs and symptoms of CRS during treatment with IMDELLTRA. At the first sign of CRS, immediately discontinue IMDELLTRA infusion, evaluate the patient for hospitalization and institute supportive care based on severity. Withhold or permanently discontinue IMDELLTRA based on severity *[see Dosage and Administration (2.5)].* Counsel patients to seek medical attention should signs if symptoms of CRS occur.

5.2 Neurologic Toxicity Including ICANS

IMDELLTRA can cause serious or life-threatening neurologic toxicity, including ICANS.

In the pooled safety population *[see Adverse Reactions (6.1)],* neurologic toxicity including ICANS, occurred in 47% of patients who received IMDELLTRA, including 10% Grade 3. The most frequent neurologic toxicities were headache (14%), peripheral neuropathy (7%), dizziness (7%), insomnia (6%), muscular weakness (3.7%), delirium (2.1%), syncope (1.6%) and neurotoxicity (1.1%).

ICANS occurred in 9% of IMDELLTRA-treated patients *[see Adverse Reactions (6.1)].* Recurrent ICANS occurred in 1.6% of patients. Most patients experienced ICANS following cycle 2 day 1 (24%). Following Day 1, Day 8, and Day 15 infusions, 0.5%, 0.5% and 3.7% of patients experienced ≥ Grade 2 ICANS, respectively. The median time to onset of ICANS from the first dose of IMDELLTRA was 29.5 days (range: 1 to 154 days). ICANS can occur several weeks following administration of IMDELLTRA. The median time to resolution of ICANS was 33 days (range: 1 to 93 days).

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.

Patients receiving IMDELLTRA are at risk of neurologic adverse reactions and ICANS resulting in depressed level of consciousness. Advise patients to refrain from driving and engaging in hazardous occupations or activities, such as operating heavy or potentially dangerous machinery, in the event of any neurologic symptoms until they resolve.

Closely monitor patients for signs and symptoms of neurologic toxicity and ICANS during treatment. At the first sign of ICANS, immediately evaluate the patient and provide supportive therapy based on severity. Withhold IMDELLTRA or permanently discontinue based on severity *[see Dosage and Administration (2.5)].*

5.3 Cytopenias

IMDELLTRA can cause cytopenias including neutropenia, thrombocytopenia, and anemia.

In the pooled safety population, *[see Adverse Reactions (6.1)],* decreased neutrophils occurred in 12% including 6% Grade 3 or 4 of IMDELLTRA-treated patients. The median time to onset for Grade 3 or 4 neutropenia was 29.5 days (range: 2 to 213). Decreased platelets occurred in 33% including 3.2% Grade 3 or 4. The median time to onset for Grade 3 or 4 decreased platelets was 50 days (range: 3 to 420). Decreased hemoglobin occurred in 58% including 5% Grade 3 or 4. Febrile neutropenia occurred in 0.5% of patients treated with IMDELLTRA.

Monitor patients for signs and symptoms of cytopenias. Perform complete blood counts prior to treatment with IMDELLTRA, before each dose, and as clinically indicated. Based on the severity of cytopenias, temporarily withhold, or permanently discontinue IMDELLTRA *[see Dosage and Administration (2.5)].*

5.4 Infections

IMDELLTRA can cause serious infections, including life-threatening and fatal infections.

In the pooled safety population, *[see Adverse Reactions (6.1)],* infections including opportunistic infections occurred in 41% of patients who received IMDELLTRA. Grade 3 or 4 infections occurred in 13% of patients. The most frequent infections were COVID-19 (9%, majority during the COVID-19 pandemic), urinary tract infection (10%), pneumonia (9%), respiratory tract infection (3.2%), and candida infection (3.2%). Monitor patients for signs and symptoms of infection prior to and during treatment with IMDELLTRA and treat as clinically indicated. Withhold or permanently discontinue IMDELLTRA based on severity *[see Dosage and Administration (2.5)].*

5.5 Hepatotoxicity

IMDELLTRA can cause hepatotoxicity.

In the pooled safety population *[see Adverse Reactions (6.1)],* elevated ALT occurred in 42% with Grade 3 or 4 ALT elevation occurring in 2.1% of IMDELLTRA-treated patients. Elevated AST occurred in 44% of patients, with Grade 3 or 4 AST elevation occurring in 3.2%. Elevated bilirubin occurred in 15% of patients, with Grade 3 or 4 total bilirubin elevations occurred in 1.6% of patients *[see Adverse Reactions (6.1)].* Liver enzyme elevation can occur with or without concurrent CRS. Monitor liver enzymes and bilirubin

prior to treatment with IMDELLTRA, before each dose, and as clinically indicated. Withhold IMDELLTRA or permanently discontinue based on severity *[see Dosage and Administration (2.5)].*

5.6 Hypersensitivity

IMDELLTRA can cause severe hypersensitivity reactions.

Clinical signs and symptoms of hypersensitivity may include, but are not limited to, rash and bronchospasm. Monitor patients for signs and symptoms of hypersensitivity during treatment with IMDELLTRA and manage as clinically indicated. Withhold or consider permanent discontinuation of IMDELLTRA based on severity *[see Dosage and Administration (2.5)]*.

5.7 Embryo-Fetal Toxicity

Based on its mechanism of action, IMDELLTRA may cause fetal harm when administered to a pregnant woman. Advise patients of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with IMDELLTRA and for 2 months after the last dose *[see Use in Specific Populations (8.1, 8.3)].*

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Cytokine Release Syndrome (CRS) *[see Warnings and Precautions (5.1)]*
- Neurologic Toxicity Including ICANS *[see Warnings and Precautions (5.2)]*
- Cytopenias *[see Warnings and Precautions (5.3)]*
- Infections *[see Warnings and Precautions (5.4)]*
- Hepatotoxicity *[see Warnings and Precautions (5.5)]*
- Hypersensitivity *[see Warnings and Precautions (5.6)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Extensive Stage Small Cell Lung Cancer

The pooled safety population described in the WARNINGS AND PRECAUTIONS and below reflects exposure to intravenous IMDELLTRA, as a single agent, at the recommended dosage of IMDELLTRA 1 mg on Cycle 1 Day 1 followed by 10 mg on Days 8 and 15, and then every 2 weeks until disease progression or intolerable toxicity in 187 patients with extensive stage small cell lung cancer enrolled in Study DeLLphi-300 and Study DeLLphi-301. Among 187 patients who received IMDELLTRA, 31% were exposed for 6 months or longer and 14% were exposed for greater than one year.

The most common (>20%) adverse reactions were cytokine release syndrome (55%), fatigue (51%), pyrexia (36%), dysgeusia (36%), decreased appetite (34%), musculoskeletal pain (30%), constipation (30%), anemia (27%) and nausea (22%). The most common (≥2%) Grade 3 or 4 laboratory abnormalities were decreased lymphocytes (57%), decreased sodium (16%), increased uric acid (10%), decreased

total neutrophils (6%), decreased hemoglobin (5%), increased activated partial thromboplastin time (5%), decreased potassium (5%), increased aspartate aminotransferase (3.2%), decreased white blood cells (3.8%), decreased platelets (3.2%) and increased alanine aminotransferase (2.1%).

The demographic characteristics of patients who received IMDELLTRA were: median age 66 years (range: 35 to 82); 65% male; 70% White, 26% Asian, 2.1% Black or African American; and 2.1% Hispanic or Latino.

Serious adverse reactions occurred in 58% of patients who received IMDELLTRA. Serious adverse reactions in >3% of patients included cytokine release syndrome (24%), pneumonia (6%), pyrexia (3.7%) and hyponatremia (3.6%). Fatal adverse reactions occurred in 2.7% of patients who received IMDELLTRA including pneumonia 0.5%, aspiration (0.5%), pulmonary embolism (0.5%), respiratory acidosis (0.5%), and respiratory failure (0.5%).

Permanent discontinuation of IMDELLTRA due to an adverse reaction occurred in 7% of patients. Adverse reactions which resulted in permanent discontinuation of IMDELLTRA in >1% of patients included cytokine release syndrome (1.6%) and tumor lysis syndrome (1.1%).

Dosage interruptions of IMDELLTRA due to an adverse reaction occurred in 27% of patients. Adverse reactions which required dosage interruption in ≥2% of patients included fatigue (3.2%), cytokine release syndrome (2 .7%) and respiratory tract infection (2.1%).

Table 13 summarizes adverse reactions observed in Study DeLLphi-300 and Study DeLLphi-301.

Table 13. Adverse Reactions (≥ 15%) in Patients with ES-SCLC Who Received IMDELLTRA in Study DeLLphi-300 and Study DeLLphi-301

Adverse Reaction	IMDELLTRA* (N = 187)	
	Any Grade (%)	Grade 3 or 4 (%)
Immune system disorders		
Cytokine release syndrome†	55	1.6
General disorders and administration site conditions		
Fatigue‡	51	10
Pyrexia	36	0
Nervous system disorders		
Dysgeusia	36	0
Metabolism and nutrition disorders		
Decreased appetite	34	2.7
Nausea	22	1.6
Gastrointestinal disorders		
Constipation	30	0.5
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain§	30	1.1

Blood and Lymphatic System Disorders		
Anemia	27	6
Respiratory, thoracic and mediastinal disorders		
Dyspnea¶	17	2.1
Cough	17	0

* Graded using CTCAE Version 4.0 and Version 5.0.
† Based on American Society for Transplantation and Cellular Therapy (ASTCT) 2019.
‡ Includes fatigue and asthenia.
§ Includes myalgia, arthralgia, back pain, pain in extremity, neck pain, musculoskeletal chest pain, non-cardiac chest pain and bone pain.
¶ Includes dyspnea and exertional dyspnea.

Table 14 summarizes laboratory abnormalities in Study DeLLphi-300 and Study DeLLphi-301.

Table 14. Laboratory Abnormalities (≥ 20%) That Worsened from Baseline in Patients with ES - SCLC in Study DeLLphi-300 and Study DeLLphi-301

Laboratory Abnormality	IMDELLTRA*	
	All Grades (%)	Grade 3 or 4 (%)
Hematology		
Decreased lymphocytes	84	57
Decreased hemoglobin	58	5
Decreased white blood cells	44	3.8
Decreased platelets	33	3.2
Decreased neutrophils†	12	6
Chemistry		
Decreased sodium	68	16
Decreased potassium	50	5
Increased aspartate amino transferase	44	3.2
Increased alanine aminotransferase	42	2.1
Decreased magnesium	33	1.6
Increased creatinine	29	0.5
Increased sodium	26	0.0
Increased alkaline phosphate	22	0.0

* The denominator used to calculate the rate varied from 41 to 187 based on the number of patients with a baseline value and at least one post-treatment value.
† All Grade lab abnormalities occurring at a frequency less than 20% included decreased neutrophils.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action, IMDELLTRA may cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1)]*. There are no available data on the use of IMDELLTRA in pregnant women to inform a drug-associated risk.

In an animal reproduction study, a murine surrogate molecule administered intravenously to pregnant mice crossed the placental barrier.

Tarlatamab-dlle causes T-cell activation and cytokine release; immune activation may compromise pregnancy maintenance.

Human immunoglobulin G (IgG) and proteins comprising IgG-derived fragment crystallizable (Fc) domains are known to cross the placental barrier; therefore, IMDELLTRA has the potential to be transmitted from the mother to the developing fetus. Advise women of the potential risk to the fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% - 4% and 15% - 20%, respectively.

Data

Animal Data

Animal reproduction studies have not been conducted with tarlatamab-dlle. In an embryo-fetal developmental toxicity study, a murine surrogate molecule was administered intravenously to pregnant mice during the period of organogenesis. The surrogate molecule crossed the placental barrier and did not cause maternal toxicity, embryo-fetal toxicity or teratogenicity.

8.2 Lactation

Risk Summary

There are no data on the presence of tarlatamab-dlle in human milk or the effects on the breastfed child or on milk production. Maternal IgG is known to be present in human milk. The effects of local gastrointestinal exposure and limited systemic exposure in the breastfed child to IMDELLTRA are unknown. Because of the potential for serious adverse reactions in a breastfed child, advise patients not to breastfeed during treatment with IMDELLTRA and for 2 months after the last dose.

8.3 Females and Males of Reproductive Potential

IMDELLTRA may cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*.

Pregnancy Testing

Verify pregnancy status of females of reproductive potential prior to initiating IMDELLTRA.

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment

with IMDELLTRA and for 2 months after the last dose.

8.4 Pediatric Use

The safety and effectiveness of IMDELLTRA have not been established in pediatric patients.

8.5 Geriatric Use

Of the 187 patients with SCLC who received IMDELLTRA 10 mg as a single agent, 54% were 65 years of age or older and 12% were 75 years of age or older. No overall differences in IMDELLTRA pharmacokinetics, or safety were observed between older patients (≥ 65 years of age) and younger patients. Clinical studies of IMDELLTRA did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients.

11 DESCRIPTION

Tarlatamab-dlle is a bispecific DLL3-directed CD3 T-cell engager that binds to DLL3 expressed on the surface of cells, including tumor cells, and CD3 expressed on the surface of T cells. Tarlatamab-dlle is produced using recombinant DNA technology in Chinese hamster ovary cells. It consists of 982 amino acids and has a molecular weight of approximately 105 kilodaltons.

IMDELLTRA (tarlatamab-dlle) for injection is supplied as a sterile, preservative-free, white to slightly yellow, lyophilized powder in a single-dose vial for reconstitution and further dilution.

Each 1 mg vial contains tarlatamab-dlle (1 mg), glutamic acid (0.72 mg), polysorbate 80 (0.04 mg), sucrose (37.1 mg), and sodium hydroxide to adjust pH to 4.2. After reconstitution with 1.3 mL of Sterile Water for Injection the resulting concentration is 0.9 mg/mL IMDELLTRA.

Each 10 mg vial contains tarlatamab-dlle (10 mg), glutamic acid (3.7 mg), polysorbate 80 (0.2 mg), sucrose (194.4 mg), and sodium hydroxide to adjust pH to 4.2. After reconstitution with 4.4 mL of Sterile Water for Injection the resulting concentration is 2.4 mg/mL IMDELLTRA.

IV Solution Stabilizer is supplied as a sterile, preservative-free, colorless to slightly yellow, clear solution. Each vial of IV Solution Stabilizer contains citric acid monohydrate (36.75 mg), lysine hydrochloride (1598.8 mg), polysorbate 80 (7 mg), sodium hydroxide to adjust pH to 7.0, and water for injection.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Tarlatamab-dlle is a bispecific T-cell engager that binds to DLL3 expressed on the surface of cells, including tumor cells, and CD3 expressed on the surface of T-cells. Tarlatamab-dlle causes T-cell activation, release of inflammatory cytokines, and lysis of DLL3-expressing cells. Tarlatamab-dlle had anti-tumor activity in mouse models of SCLC.

12.2 Pharmacodynamics

Exposure-Response Relationships

There are no clinically significant exposure-response relationships for efficacy over the exposure range observed between tarlatamab-dlle 10 mg and 100 mg (10 times the highest approved recommended dosage).

There is an exposure-response relationship between tarlatamab-dlle exposure and neutropenia or neurologic toxicity including ICANS with a higher risk of any grade neutropenia or neurologic toxicity including ICANS at higher exposure.

Serum Cytokines

Transient elevation of serum cytokines IL-2, IL-6, IL-8, IL-10, and IFN-γ were observed at a tarlatamab-dlle dosage of 0.3 mg and above. Peak elevation of cytokines was generally observed 24 hours following the initial dose of IMDELLTRA at 1 mg on Cycle 1 Day 1 and generally returned to baseline levels prior to the next infusion on Cycle 1 Day 8.

12.3 Pharmacokinetics

Tarlatamab-dlle pharmacokinetic parameters are presented as geometric mean (CV%) unless otherwise specified. The exposure of tarlatamab-dlle increased dose proportionally in the evaluated dose range of IMDELLTRA 1 mg to 100 mg every 2 weeks (10 times the highest approved recommended dosage). Tarlatamab-dlle steady state exposures were achieved by Cycle 2 Day 15. Pharmacokinetic exposures are summarized for the recommended dosage of IMDELLTRA in Table 15.

Table 15. Pharmacokinetic Parameters of Tarlatamab-dlle

	Parameter*		
	C_{avg} (ng/mL)	**C_{max} (ng/mL)**	**C_{trough} (ng/mL)**
First step-up dose 1 mg	102 (29%)	285 (41%)	47 (38%)
First treatment dose 10 mg	1050 (29%)	2900 (41%)	502 (39%)
Steady state 10 mg every 2 weeks	1040 (44%)	3400 (40%)	495 (73%)

* Parameters are reported as geometric mean (CV%).

Distribution

Tarlatamab-dlle steady state volume of distribution is 8.6 L (18.3%).

Metabolism

Tarlatamab-dlle is expected to be metabolized into small peptides by catabolic pathways.

Elimination

Tarlatamab-dlle's median terminal elimination half-life (min, max) is 11.2 (4.3 to 26.5) days and the estimated systemic clearance is 0.65 L/day (44%) in patients with SCLC.

Specific Populations

No clinically significant differences in the pharmacokinetics of tarlatamab-dlle were observed based on age (32 to 82 years), body weight (35 to 149 kg), sex, race (White and Asian), mild or moderate renal impairment (eGFR ≥ 30 to < 90 mL/min), or mild hepatic impairment (total bilirubin ≤ upper limit of normal (ULN) and AST > ULN).

The effects of severe renal impairment (eGFR 15 to 29 mL/min), end-stage renal disease (eGFR <15 mL/min), or moderate to severe hepatic impairment (total bilirubin > 1.5 × ULN, any AST) on the pharmacokinetics of tarlatamab-dlle are unknown.

Effects of Tarlatamab-dlle on CYP450 Substrates

Tarlatamab-dlle causes transient release of cytokines that may suppress CYP450 enzymes and may result in an increased exposure of concomitant CYP substrates during and up to 14 days after occurrence of cytokine release syndrome *[see Clinical Pharmacology (12.2)]*.

12.6 Immunogenicity

The observed incidence of antidrug antibodies (ADA) is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of ADA in the studies described below with the incidence of ADA in other studies, including those of tarlatamab-dlle or of other tarlatamab products.

In Study DeLLphi-301, of the patients who received recommended step-up and full dosage of IMDELLTRA and were evaluable for presence of ADA against tarlatamab-dlle, 3.2% (4/124) of patients tested positive for anti-tarlatamab-dlle antibodies and none of the patients developed neutralizing antibodies against tarlatamab-dlle based on a cell-based bioassay. Because of the low occurrence of ADA, the effect of these antibodies on the pharmacokinetics, pharmacodynamics, safety, and effectiveness of tarlatamab-dlle is unknown.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity or genotoxicity studies have been conducted with tarlatamab-dlle.

No studies have been conducted to evaluate the effects of tarlatamab-dlle on fertility.

14 CLINICAL STUDIES

14.1 Small Cell Lung Cancer

The efficacy of IMDELLTRA was evaluated in Study DeLLphi-301 [NCT05060016], an open-label, multicenter, multi-cohort clinical trial. Eligible patients were required to have relapsed/refractory SCLC with disease progression after receiving previous treatment with platinum-based chemotherapy and at least one other line of prior therapy, an ECOG Performance Status of 0 or 1, and at least one measurable lesion as defined by Response Evaluation Criteria in Solid Tumors (RECIST v1.1) The trial excluded patients with symptomatic brain metastases, evidence of interstitial lung disease or non-infectious pneumonitis, and active immunodeficiency.

A total of 99 patients received IMDELLTRA intravenously at an initial dose of 1 mg on Cycle 1 Day 1 followed by 10 mg on Days 8, 15, and every 2 weeks thereafter until disease progression or unacceptable toxicity.

The study population characteristics were: median age 64 years (range: 35 to 82); 48% of patients ≥65 years and 10% of patients ≥75 years; 72% male; 58% White, 41% Asian; 1% Hispanic or Latino; and 74% have ECOG 1.

Ninety-seven percent of patients had metastatic disease at baseline; 22% had brain metastases at baseline; and 92% were former/current smokers. All patients received prior platinum-based chemotherapy (median two lines); 74% received prior anti-PD-(L)1 therapy (including 59% who received anti-PD[L]1 therapy in combination with platinum-based chemotherapy in the frontline setting); 51% received prior topoisomerase I inhibitor (including 20% who received topotecan). Platinum sensitivity status, defined by time to progression after first line platinum therapy, was known for 69/99 patients. Twenty-seven patients (27%) had platinum-resistant SCLC, defined as time to progression < 90 days after first line platinum therapy, while 42 patients (42%) had platinum-sensitive SCLC.

Tumor assessments were performed every 6 weeks for the first 48 weeks and every 12 weeks thereafter. The major efficacy outcome measures were overall response rate (ORR) and duration of response (DOR) as evaluated by Blinded Independent Central Review (BICR) according to RECIST v1.1.

Efficacy results are presented in Table 16.

Table 16. Efficacy Results for Study DeLLphi-301

Efficacy Parameter	IMDELLTRA (N = 99)
Overall Response Rate (ORR)	
ORR, % (95% CI)*	40 (31, 51)
Complete Response, n (%)	2 (2)
Partial Response, n (%)	38 (38)
Duration of Response (DOR)*	
Median†, months (range)	9.7 (2.7, 20.7+)
Duration ≥ 6 months‡, %	68
Duration ≥ 12 months‡, %	40

* Assessed by Blinded Independent Central Review, CI= Confidence Interval
† Median based on Kaplan-Meier estimate.
‡ Based on observed duration of response.

Of the 69 patients with available data regarding platinum sensitivity status, the ORR was 52% (95% CI 32, 71) in 27 patients with platinum-resistant SCLC and 31% (95% CI 18, 47) in 42 patients with platinum-sensitive SCLC.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

IMDELLTRA (tarlatamab-dlle) for injection is a sterile, preservative-free, white to slightly

yellow, lyophilized powder supplied as follows:

- 1 mg package (NDC 55513-059-01) contains 1 single-dose vial of 1 mg IMDELLTRA and 2 vials of 7 mL IV Solution Stabilizer.
- 10 mg package (NDC 55513-077-01) contains 1 single-dose vial of 10 mg IMDELLTRA and 2 vials of 7 mL IV Solution Stabilizer.

16.2 Storage and Handling

Store IMDELLTRA and IV Solution Stabilizer (IVSS) vials refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light until time of use. Do not freeze.

IMDELLTRA and IV Solution Stabilizer (IVSS) vials may be kept at room temperature between 20°C to 25°C (68°F to 77°F) for up to 24 hours in the original carton to protect from light.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Cytokine Release Syndrome (CRS)

Advise patients of the risk of CRS, and to immediately contact their healthcare provider for signs and symptoms associated with CRS including pyrexia, hypotension, fatigue, tachycardia, headache, hypoxia, nausea and vomiting *[see Warnings and Precautions (5.1)]*.

Advise patients that they should be monitored from the start of the IMDELLTRA infusion for 22 to 24 hours on Cycle 1 Day 1 and Cycle 1 Day 8 in an appropriate healthcare setting *[see Warnings and Precautions (5.1)].*

Advise patients to remain within 1-hour of an appropriate healthcare setting for a total of 48 hours from start of the infusion with IMDELLTRA following Cycle 1 Day 1 and Cycle 1 Day 8 doses, accompanied by a caregiver.

Neurologic Toxicity Including Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)

Discuss the signs and symptoms associated with ICANS. Advise patients to immediately contact their healthcare provider if they experience any signs or symptoms of ICANS, such as encephalopathy, confusion, delirium, seizure, ataxia, weakness or numbness of arms and legs, tremor, and headache.

Advise patients who experience neurologic toxicity or symptoms of ICANS to refrain from driving or operating heavy or potentially dangerous machinery and engaging in hazardous occupations or activities during treatment with IMDELLTRA *[see Warnings and Precautions (5.2)]*.

Cytopenias

Discuss the signs and symptoms associated with cytopenias, including neutropenia and febrile neutropenia, anemia, and thrombocytopenia *[see Warnings and Precautions (5.3)].* Inform patients that they will need to undergo lab tests to monitor blood counts. Advise patients to immediately contact their healthcare provider if they experience any signs or symptoms of cytopenias.

Infections

Discuss the signs and symptoms of infections. Advise patients of the risk of serious infections, and to immediately contact their healthcare provider for signs or symptoms of infections *[see Warnings and Precautions (5.4)].*

Hepatotoxicity

Discuss the signs and symptoms of hepatotoxicity. Inform patients that they will need to undergo lab tests to monitor liver function. Advise patients to immediately contact their healthcare provider for signs and symptoms of liver dysfunction *[see Warnings and Precautions (5.5)].*

Hypersensitivity

Discuss the signs and symptoms of allergic reactions. Advise patients to immediately seek medical attention for any signs and symptoms of severe reactions *[see Warnings and Precautions (5.6)].*

Embryo-Fetal Toxicity

Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to inform their healthcare provider if they are pregnant or become pregnant. Advise females of reproductive potential to use effective contraception during treatment with IMDELLTRA and for 2 months after the last dose *[see Warnings and Precautions (5.7), Use in Specific Populations (8.1, 8.3)]*.

Lactation

Advise women not to breastfeed during treatment with IMDELLTRA and for 2 months after the last dose *[see Use in Specific Populations (8.2)].*

IMDELLTRA™ (tarlatamab-dlle)

Manufactured by:
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U.S. License No. 1080
Patent: http://pat.amgen.com/imdelltra/

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MEDICATION GUIDE
IMDELLTRA™ (im del trah)
(tarlatamab-dlle)
for injection, for intravenous use

What is the most important information I should know about IMDELLTRA?
IMDELLTRA may cause serious side effects, including:

- **Cytokine Release Syndrome (CRS).** CRS is common during treatment with IMDELLTRA and can also be serious or life-threatening. Tell your healthcare provider or get medical help right away if you develop any signs or symptoms of CRS, including:

- fever of 100.4°F (38°C) or higher
- low blood pressure
- tiredness
- fast heartbeat or dizziness
- headache
- shortness of breath or trouble breathing
- nausea and vomiting
- confusion, restlessness, or feeling anxious
- problems with balance and movement, such as trouble walking
- heart, liver, or kidney problems
- unusual bleeding or bleeding that lasts a long time

Due to the risk of CRS, you will receive IMDELLTRA on a "step-up dosing schedule":

- The step-up dosing schedule is when you receive a smaller dose of IMDELLTRA on Day 1 of your first treatment cycle (Cycle 1).
- You will receive the full treatment dose of IMDELLTRA on Day 8 and Day 15 of Cycle 1. You will receive the full treatment dose 1 time every 2 weeks after Day 15 of Cycle 1.
- If your dose of IMDELLTRA is delayed for any reason, you may need to repeat the "step-up dosing schedule".
- Before receiving your Day 1 and Day 8 doses of Cycle 1 of IMDELLTRA, you will be given a medicine to help reduce your risk of CRS. This will be given into your vein by intravenous (IV) infusion. You will also receive IV fluids after each of your Cycle 1 doses of IMDELLTRA (on Day 1, Day 8, and Day 15). Your healthcare provider will decide if you need to receive medicines to help reduce your risk of CRS with future doses.
- See **"How will I receive IMDELLTRA?"** for more information about how you will receive IMDELLTRA.

- **Neurologic Problems.** IMDELLTRA can cause neurologic problems that can be serious or life-threatening. Neurologic problems may happen days or weeks after you receive IMDELLTRA. Your healthcare provider may refer you to a healthcare provider who specializes in neurologic problems. Tell your healthcare provider right away if you develop any signs or symptoms of neurologic problems, including:

  - trouble speaking, memory loss, or personality changes
  - confusion, feeling disoriented, slow thinking, or not being able to think clearly
  - seizure
  - problems with walking, or loss of balance or coordination
  - weakness or numbness of your arms or legs
  - shaking (tremors)
  - headache
  - numbness or tingling of your hands or feet
  - trouble sleeping
  - fainting or loss of consciousness
  - feeling like you have no energy

Due to the risk of CRS and neurologic problems you will receive the following monitoring during treatment with IMDELLTRA:

- **For Day 1 and Day 8 of Cycle 1 doses**, your healthcare provider will monitor you **for 22 to 24 hours from the start of the IMDELLTRA infusion in an**

appropriate healthcare setting that can manage these side effects. **You should remain within 1 hour of an appropriate healthcare setting for a total of 48 hours** from the start of the IMDELLTRA infusion after your Day 1 and Day 8 of Cycle 1 doses **and be accompanied by a caregiver**.
- **For Day 15 of Cycle 1 and Cycle 2 doses**, your healthcare provider will watch you **for 6 to 8 hours** after the IMDELLTRA infusion.
- **For Cycle 3 and Cycle 4 doses**, your healthcare provider will watch you **for 3 to 4 hours** after the IMDELLTRA infusion.
- **For Cycle 5 and later doses**, your healthcare provider will watch you **for 2 hours** after the IMDELLTRA infusion.

Your healthcare provider will monitor you for signs and symptoms of CRS and neurologic problems during treatment with IMDELLTRA, as well as other side effects, and treat you as needed. You may be hospitalized if you develop signs or symptoms of CRS or neurologic problems during treatment with IMDELLTRA. Your healthcare provider may temporarily stop or completely stop your treatment with IMDELLTRA if you develop CRS, neurologic problems, or any other side effects that are severe.
See **"What are the possible side effects of IMDELLTRA?"** for more information about side effects.

What is IMDELLTRA?
IMDELLTRA is a prescription medicine used to treat adults with extensive stage small cell lung cancer (ES-SCLC), which is cancer that has spread throughout the lung or to other parts of the body, **and** who have received treatment with chemotherapy that contains platinum, and it did not work or is no longer working.
It is not known if IMDELLTRA is safe and effective in children.

Before receiving IMDELLTRA, tell your healthcare provider about all of your medical conditions, including if you:
- have an infection
- are pregnant or plan to become pregnant. IMDELLTRA may harm your unborn baby.
  Females who are able to become pregnant:
  - Your healthcare provider should do a pregnancy test before you start treatment with IMDELLTRA.
  - You should use an effective form of birth control (contraception) during treatment with IMDELLTRA, and for 2 months after your last dose of IMDELLTRA.
  - Tell your healthcare provider right away if you become pregnant or think that you may be pregnant during treatment with IMDELLTRA.
- are breastfeeding or plan to breastfeed. It is not known if IMDELLTRA passes into your breast milk. Do not breastfeed during treatment with IMDELLTRA and for 2 months after the last dose of IMDELLTRA.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How will I receive IMDELLTRA?
- IMDELLTRA will be given to you by your healthcare provider by intravenous (IV) infusion through a needle placed in a vein. The infusion will take about 1 hour.
- Your IMDELLTRA treatment schedule is divided into cycles that are usually 28 days (4 weeks) long.
- Your healthcare provider will decide how many treatment cycles you will receive.
- See **"What is the most important information I should know about**

IMDELLTRA?" for more information about how you will receive IMDELLTRA.

What should I avoid while receiving IMDELLTRA?

Do not drive, operate heavy or potentially dangerous machinery or do other dangerous activities, including work-related activities, during treatment with IMDELLTRA if you develop dizziness, confusion, tremors, sleepiness, or any other symptoms that impair consciousness until your signs and symptoms go away. These may be signs and symptoms of neurologic problems. See "**What is the most important information I should know about IMDELLTRA**" for more information about signs and symptoms of neurologic problems.

What are the possible side effects of IMDELLTRA?

IMDELLTRA may cause serious side effects, including:

- See **"What is the most important information I should know about IMDELLTRA?"**
- **Low blood cell counts (cytopenia).** Decreased blood cell counts are common with IMDELLTRA and can also be severe. IMDELLTRA may cause the following low blood cell counts:
  - low white blood cell counts (neutropenia). Low white blood cells can increase your risk for infection.
  - low red blood cell counts (anemia). Low red blood cells can cause tiredness and shortness of breath.
  - low platelet counts (thrombocytopenia). Low platelet counts can cause bruising or bleeding problems.
- **Infections.** IMDELLTRA can cause serious infections that can be life-threatening and may lead to death. Your healthcare provider will check you for signs and symptoms of infection before and during treatment with IMDELLTRA. Tell your healthcare provider right away if you develop any signs or symptoms of infection during treatment with IMDELLTRA, including:
  - fever of 100.4°F (38°C) or higher
  - cough
  - chest pain
  - tiredness
  - shortness of breath
  - painful rash
  - sore throat
  - pain during urination
  - feeling weak or generally unwell
- **Liver problems.** IMDELLTRA can cause increased liver enzymes and bilirubin in your blood. These increases can happen with or without you also having CRS. Tell your healthcare provider if you develop any signs or symptoms of liver problems, including:
  - tiredness
  - loss of appetite
  - pain in your right upper stomach-area (abdomen)
  - dark urine
  - yellowing of your skin or the white part of your eyes
- **Allergic reactions.** IMDELLTRA can cause allergic reactions that can be severe. Go to the nearest emergency room or get medical help right away if you develop any signs or symptoms of a severe allergic reaction during treatment with IMDELLTRA,

including:

- shortness of breath or trouble breathing
- pain or tightness in your chest and back
- wheezing
- coughing
- feeling lightheaded or dizzy
- rash

Your healthcare provider will do bloodwork before you start and during treatment with IMDELLTRA. Your healthcare provider will monitor you for signs or symptoms of these serious side effects during treatment and may temporarily or completely stop treatment with IMDELLTRA if you develop certain serious side effects.

The most common side effects of IMDELLTRA also include:

- tiredness
- fever
- a bad or metallic taste in your mouth
- decreased appetite
- muscle or bone pain
- constipation
- nausea

The most common severe abnormal lab test results with IMDELLTRA include: decreased white blood cells, decreased sodium, increased uric acid, decreased red blood cells, increased blood clotting time, decreased potassium, increased liver enzymes, and decreased platelets.

These are not all of the possible side effects of IMDELLTRA.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of IMDELLTRA

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. You can ask your pharmacist or healthcare provider for information about IMDELLTRA that is written for health professionals.

What are the ingredients in IMDELLTRA?

Active ingredients: tarlatamab-dlle

Inactive ingredients: glutamic acid, polysorbate 80, sucrose, and sodium hydroxide.

Inactive ingredients of IV Solution Stabilizer: citric acid monohydrate, lysine hydrochloride, polysorbate 80, sodium hydroxide and water for Injection.

Manufactured by: Amgen Inc., One Amgen Center Drive, Thousand Oaks, CA 91320-1799

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For more information, go to www.imdelltra.com or call Amgen at 1-800-772-6436.

This Medication Guide has been approved by the U.S. Food and Drug Administration. Issued: 05/2024

PRINCIPAL DISPLAY PANEL - Kit Package - 55513-059

Contains 1 IMDELLTRA Single-Dose Vial
Contains 2 IV Solution Stabilizer Vials

NDC 55513-059-01

AMGEN®

IMDELLTRA™
(tarlatamab-dlle)
for injection

1 mg/vial

For Intravenous Infusion after Dilution

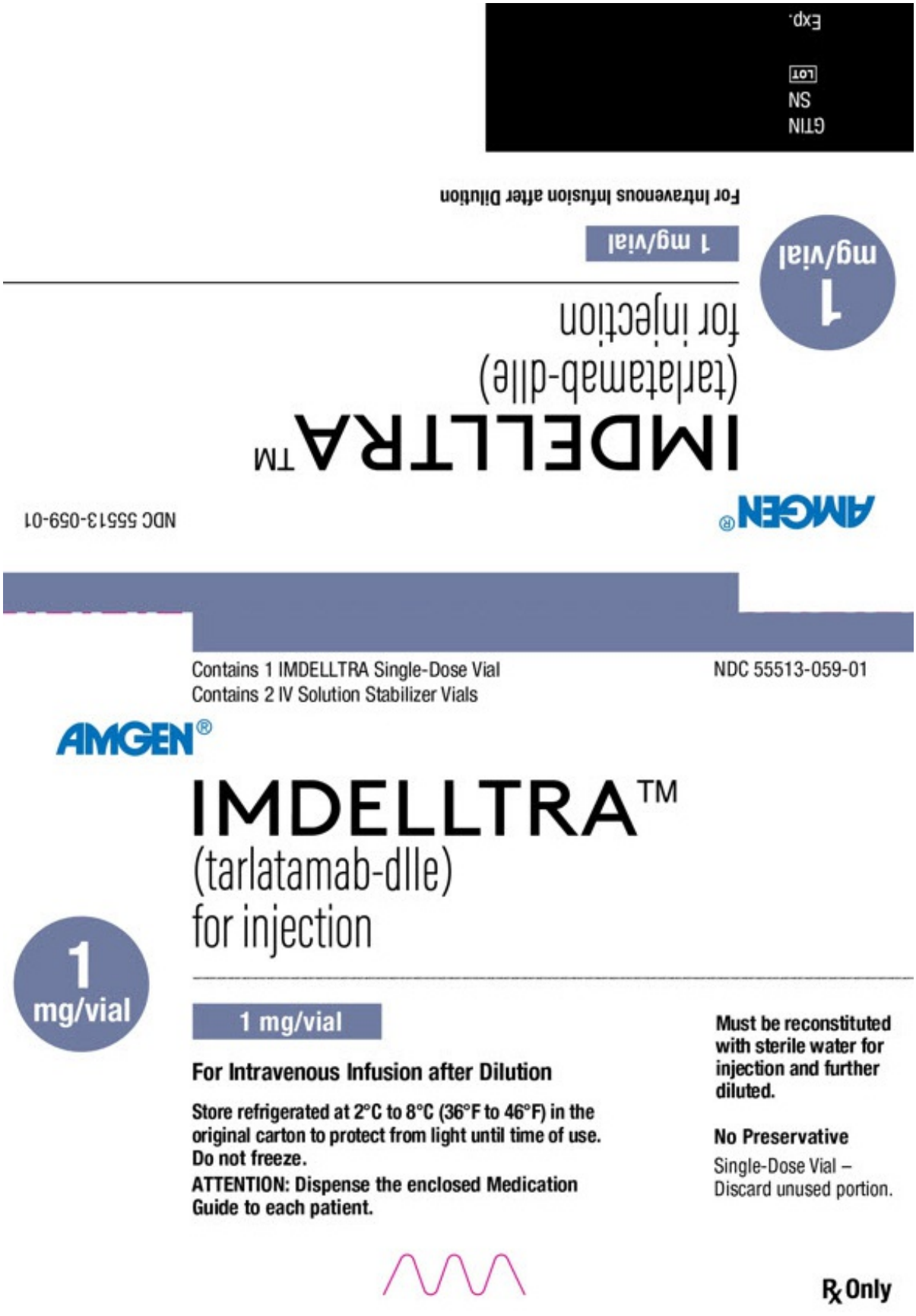
Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light until time of use.
Do not freeze.
ATTENTION: Dispense the enclosed Medication Guide to each patient.

Must be reconstituted with sterile water for injection and further diluted.

No Preservative

Single-Dose Vial –
Discard unused portion.

Rx Only



PRINCIPAL DISPLAY PANEL - Kit Package - 55513-077

Contains 1 IMDELLTRA Single-Dose Vial
Contains 2 IV Solution Stabilizer Vials

NDC 55513-077-01

AMGEN®

IMDELLTRA™
(tarlatamab-dlle)
for injection

10 mg/vial

For Intravenous Infusion after Dilution

Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light until time of use.
Do not freeze.
ATTENTION: Dispense the enclosed Medication Guide to each patient.

Must be reconstituted with sterile water for injection and further diluted.

No Preservative

Single-Dose Vial –
Discard unused portion.

Rx Only

IMDELLTRA (AMG757)
tarlatamab-dlle kit

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:55513-059

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:55513-059-01	1 in 1 PACKAGE	05/16/2024	

Quantity of Parts		
Part #	**Package Quantity**	**Total Product Quantity**
Part 1	1 VIAL	1 mg
Part 2	1 VIAL	7 mL

Part 1 of 2

IMDELLTRA

tarlatamab-dlle injection, powder, lyophilized, for solution

Product Information	
Item Code (Source)	NDC:55513-103
Route of Administration	INTRAVENOUS

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
TARLATAMAB (UNII: 74X82ST8Q1) (TARLATAMAB - UNII:74X82ST8Q1)	TARLATAMAB	0.9 mg in 1 mg

Inactive Ingredients	
Ingredient Name	**Strength**
SUCROSE (UNII: C151H8M554)	37.1 mg in 1 mg
GLUTAMIC ACID (UNII: 3KX376GY7L)	0.72 mg in 1 mg
POLYSORBATE 80 (UNII: 6OZP39ZG8H)	0.04 mg in 1 mg
SODIUM HYDROXIDE (UNII: 55X04QC32I)	

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:55513-103-01	1 mg in 1 VIAL; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA761344	05/16/2024	

Part 2 of 2

IV STABILIZER

iv stabilizer solution

Product Information

Item Code (Source)	NDC:55513-068
Route of Administration	INTRAVENOUS

Inactive Ingredients

Ingredient Name	Strength
CITRIC ACID MONOHYDRATE (UNII: 2968PHW8QP)	36.75 mg in 1 mL
LYSINE HYDROCHLORIDE (UNII: JNJ23Q2COM)	1598.8 mg in 1 mL
POLYSORBATE 80 (UNII: 6OZP39ZG8H)	7 mg in 1 mL
SODIUM HYDROXIDE (UNII: 55X04QC32I)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:55513-068-01	7 mL in 1 VIAL; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA761344	05/16/2024	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA761344	05/16/2024	

IMDELLTRA (AMG757)

tarlatamab-dlle kit

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:55513-077

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:55513-077-01	1 in 1 PACKAGE	06/12/2024	

Quantity of Parts		
Part #	**Package Quantity**	**Total Product Quantity**
Part 1	10 VIAL	10 mg
Part 2	1 VIAL	7 mL

Part 1 of 2

IMDELLTRA (AMG757)

tarlatamab-dlle injection, powder, lyophilized, for solution

Product Information	
Item Code (Source)	NDC:55513-069
Route of Administration	INTRAVENOUS

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
TARLATAMAB (UNII: 74X82ST8Q1) (TARLATAMAB - UNII:74X82ST8Q1)	TARLATAMAB	2.4 mg in 1 mg

Inactive Ingredients	
Ingredient Name	**Strength**
SUCROSE (UNII: C151H8M554)	194.4 mg in 1 mg
GLUTAMIC ACID (UNII: 3KX376GY7L)	3.7 mg in 1 mg
POLYSORBATE 80 (UNII: 6OZP39ZG8H)	0.2 mg in 1 mg
SODIUM HYDROXIDE (UNII: 55X04QC32I)	

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:55513-069-01	1 mg in 1 VIAL; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA761344	05/16/2024	

Part 2 of 2

IV STABILIZER

iv stabilizer solution

Product Information

Item Code (Source)	NDC:55513-068
Route of Administration	INTRAVENOUS

Inactive Ingredients

Ingredient Name	Strength
CITRIC ACID MONOHYDRATE (UNII: 2968PHW8QP)	36.75 mg in 1 mL
LYSINE HYDROCHLORIDE (UNII: JNJ23Q2COM)	1598.8 mg in 1 mL
POLYSORBATE 80 (UNII: 6OZP39ZG8H)	7 mg in 1 mL
SODIUM HYDROXIDE (UNII: 55X04QC32I)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:55513-068-01	7 mL in 1 VIAL; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA761344	05/16/2024	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA761344	05/16/2024	

Labeler - Amgen Inc (039976196)

Establishment

Name	Address	ID/FEI	Business Operations
Amgen, Inc		039976196	ANALYSIS(55513-059, 55513-077) , MANUFACTURE(55513-059, 55513-077)

Revised: 5/2024

Amgen Inc