## 1. NAME OF THE MEDICINAL PRODUCT

IMDELLTRA 1 mg powder for solution for infusion
IMDELLTRA 10 mg powder for solution for infusion

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Single-use vial containing 1 mg tarlatamab lyophilized powder. After reconstitution with 1.3 mL of Sterile Water for Injection, the resulting concentration is 0.9 mg/mL tarlatamab.

Single-use vial containing 10 mg tarlatamab lyophilized powder. After reconstitution with 4.4 mL Sterile Water for Injection, the resulting concentration is 2.4 mg/mL tarlatamab.

## 3. PHARMACEUTICAL FORM

Powder for solution for infusion.

IMDELLTRA for injection is supplied as a sterile, single-dose, preservative-free white to slightly yellow, lyophilized powder with a deliverable dose of 1 or 10 mg; it is intended for dilution in an intravenous (IV) bag with IV Solution Stabilizer (IVSS) and 0.9% saline.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

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.

### 4.2 Posology and Method of Administration

#### 4.2.1 Posology

The recommended dosage and schedule of IMDELLTRA is an initial dose of 1 mg on Day 1 followed by 10 mg on Days 8, 15, and every 2 weeks thereafter as shown in Table 1. Treat patients until disease progression or unacceptable toxicity.

**Table 1. Recommended Dosage Schedule of IMDELLTRA**

| **Dose of IMDELLTRA** | |
|---|---|
| Day 1 | 1 mg |
| Day 8 | 10 mg |
| Day 15 and every 2 weeks thereafter | 10 mg |

- Administer IMDELLTRA as a 1-hour intravenous infusion in an appropriate healthcare setting (see section 4.2.2). See Table 2 for recommended concomitant medications.

- Monitor patients during the infusion and for at least 16 hours after the first infusion (Day 1). On Day 1 and Day 8, recommend patients to remain within 1-hour of an appropriate healthcare setting for 24 hours starting from each IMDELLTRA infusion, accompanied by a caregiver.

- Instruct patients on signs and symptoms of cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) prior to discharge.

- On Day 8 and subsequent infusions, monitor patients at the discretion of the healthcare provider.

**Recommended Concomitant Medications for IMDELLTRA Administration for Days 1, 8 and 15**

Administer recommended concomitant medications for IMDELLTRA administration as presented in Table 2 to reduce the risk of cytokine release syndrome (see section 4.4.1)

**Table 2. Recommended Concomitant Medications for IMDELLTRA Administration for Days 1, 8 and 15**

| 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 IMDELLLTRA infusion |

**Restarting IMDELLTRA After Dosage Delay**

If a dose of IMDELLTRA is delayed, restart therapy based on the recommendations listed in Table 3 and resume the dosing schedule accordingly (see section 4.2.1.1). Administer recommended concomitant medications as indicated in section 4.2.1.

**Table 3. Recommendations for Restarting Therapy with IMDELLTRA After Dosage Delay**

| Last Dose Administered | Time Since the Last Dose Administered | Action[a] |
|---|---|---|
| 1 mg on 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 1 mg. If tolerated, increase to 10 mg 1 week later. Then resume with the planned dosage schedule. |
| 10 mg on 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 1 mg. If tolerated, increase to 10 mg 1 week later. Then resume with the planned dosage schedule. |
| 10 mg on Day 15 and 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 1 mg. If tolerated, increase to 10 mg 1 week later. Then resume with the planned dosage schedule. |

[a]Administer required concomitant medications before and after Day 1 and Day 8 of IMDELLTRA infusions and monitor patients accordingly (see section 4.2.1, Table 1 and Table 2).

### 4.2.1.1 Recommended Dose Modification and Adverse Reaction Management

No dosage reduction for IMDELLTRA is recommended. See Table 4 for recommended actions for the management of CRS, Table 5 for recommended actions for the management of ICANS, and Table 6 for the management of neutropenia and other adverse reactions.

Cytokine Release Syndrome (CRS)

Diagnose CRS based on clinical presentation (see section 4.4.1). Evaluate for and treat other causes of fever, hypoxia, and hypotension. If CRS is suspected, manage according to the recommendations in Table 4. Patients who experience Grade 2 or higher CRS (e.g., hypotension not responsive to fluids, or hypoxia requiring supplemental oxygen) should be monitored with continuous cardiac telemetry and pulse oximetry. For severe or life-threatening CRS, recommend anti-IL-6 therapy, for example, tocilizumab and admission in an intensive-care unit (ICU) for supportive therapy.

**Table 4. Guidelines for Grading, Dosage Modification and Management of Cytokine Release Syndrome[a]**

| CRS Grade | Defining Symptoms | IMDELLTRA Dosage Modification | Management |
|---|---|---|---|
| Grade 1 | Symptoms require symptomatic treatment only (e.g., fever ≥ 38°C (100.4°F) without hypotension or hypoxia). | Withhold IMDELLTRA until event resolves, then resume IMDELLTRA at the next scheduled dose[b]. | • Administer symptomatic treatment (e.g., acetaminophen) for fever. |
| Grade 2 | Symptoms require and respond to moderate intervention.<br>• Fever ≥ 38°C (100.4°F),<br>• Hypotension responsive to fluids not requiring vasopressors, and/or<br>• Hypoxia requiring low flow nasal cannula or blow-by. | Withhold IMDELLTRA until event resolves, then resume IMDELLTRA at the next scheduled dose[b]. | • Recommend hospitalization with cardiac telemetry and pulse oximetry.<br>• Administer symptomatic treatment (e.g., acetaminophen) for fever.<br>• Administer supplemental oxygen and intravenous fluids when indicated.<br>• Consider dexamethasone[c] (or equivalent) 8 mg IV.<br>• Consider tocilizumab (or equivalent).<br><br>When resuming treatment at the next planned dose, monitor patients at the physician's discretion in an appropriate healthcare setting.[b] |
| Grade 3 | Severe symptoms defined as temperature ≥ 38°C (100.4°F) with:<br>• Hemodynamic instability requiring a vasopressor (with or without vasopressin) and/or<br>• 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[b].<br><br>For recurrent Grade 3 events, permanently discontinue IMDELLTRA. | In addition to Grade 2 treatment:<br>• Recommend intensive monitoring, e.g., ICU care.<br>• Administer dexamethasone[c] (or equivalent) 8 mg IV every 8 hours up to 3 doses.<br>• Vasopressor support as needed.<br>• High flow oxygen support as needed.<br>• Recommend tocilizumab (or equivalent)<br>• Prior to the next dose, administer concomitant medications as recommended for Days 1, 8 and 15 (see Table 2).<br><br>When resuming treatment at the next planned dose, monitor patients at the physician's discretion in an appropriate healthcare setting.[b] |

| CRS Grade | Defining Symptoms | IMDELLTRA Dosage Modification | Management |
|---|---|---|---|
| Grade 4 | Life-threatening symptoms defined as temperature ≥ 38°C (100.4°F) with:<br>• Hemodynamic instability requiring multiple vasopressors (excluding vasopressin) and/or<br>• Worsening hypoxia or respiratory distress despite oxygen administration requiring positive pressure. | Permanently discontinue IMDELLTRA. | • ICU care.<br>• Per Grade 3 treatment. |

[a] CRS based on American Society for Transplantation and Cellular Therapy (ASTCT) Consensus Grading (2019).
[b] See section 4.2.1, Table 3 for recommendations on restarting IMDELLTRA after dose delays.
[c] Taper steroids per standard of care guidelines.

Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)

Monitor patient for signs and symptoms of ICANS. Rule out other causes of neurologic symptoms. Provide intensive care for severe or life-threatening neurologic toxicities. If ICANS is suspected, manage according to the recommendations in Table 5.

**Table 5. Guidelines for Grading, Dose Modification and Management of Immune Effector Cell-Associated Neurotoxicity Syndrome[a]**

| ICANS Grade[a] | Defining Symptoms | IMDELLTRA Dosage Modifications | Management |
|---|---|---|---|
| **Grade 1**[a] | ICE score 7-9[b] with no depressed level of consciousness. | • Withhold IMDELLTRA until ICANS resolves, then resume IMDELLTRA at the next scheduled dose[c]. | • Supportive care. |
| **Grade 2**[a] | ICE score 3-6[b] and/or mild somnolence awaking to voice. | • Withhold IMDELLTRA until ICANS resolves, then resume IMDELLTRA at the next scheduled dose[c]. | • Supportive care.<br>• Dexamethasone[d] (or equivalent) 10 mg IV. Repeat every 6 hours or methylprednisolone 1 mg/kg IV every 12 hours if symptoms worsen.<br>• Monitor neurologic symptoms and consider consultation with neurologist and other specialists for further evaluation and management.<br>• Monitor patients at the physician's discretion following the next dose of IMDELLTRA[c]. |
| **Grade 3**[a] | ICE score 0-2[b] and/or depressed level of consciousness awakening only to tactile stimulus and/or any clinical seizure focal or generalized | • Withhold IMDELLTRA until the ICANS resolves, then resume IMDELLTRA at the next scheduled dose[c].<br>• If there is no | • Recommend intensive monitoring, e.g., ICU care.<br>• Consider mechanical ventilation for airway protection. Dexamethasone[d] (or equivalent) 10 mg IV every 6 hours or methylprednisolone 1 mg/kg IV every 12 hours. |

| ICANS Grade[a] | Defining Symptoms | IMDELLTRA Dosage Modifications | Management |
|---|---|---|---|
| | that resolves rapidly<br><br>Or<br><br>Nonconvulsive seizures on EEG that resolve with intervention and/or focal or local edema seen on neuroimaging | improvement to Grade ≤ 1 within 7 days, permanently discontinue IMDELLTRA.<br>• For recurrent Grade 3 events, permanently discontinue. | • Consider repeat neuroimaging (CT or MRI) every 2-3 days if patient has persistent Grade ≥ 3 neurotoxicity.<br>• Monitor patients at the physician's discretion following the next dose of IMDELLTRA[c]. |
| **Grade 4**[a] | ICE score 0[b] (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.<br>• Consider mechanical ventilation for airway protection.<br>• High-dose corticosteroids[d].<br>• Consider repeat neuroimaging (CT or MRI) every 2-3 days if patient has persistent Grade ≥ 3 neurotoxicity.<br>• Treat convulsive status epilepticus per institutional guidelines. |

[a] ICANS based on American Society for Transplantation and Cellular Therapy (ASTCT) Consensus Grading (2019).
[b] 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.
[c] See Table 3 for recommendations on restarting IMDELLTRA after dose delays (see section 4.2.1).
[d] Taper steroids per standard of care guidelines.

**Table 6. Recommended Treatment Interruptions of IMDELLTRA for the Management of Neutropenia and Other Adverse Reactions[a,b]**

| Adverse Reactions | Severity[b] | Dosage Modification[a] |
|---|---|---|
| Neutropenia (see section 4.5) | Grades 1 and 2 | No treatment interruption needed. |
| | Grade 3 | • Interrupt IMDELLTRA for at least 3 days and until the event improves to Grade ≤ 2, then restart IMDELLTRA.<br>• If there is no improvement to Grade ≤ 1 in 3 weeks, permanently discontinue IMDELLTRA.<br>Consider using granulocyte colony stimulating factor (G-CSF). |
| | Grade 4 | • Interrupt IMDELLTRA for at least 3 days and until the event improves to Grade ≤ 2, then restart IMDELLTRA.<br>• If event lasts for > 7 days or Grade 4 event |

| Adverse Reactions | Severity[b] | Dosage Modification[a] |
|---|---|---|
| | | reoccurs, permanently discontinue IMDELLTRA. Consider using granulocyte colony stimulating factor (G-CSF). |
| Other Adverse Reactions (see section 4.8) | Grade 3 or 4 | Withhold IMDELLTR until recovery to ≤ Grade 1 or baseline.<br><br>Consider permanently discontinuing if adverse reaction does not resolve within 28 days.<br><br>• Consider permanent discontinuation for Grade 4 events. |

[a] Severity based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 5.0.
[b] See Table 3 for recommendations on restarting IMDELLTRA after dose delays (see section 4.2.1).

**Special Populations**

Pediatrics

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

Geriatrics

Of the 160 patients with SCLC who received 10 mg IMDELLTRA as monotherapy, 52.5% were age 65 or older and 12.5% were 75 years or older. In clinical studies, no overall differences in IMDELLTRA pharmacokinetics, safety or efficacy were observed between geriatric patients (≥ 65 years old) and younger patients. No dose adjustment is required for geriatric patients.

Hepatic Impairment

Based on the population pharmacokinetic results, no dose adjustment is required in patients with mild or moderate hepatic impairment (see section 5.2). IMDELLTRA has not been studied in patients with severe hepatic impairment.

Renal Impairment

Based on the population pharmacokinetic results, no dose adjustment is required in patients with mild or moderate renal impairment (see section 5.2). IMDELLTRA has not been studied in patients with severe renal impairment.

### 4.2.2 Method of Administration

- IV line for premedication can be used for IMDELLTRA. IV line flush should be administered over 3 – 5 mins using 0.9% Sodium Chloride for Injection.

- Administer the entire contents of IMDELLTRA as an intravenous infusion over 1-hour at a constant flow rate using an infusion pump. The pump should be programmable, lockable, non-elastomeric, and have an alarm (see section 6.6).

**Table 7. IMDELLTRA Administration Information**

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

- IV tubing is primed with 0.9% Sodium Chloride for Injection OR final prepared IMDELLTRA.

- For the infusion rate per infusion duration, refer to Table 7.
- The empty IV bag and IV tubing should be disposed of in accordance with local requirements.

## 4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

## 4.4 Special Warnings and Precautions for Use

### 4.4.1 Cytokine Release Syndrome (CRS)

Administration of IMDELLTRA has been associated with CRS which may be serious or life-threatening. CRS may be associated with symptoms including pyrexia, hypotension, hypoxia, fatigue, tachycardia, headache, chills, nausea, and vomiting. The majority of these events did not lead to IMDELLTRA discontinuation in clinical trials.

Administer IMDELLTRA in a healthcare facility equipped to monitor and manage CRS. Ensure patients are euvolemic prior to initiating the infusions. Closely monitor patients for signs and symptoms of CRS during the initiation of IMDELLTRA treatment.

### 4.4.2 Immune Effector Cell-associated Neurotoxicity Syndrome (ICANS)

Administration of IMDELLTRA has been associated with ICANS which may be serious or life-threatening. ICANS can occur up to several weeks following administration of IMDELLTRA. Adverse events that may be associated with ICANS include headache, encephalopathy, confusion, delirium, seizure, ataxia, neurotoxicity, and tremor. Patients should be closely monitored for signs and symptoms of neutropenia.

Administration of IMDELLTRA has been associated with neutropenia. Events were mainly non-serious and resolved spontaneously or with the use of G-CSF. Patients should be closely monitored for signs and symptoms of neutropenia during IMDELLTRA treatment.

### 4.4.3 Hypersensitivity

Hypersensitivity reactions have been reported in patients treated with IMDELLTRA including rare severe events. 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 sections 4.2.1.1).

## 4.5 Interactions with Other Medicinal Products and Other Forms of Interaction

No formal drug interaction studies have been conducted with IMDELLTRA. Initiation of IMDELLTRA treatment causes transient release of cytokines that may suppress CYP450 enzymes and may result in increased exposures of concomitant CYP substrates. In patients who are receiving concomitant CYP450 substrates, particularly those with a narrow therapeutic index, monitor for known adverse events. Adjust the dose of the concomitant drug as needed.

## 4.6 Fertility, Pregnancy and Lactation

### 4.6.1 Pregnancy

There are no data from the use of IMDELLTRA in pregnant women.

### 4.6.2 Lactation

It is unknown whether IMDELLTRA is secreted in human milk. Because many medicinal products, including antibodies, can be secreted in human milk, a risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue IMDELLTRA treatment taking into account the benefit of breast-feeding for the child and the benefit of IMDELLTRA treatment for the woman.

### 4.6.3 Fertility

There are no clinical studies to evaluate the effect of IMDELLTRA on fertility.

## 4.7 Effects on Ability to Drive and Use Machines

Studies of the effects of IMDELLTRA on the ability to drive and use machines have not been performed. However, due to the potential for ICANS-associated neurological events, following IMDELLTRA infusion, 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.

## 4.8 Undesirable Effects

### 4.8.1 Clinical Trials

**SCLC (Study DeLLphi-300 and Study DeLLphi-301) at 10 mg as monotherapy**

The safety of IMDELLTRA was evaluated in 160 patients with extensive-stage small cell lung cancer (SCLC) who received 10 mg as monotherapy. The median duration of exposure to IMDELLTRA was 14.14 weeks (range: 0.1 to 93.4).

Adverse reactions reported in IMDELLTRA clinical studies are displayed in Table 8 below. Frequency is provided by Council for International Organizations of Medical Sciences (CIOMS) category: very common (≥ 10%), common (≥ 1% and < 10%), uncommon (≥ 0.1% and < 1%), rare (≥ 0.01% and < 0.1%), very rare (< 0.01%).

**Table 8. Adverse Reactions Reported in IMDELLTRA 10 mg Pooled Clinical Studies**

| System Organ Class | Adverse Reaction Preferred Term | Frequency | Overall Subject Incidence (treatment arm) (N = 160) n (%) |
|---|---|---|---|
| Blood and lymphatic system disorders | Anemia | Very common | 43 (26.9) |
| | Neutropenia | Common | 14 (8.8) |
| Gastrointestinal disorders | Constipation | Very common | 47 (29.4) |
| | Nausea | Very common | 31 (19.4) |
| General disorders and administration site conditions | Pyrexia | Very common | 62 (38.8) |
| | Asthenia | Very common | 38 (23.8) |
| | Fatigue | Very common | 45 (28.1) |
| Immune system disorders | Cytokine release syndrome | Very common | 86 (53.8) |
| Investigations | Neutrophil count decreased | Common | 8 (5.0) |
| Metabolism and nutrition disorders | Decreased appetite | Very common | 54 (33.8) |
| | Hyponatremia | Very common | 25 (15.6) |

| System Organ Class | Adverse Reaction Preferred Term | Frequency | Overall Subject Incidence (treatment arm) (N = 160) n (%) |
|---|---|---|---|
| Nervous system disorders | Dysgeusia | Very common | 50 (31.3) |
| | Immune effector cell-associated neurotoxicity syndrome | Common | 7 (4.4) |
| | Neurotoxicity | Common | 2 (1.3) |
| | Tremor | Common | 4 (2.5) |
| Psychiatric disorders | Confusional state | Common | 6 (3.8) |
| | Delirium | Common | 3 (1.9) |
| Respiratory, thoracic and mediastinal disorders | Dyspnea | Very common | 27 (16.9) |

Adverse Drug Reactions for IMDELLTRA occurring at doses other than the 10 mg dose in monotherapy cohorts.
Encephalopathy: Common
Seizure: Uncommon
Ataxia: Uncommon

### 4.8.3 Description of Selected Adverse Reactions

**Cytokine Release Syndrome (CRS)**

In clinical trials with pooled safety data from 160 patients with SCLC enrolled in Study DeLLphi-300 and Study DeLLphi-301 receiving the IMDELLTRA 10 mg dose, CRS occurred in 53.8% of patients, with Grade 1 in 32.5%, Grade 2 in 20% of patients, Grade 3 in 0.6% of patients and Grade 4 events in 0.6% of patients. No patients had Grade 5 events. Serious events of CRS were reported in 23.1% of patients. After the first dose of IMDELLTRA, 41.3% of patients experienced any grade CRS, with 28.8% of patients experiencing any grade CRS after the second dose. The majority of CRS events occurred after the first two doses, with 8.8% of patients experiencing CRS following third dose or later. Following the Day 1 infusion, 15.6% of patients experienced ≥ Grade 2 CRS. Following the Day 8 infusion, 4.4% of patients experienced ≥ Grade 2 CRS. The median time from the first dose of IMDELLTRA to the first onset of CRS was 2 days (range: 1 to 25 days).

In patients treated with IMDELLTRA at 10 mg enrolled in Study DeLLphi-301 (n = 133), CRS occurred in 52.6% of patients, including Grade 1 in 31.6%, Grade 2 in 20.3% and Grade 3 in 0.8% of patients. No patients had Grade 4 or Grade 5 events. Most patients experienced CRS after the first two doses of IMDELLTRA with 9.8% experiencing CRS after the third dose or later. Following the Day 1 infusion, 16.5% of patients experienced ≥ Grade 2 CRS. Following the Day 8 infusion, 3.0% of patients experienced ≥ Grade 2 CRS. Median time to onset of first CRS symptom was 15.5 hours. For those Grade 1 events that progressed to Grade 2 or greater, the median time from Grade 1 event to Grade 2 events was 22.1 hours.

**Immune Effector Cell-associated Neurotoxicity Syndrome (ICANS)**

In clinical trials with pooled safety data from 160 patients with SCLC enrolled in Study DeLLphi-300 and Study DeLLphi-301 receiving IMDELLTRA 10 mg, ICANS was reported in 9.4% of patients. The median time from the first dose of IMDELLTRA to the first onset of ICANS was 30 days (range: 1 to 154 days). The median time to resolution of ICANS was 33 days (range: 1 to 93 days).

**Neutropenia**

In clinical trials with pooled safety data for 160 patients with SCLC enrolled in Study DeLLphi-300 and Study DeLLphi-301 receiving IMDELLTRA 10 mg, neutropenia occurred in 14.4% of patients including Grade 3 or higher events in 6.3% of patients, and Grade 4 events in 2.5% of patients. The median time from the first dose of IMDELLTRA to the first onset of neutropenia was 43 days (range:

3 to 244 days). Neutropenia leading to dose interruption occurred in 0.6% patients with none leading to treatment discontinuation.

### 4.8.4 Immunogenicity

The observed incidence of anti-drug antibodies is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies in the studies described below with the incidence of anti-tarlatamab antibodies in other studies, including those of tarlatamab or of other DLL3 T-cell engager products.

Across Study DeLLphi-300 and Study DeLLphi-301, the incidence of anti-tarlatamab antibody development was 4.7% (7/149) in patients receiving the dose of 10 mg. In the phase 2 Study DeLLphi-301 which employed the neutralizing assay, none of the patients developed neutralizing antibodies. Positive anti-tarlatamab antibody status had no clinically relevant impact on efficacy and safety.

## 4.9 Overdose

There is no clinical experience with overdose with IMDELLTRA. Doses up to 100 mg every two weeks and 200 mg every three weeks have been administered in clinical trials. In the event of an overdose, the patient should be treated symptomatically, and supportive measures instituted as required.

# 5. PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: antineoplastic and immunomodulating agents, antineoplastic agents, monoclonal antibodies and antibody drug conjugates, ATC code: L01FX33. Pharmacological class: bispecific T-cell engager molecule.

Structural Formula/Description: IMDELLTRA is a bispecific T-cell engager molecule that selectively binds to DLL3 (expressed on tumor cells) and CD3 (expressed on T-cells). IMDELLTRA is produced using recombinant DNA technology in Chinese hamster ovary (CHO) cells. IMDELLTRA consists of 982 amino acids and has a molecular weight of approximately 105 kilodaltons.

**Mechanism of Action**

IMDELLTRA is a bispecific DLL3-directed CD3 T-cell engager that binds to DLL3 expressed on the surface of tumor cells and CD3 expressed on the surface of T-cells. The bispecific binding of tarlatamab to T-cells and DLL3-positive tumor cells triggers T-cell activation, production of inflammatory cytokines, and release of cytotoxic proteins, which results in redirected lysis of tumor cells.

**Pharmacodynamics**

The pharmacodynamic response after a single infusion of tarlatamab was characterized by T-cell redistribution and activation, and transient cytokine elevation. Peripheral T-cell redistribution (i.e., T-cell adhesion to blood vessel endothelium and/or transmigration into tissue) occurred within 24 hours after the initial dose of tarlatamab at 1 mg on Day 1. T-cell counts declined within 6 hours post infusion and returned to baseline levels in the majority of the patients prior to the next infusion on Day 8.

Serum cytokines IL-2, IL-6, IL-8, IL-10, IFN-γ and TNF-α were transiently elevated following the initial dose of tarlatamab at 1 mg on Day 1. Cytokine levels peaked within the first 2 days following the start of tarlatamab infusion and generally returned to baseline levels prior to the next infusion on

Day 8. In subsequent treatments, cytokine elevation occurred in fewer patients with lesser intensity compared to the initial infusion on Day 1.

### 5.1.1 Clinical Data

The efficacy of IMDELLTRA was demonstrated in patients enrolled in a phase 2, open-label, multicenter trial, Study DeLLphi-301. Eligible patients were required to have extensive-stage SCLC with disease progression after receiving previous treatment including platinum-based chemotherapy, an ECOG Performance Status of 0-1, and at least one measurable lesion as defined by Response Evaluation Criteria in Solid Tumors (RECIST v1.1). The trials excluded patients with symptomatic brain metastases and active immunodeficiency.

Study DeLLphi-301 Part 1 was a dose comparison that randomized 176 patients in a 1:1 ratio to receive either 10 mg or 100 mg of tarlatamab (as a 60-minute IV infusion). At the prespecified interim analysis, 30 patients per arm were used to determine the selected dose for Part 2. Part 2 was a dose expansion that enrolled 100 patients (Part 1 and 2 combined) at the selected dose of 10 mg. A total of 99 patients received IMDELLTRA 10 mg intravenously every 2 weeks across Part 1 and Part 2 (combined), and a total of 87 patients received IMDELLTRA 100 mg intravenously every 2 weeks in Part 1. Treatment continued until disease progression or unacceptable toxicity. Patients were eligible to continue receiving IMDELLTRA after radiographic progression, if they continued to have clinical benefit in the investigator's judgment and had no significant or unacceptable toxicities. Tumor assessments were performed every 6 weeks for the first 48 weeks and every 12 weeks thereafter.

The key efficacy outcome measures were ORR and DOR as assessed by Blinded Independent Central Review (BICR) according to RECIST v1.1.

For patients who received IMDELLTRA 10 mg, the baseline demographics and disease characteristics of the study population were: median age of 64 years (range: 35 to 82); 48.5% age 65 or older; 71.7% male; 57.6% White and 41.4% Asian; 26.3% ECOG PS of 0 and 73.7% ECOG PS of 1; 2% had M0 disease and 98% had M1 disease; and 22.2% had a history of brain metastases. 100% received prior platinum therapy, 20.2% received prior topotecan therapy, 69.7% received prior anti-PD-L1 therapy; 8.1% were never smokers, 73.7% former smokers, and 18.2% current smokers. Time to progression after first-line platinum therapy was known for 69/99 subjects. Time to progression was < 90 days for 27/69 (39.1%) subjects and ≥ 90 days for 42/69 (60.9%) subjects.

ORR and DOR were generally similar to the total population in the subgroups that had < 90 or ≥ 90 days to progression after first-line platinum therapy. Efficacy results are summarized in Table 9.

**Table 9. Efficacy Results for Patients with SCLC Who Received IMDELLTRA 10 mg**

| Efficacy Parameter | IMDELLTRA (N = 99) |
|---|---|
| **Overall Response Rate (ORR)** | |
| ORR, % (95% CI)[a] | 41 (32, 52) |
| Complete Response, n (%) | 1 (1) |
| Partial Response, n (%) | 40 (40) |
| **Duration of Response (DOR)**[a, f] | |
| Median[b], months (range) | 9.7 (5.9, NE) |
| Responders with duration ≥ 6 months[c], % | 66 |
| Responders with duration ≥ 9 months[d], % | 49 |
| Responders with duration ≥ 12 months[e], % | 39 |

[a] Assessed by Blinded Independent Central Review, CI = Confidence Interval
[b] Median based on Kaplan-Meier estimate.
[c] Observed proportion of responders beyond the 6-month landmark.
[d] Observed proportion of responders beyond the 9-month landmark.
[e] Observed proportion of responders beyond the 12-month landmark.
[f] DOR based on DCO of Jan 12, 2024.

## 5.2 Pharmacokinetic Properties

The peak serum concentration ($C_{max}$), trough serum concentration ($C_{trough}$) and area under the serum concentration versus time curve at steady state ($AUC_{tau}$), of tarlatamab increased dose proportionally in the evaluated dose range of 0.003 mg to 100 mg Q2W and 200 mg Q3W (20 times the recommended dosage). Approximate steady state in serum tarlatamab exposures were achieved by Day 28.

### Distribution

The geometric mean value (CV%) for volume of distribution at steady state is 8.6 L (18.3%).

### Metabolism

The metabolic pathway of tarlatamab has not been characterized. Like other protein therapeutics, tarlatamab is expected to be degraded into small peptides and amino acids via catabolic pathways.

### Elimination

The estimated systemic clearance (inter-subject CV%) was 0.65 L/day (44%) and terminal elimination half-life was approximately 11.2 days in subjects with SCLC.

### Special populations

No clinically meaningful differences in the clearance of tarlatamab were observed based on age, body weight, sex, race, mild or moderate renal impairment (eGFR ≥ 30 mL/min), or mild hepatic impairment (total bilirubin ≤ upper limit of normal (ULN) and AST > ULN) to moderate hepatic impairment (total bilirubin > 1.5 to 3 × ULN, any AST).

## 5.3 Preclinical Safety Data/Nonclinical Toxicology

### Carcinogenicity

No carcinogenicity or genotoxicity studies have been conducted with tarlatamab.

### Impairment of Fertility

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

### Reproductive and Development Toxicity

There are no available data from the use of tarlatamab in pregnant women. Based on its mechanism of action, IMDELLTRA may cause fetal harm when administered to a pregnant woman (see section 5.1). In a murine embryo-fetal development study, there were no effects of the murine surrogate molecule of tarlatamab, designated muS757, on any maternal parameter, including mean maternal body weights or body weight gains. In addition, there were no muS757-related macroscopic findings or effects on any ovarian, uterine, or litter parameters at any dose level and administration of muS757 did not produce any fetal external, visceral, or skeletal malformations or variations.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of Excipients

IMDELLTRA

- L-glutamic acid
- Sucrose
- Polysorbate 80
- Sodium hydroxide

IV Solution Stabilizer (IVSS)

- Citric acid monohydrate
- Lysine hydrochloride
- Polysorbate 80
- Sodium hydroxide
- Water for injection

### 6.2 Incompatibilities

No known incompatibilities.

### 6.3 Shelf Life

Please refer to the packaging for the expiry date.

### 6.4 Special Precautions for Storage

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

The information in Table 10 indicates the storage time for the prepared IMDELLTRA infusion bag. Store lyophilized IMDELLTRA and IV Solution Stabilizer (IVSS) vials for a maximum of 24 hours at room temperature in the original carton to protect from light.

**Table 10. Maximum Storage Time**

| | **Room Temperature**<br>**20°C to 25°C (68°F to 77°F)** | **Refrigerated**<br>**2°C to 8°C (36°F to 46°F)** |
|---|---|---|
| Prepared IMDELLTRA Infusion Bag | 8 hours* | 7 days* |

* Storage time includes total time permitted from point of reconstitution of the vial to the end of administration. If the prepared IMDELLTRA infusion bag is not administered within the time frames and temperatures indicated, it must be discarded; it should not be refrigerated again.

### 6.5 Nature and Contents of Container

IMDELLTRA consists of two packaging configurations:

- **1 mg** package contains 1 vial of 1 mg IMDELLTRA and 2 vials of 7 mL IV Solution Stabilizer.
- **10 mg** package contains 1 vial of 10 mg IMDELLTRA and 2 vials of 7 mL IV Solution Stabilizer.

- **Do not use IV Solution Stabilizer (IVSS) for reconstitution of IMDELLTRA.** The IV Solution Stabilizer is used to coat the intravenous bag prior to addition of reconstituted IMDELLTRA to prevent adsorption of IMDELLTRA to IV bags and IV tubing.

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

Material Compatibility Information

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

## 6.6 Special Instructions for Use and Handling

### Preparation

Aseptic preparation

**Strictly observe aseptic technique when preparing the solution for infusion since IMDELLTRA vials do not contain antimicrobial preservatives. Reconstitution of IMDELLTRA is with Sterile Water for Injection.**

**Table 11. Required Amount of Sterile Water for Injection (SWFI) to Reconstitute IMDELLTRA[a]**

| IMDELLTRA Vial Strength (mg) | Amount of Sterile Water for Injection needed to Reconstitute IMDELLTRA (mL) | Final Concentration (mg/mL) |
|---|---|---|
| 1 mg | 1.3 mL | 0.9 mg/mL |
| 10 mg | 4.4 mL | 2.4 mg/mL |

[a] 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


Sterile Water for Injection, Preservative-Free *(Not Included)*

IMDELLTRA vial

Reconstituted IMDELLTRA

a. Transfer required amount of Sterile Water for Injection **(Refer to Table 11)** into the IMDELLTRA vial to provide a final IMDELLTRA concentration of 0.9 mg/mL (1 mg vial) or 2.4 mg/mL (10 mg vial). Direct Sterile Water for Injection along the walls of the IMDELLTRA vial and not directly on the lyophilized powder.
   - Do not use IV Solution Stabilizer to reconstitute IMDELLTRA.
b. Gently swirl contents. Do not shake.

c. Inspect that the solution is clear to slightly opalescent, colorless to slightly yellow. Do not use if solution is cloudy or has particulates.

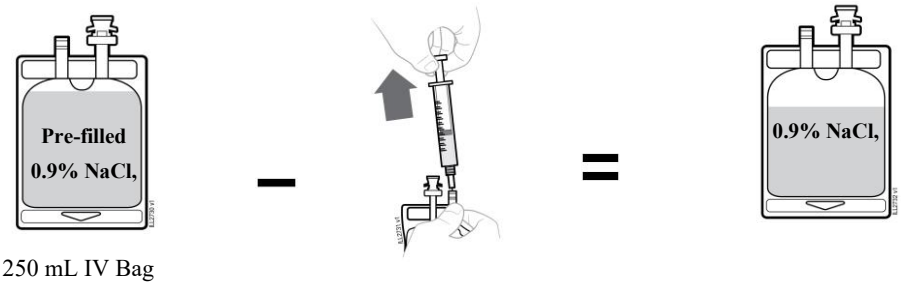
**Preparation of IMDELLTRA**

**Table 12. Preparation Guide for 1-hour Infusion**

| IMDELLTRA Vial Strength[a] | IMDELLTRA Dose | Volume of 0.9% NaCl to Withdraw from IV Bag | Volume of IV Solution Stabilizer (IVSS) to Add to IV Bag | Volume of Reconstituted IMDELLTRA to Add to IV Bag |
|---|---|---|---|---|
| 1 mg | 1 mg | 14 mL | 13 mL | 1.1 mL |
| 10 mg | 10 mg | 17 mL | 13 mL | 4.2 mL |

**NOTE:** The final concentrations for the different strength vials are NOT the same following reconstitution.

Withdraw 0.9% Sodium Chloride for Injection




250 mL IV Bag

- Withdraw the required volume from a pre-filled 250 mL 0.9% Sodium Chloride bag. Refer to Table 12. Disregard any overfill in the IV bag.

Add IV Solution Stabilizer (IVSS)


Stabilized

- Transfer 13 mL of IVSS to the IV bag containing 0.9% Sodium Chloride for Injection.
- Gently mix the contents of the bag to avoid foaming. Do not shake.

Add Reconstituted IMDELLTRA


Stabilized | Reconstituted IMDELLTRA | Completed 1-Hour Infusion

- Transfer the required volume of reconstituted IMDELLTRA into the stabilized IV bag containing 0.9% Sodium Chloride for Injection and IVSS. Refer to Table 12.
- Gently mix the contents of the bag to avoid foaming. Do not shake.

Remove air from the IV bag

- Remove air from the IV bag using an empty syringe to avoid foaming, Prime IV tubing with 0.9% Sodium Chloride for Injection or Final Prepared Product

- Prime the IV tubing separately with 0.9% Sodium Chloride for Injection OR final prepared product.

## 7. MARKETING AUTHORISATION HOLDER

Amgen (Thailand) Limited, Bangkok, Thailand

## 8. MARKETING AUTHORISATION NUMBER(S)

1C xxx/xx (NBC)

## 9. DATE OF AUTHORISATION

## 10. DATE OF REVISION OF THE TEXT

Revision Date: July 2024
Version No: THIMDPI01

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AMGEN

**Patient Information Leaflet: Information for the patient**

**IMDELLTRA 1 mg powder for solution for infusion**
**IMDELLTRA 10 mg powder for solution for infusion**
**tarlatamab**

**Read all of this leaflet carefully before taking IMDELLTRA because it contains important information for you.**
- Keep this leaflet. You may need to read it again.
- If you have any further questions, contact your doctor, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

**What is in this leaflet**



## 1. What is IMDELLTRA and what is it used for

Tarlatamab is the active ingredient in IMDELLTRA.

IMDELLTRA is used to treat adult with small cell lung cancer (SCLC):
- that has spread throughout the lungs and/or to other parts of the body, and
- you have received treatment with chemotherapy that contains platinum, and it did not work or is no longer working.

How does IMDELLTRA work?

IMDELLTRA is different from chemotherapy. IMDELLTRA works with your immune system to find and destroy small cell lung cancer cells.

If you have any questions about how IMDELLTRA works or why this medicine has been prescribed for you, ask your doctor, pharmacist or nurse.

## 2. What you need to know before you receive IMDELLTRA

**Do not use IMDELLTRA**

- if you are allergic to tarlatamab or any of the other ingredients of this medicine (listed in section 6).

If you have any questions, talk to your doctor, pharmacist or nurse before you are given IMDELLTRA.

**Warnings and precautions**

Tell your doctor immediately if you experience any of the following while receiving IMDELLTRA as they may need to treat the symptoms:

- Cytokine Release Syndrome (CRS):
    - fever
    - shortness of breath, confusion, restlessness, trouble breathing
    - fast or irregular heartbeat: palpitations, dizziness
    - headache
    - chills
    - nausea
    - vomiting

- Neurological problems- Immune effector cell-associated neurotoxicity syndrome (ICANS):
    - trouble speaking, memory loss, personality changes (encephalopathy)
    - confusion
    - feeling disoriented or having difficulty thinking clearly (delirium)
    - seizure
    - loss of balance or coordination (ataxia)
    - weakness or numbness of arms and legs
    - shakiness of your hands or limbs (tremor)
    - headache

- Low white blood cell counts (neutropenia):
    - chills or shivering
    - feel warm
    - high body temperature

- Allergic reactions (hypersensitivity):
    - rash
    - difficulty breathing

Your doctor will monitor for signs and symptoms of these reactions during and after the infusion.

**Children and adolescents**

IMDELLTRA has not been studied in children or adolescents. Treatment with IMDELLTRA is not recommended in persons under 18 years of age.

**Other medicines and IMDELLTRA**

Tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take any other medicines.

**Pregnancy and breast-feeding**

The effects of IMDELLTRA in pregnant women are not known.

- Tell your doctor if you are pregnant, think you are pregnant, or if you are planning to become pregnant. Your doctor will help you weigh the benefit against the risk of taking IMDELLTRA while you are pregnant.
- Tell your doctor if you become pregnant during treatment with IMDELLTRA. Your doctor may need to talk to you about potential risks.
- Women who are able to become pregnant should use birth control during treatment. You must also do this for 2 months after your last dose. Talk to your doctor about suitable methods of birth control.

- It is not known whether the ingredients in IMDELLTRA pass into breast milk. Tell your doctor if you are breast-feeding or are planning to breast-feed.
- You should not breast-feed during treatment with IMDELLTRA and for at least 2 months after your last dose.

**Driving and using machines**

Refrain from driving, operating heavy or potentially dangerous machinery and engaging in hazardous occupations or activities following IMDELLTRA infusion in the event of ICANS-associated neurological symptoms, such as dizziness, seizures, and confusion until they resolve.

## 3. How to use IMDELLTRA

- IMDELLTRA will be given to you by your doctor or nurse by intravenous (IV) infusion into your vein for 1-hour.
- IMDELLTRA will be given on the following schedule: Day 1, Day 8, Day 15 and then every 2 weeks thereafter. One hour before receiving your first two doses of IMDELLTRA you will be given a medicine called dexamethasone. This will be given to you by IV infusion into your vein. You may also get IV fluids after your first two doses of IMDELLTRA.
- Your doctor will determine how long you should stay on IMDELLTRA.
- Your doctor may delay or completely stop treatment with IMDELLTRA if you have certain side effects.
- Your doctor will monitor you for 16 hours after the first infusion of IMDELLTRA (Day 1).
- You should plan to stay within 1-hour of a healthcare facility for 24 hours after each IMDELLTRA infusion is complete on Day 1 and Day 8 and have a caregiver with you.
- After the second infusion (Day 8), and for all future infusions your doctor will inform you about how long you may need to be monitored after the infusion of IMDELLTRA.

## 4. Possible side effects

Like all medicines, IMDELLTRA can cause side effects, although not everybody gets them.

**Very common** (may affect more than 1 in 10 people):
- decreased levels of red blood cells (anemia)
- constipation
- nausea
- fever (pyrexia)
- tiredness (fatigue)
- physical weakness or lack of energy (asthenia)
- decreased levels of white blood cells (neutrophil count decrease)
- decreased appetite
- low level of sodium in blood (hyponatremia)
- bad taste in mouth (dysgeusia)
- dry or wet cough, shortness of breath (dyspnea)

**Common** (may affect up to 1 in 10 people):
- change in normal activity of nervous system (neurotoxicity)
- shakiness of hands and limbs (tremor)
- confusion (confusional state)
- feeling disoriented (delirium)

**Reporting of side effects**

These are not all the possible side effects of IMDELLTRA. Talk to your doctor, pharmacist or nurse if you get any side effects.

## 5. How to store IMDELLTRA

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the outer carton and on the vial label after the abbreviation EXP.

Store IMDELLTRA and IV Solution Stabilizer vials in the original package refrigerated at 2°C to 8°C and protect from light until time of use. Do not freeze.

Store lyophilized IMDELLTRA and IV Solution Stabilizer (IVSS) vials for a maximum of 24 hours at room temperature in the original carton to protect from light.

## 6. Contents of the pack and other information

What IMDELLTRA Contains:

- The active ingredient in IMDELLTRA is tarlatamab. The other ingredients are sucrose, polysorbate 80, L-glutamic acid, and sodium hydroxide.
- IV Solution Stabilizer contains citric acid monohydrate, lysine hydrochloride, polysorbate 80, sodium hydroxide and water for injection.

IMDELLTRA consists of two packaging configurations:

- 1 mg package includes 1 vial of 1 mg IMDELLTRA and 2 vials of 7 mL IV Solution Stabilizer.
- 10 mg package contains 1 vial of 10 mg IMDELLTRA and 2 vials of 7 mL IV Solution Stabilizer.

Warning according to the Notification of the Ministry of Public Health: This medicine may cause serious hazard, must only be used under control by a doctor.

**Marketing Authorisation Holder**
Amgen (Thailand) Limited, Bangkok, Thailand

**DATE OF REVISION OF THE TEXT**

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