▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

IMDYLLTRA 1 mg powder for concentrate and solution for solution for infusion
IMDYLLTRA 10 mg powder for concentrate and solution for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

IMDYLLTRA 1 mg powder for concentrate and solution for solution for infusion

One vial of powder contains 1 mg of tarlatamab.

Reconstitution with water for injections results in a final tarlatamab concentration of 0.9 mg/mL.

IMDYLLTRA 10 mg powder for concentrate and solution for solution for infusion

One vial of powder contains 10 mg of tarlatamab.

Reconstitution with water for injections results in a final tarlatamab concentration of 2.4 mg/mL.

Tarlatamab is produced in Chinese hamster ovary cells by recombinant DNA technology.

Excipient with known effect

IMDYLLTRA contains 0.04 mg polysorbate 80 in each 1 mg vial and 0.2 mg polysorbate 80 in each 10 mg vial.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for concentrate and solution for solution for infusion.

Tarlatamab powder (powder for concentrate): White to slightly yellow powder.

Solution (stabiliser): Colourless-to-slightly yellow, clear solution with a pH of 7.0.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

IMDYLLTRA is indicated as monotherapy for the treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC), who require systemic therapy following disease progression on or after first-line treatment with platinum-based chemotherapy.

4.2 Posology and method of administration

IMDYLLTRA treatment should be initiated under the direction of and supervised by physicians experienced in the use of cancer therapy. It should be administered in an appropriate healthcare facility. See table 2 for recommended concomitant medicinal products.

Patients should be monitored from the start of the infusion for 6 to 8 hours on day 1 and day 8. Additional monitoring and monitoring on subsequent infusions is at the discretion of the physician.

On day 1 and day 8, patients should be instructed to remain within proximity of an appropriate healthcare facility for 24 hours starting from each infusion, accompanied by a caregiver.

Both patients and caregivers should be informed on signs and symptoms of cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) prior to discharge.

Posology

The recommended dosing schedule of IMDYLLTRA 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.

Patients should be treated until disease progression or unacceptable toxicity.

Table 1. Recommended dosing schedule of IMDYLLTRA

Dose of IMDYLLTRA	
Day 1	1 mg
Day 8	10 mg
Day 15 and every 2 weeks thereafter	10 mg

Recommended concomitant medicinal products

Concomitant medicinal products for IMDYLLTRA administration should be administered as presented in table 2 to reduce the risk of cytokine release syndrome (see section 4.4).

Table 2. Concomitant medicinal products for day 1 and day 8

Treatment day	**Medicinal products**	**Administration**
Day 1 and day 8	Administer 8 mg of dexamethasone intravenously (or equivalent)	Within 1 hour prior to IMDYLLTRA infusion
	Intravenous administration of 1 litre of sodium chloride 9 mg/mL (0.9%) solution for injection is recommended per standard of care guidelines	Immediately after completion of IMDYLLTRA infusion

Restarting IMDYLLTRA after dose delay

If a dose of IMDYLLTRA is delayed, therapy should be restarted based on the recommendations listed in table 3, and the dosing schedule should be resumed accordingly. Recommended concomitant medicinal products should be administered as indicated in table 2.

Table 3. Recommendations for restarting therapy with IMDYLLTRA after dose delay

Last dose administered	**Time since the last dose administered**	**Action[a]**
1 mg on day 1	2 weeks or less (≤ 14 days)	Administer IMDYLLTRA 10 mg, then resume with the planned dosing schedule.
	Greater than 2 weeks (> 14 days)	Administer IMDYLLTRA 1 mg. If tolerated, increase to 10 mg 1 week later. Then resume with the planned dosing schedule.

Last dose administered	Time since the last dose administered	Action[a]
10 mg on day 8	3 weeks or less (≤ 21 days)	Administer IMDYLLTRA 10 mg, then resume with the planned dosing schedule.
	Greater than 3 weeks (> 21 days)	Administer IMDYLLTRA 1 mg. If tolerated, increase to 10 mg 1 week later. Then resume with the planned dosing schedule.
10 mg on day 15 and every 2 weeks thereafter	4 weeks or less (≤ 28 days)	Administer IMDYLLTRA 10 mg, then resume with the planned dosing schedule.
	Greater than 4 weeks (> 28 days)	Administer IMDYLLTRA 1 mg. If tolerated, increase to 10 mg 1 week later. Then resume with the planned dosing schedule.

[a] Administer recommended concomitant medicinal products before and after IMDYLLTRA infusions on day 1 and day 8 and monitor patients accordingly (see table 2).

Dose modifications and management of adverse reactions

No dose reduction for IMDYLLTRA 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 other adverse reactions.

Cytokine release syndrome (CRS)

CRS should be diagnosed based on clinical presentation (see section 4.4). Patients should be evaluated and treated for other causes of fever, hypoxia, and hypotension. If CRS is suspected, it should be managed 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 for CRS signs and symptoms including fever, hypotension and hypoxia using pulse oximetry or cardiac telemetry as indicated. For severe or life-threatening CRS, anti-IL-6 therapy is recommended, for example, tocilizumab and admission in an intensive-care unit (ICU) for supportive therapy.

Table 4. Guidelines for grading, dose modification and management of cytokine release syndrome[a]

CRS grade	Defining symptoms	IMDYLLTRA dose modification	Management
Grade 1	Symptoms require symptomatic treatment only (e.g., fever ≥ 38°C without hypotension or hypoxia).	• Withhold IMDYLLTRA until event resolves, then resume IMDYLLTRA at the next scheduled dose[b].	• Administer symptomatic antipyretic treatment (e.g., paracetamol) for fever. • Consider dexamethasone[c] (or equivalent) 4 mg to 10 mg orally or intravenously.

CRS grade	Defining symptoms	IMDYLLTRA dose modification	Management
Grade 2	Symptoms require and respond to moderate intervention. • Fever ≥ 38°C, • Hypotension responsive to fluids not requiring vasopressors, and/or • Hypoxia requiring low flow nasal cannula or blow-by.	• Withhold IMDYLLTRA until event resolves, then resume IMDYLLTRA at the next scheduled dose[b].	• Hospitalisation with monitoring for fever, hypotension and hypoxia using pulse oximetry or, as indicated, cardiac telemetry, is recommended. • Administer symptomatic antipyretic treatment (e.g., paracetamol) for fever. • Administer supplemental oxygen and intravenous fluids when indicated. • Consider dexamethasone[c] (or equivalent) 8 mg orally or intravenously. • Consider tocilizumab (or equivalent). When resuming treatment at the next planned dose, monitor patients at the physician's discretion in an appropriate healthcare facility[b].
Grade 3	Severe symptoms defined as temperature ≥ 38°C with: • Haemodynamic instability requiring a vasopressor (with or without vasopressin) and/or • Worsening hypoxia or respiratory distress requiring high flow nasal canula (> 6 L/min oxygen) or face mask.	• Withhold IMDYLLTRA until the event resolves, then resume IMDYLLTRA at the next scheduled dose[b]. • For recurrent grade 3 events, permanently discontinue IMDYLLTRA.	In addition to grade 2 treatment: • Intensive monitoring, e.g., ICU care is recommended. • Administer dexamethasone[c] (or equivalent) 8 mg intravenously every 8 hours up to 3 doses. • Vasopressor support as needed. • High flow oxygen support as needed. • Tocilizumab (or equivalent) is recommended. • Prior to the next dose, administer concomitant medicinal products as recommended for day 1 and day 8 (see table 2). When resuming treatment at the next planned dose, monitor patients at the physician's discretion in an appropriate healthcare facility[b].

CRS grade	Defining symptoms	IMDYLLTRA dose modification	Management
Grade 4	Life-threatening symptoms defined as temperature ≥ 38°C with: • Haemodynamic instability requiring multiple vasopressors (excluding vasopressin) and/or • Worsening hypoxia or respiratory distress despite oxygen administration requiring positive pressure.	Permanently discontinue IMDYLLTRA.	• ICU care. • Per grade 3 treatment.

[a] CRS based on American Society for Transplantation and Cellular Therapy (ASTCT) Consensus Grading (2019).
[b] See table 3 for recommendations on restarting IMDYLLTRA after dose delays.
[c] Taper steroids per standard of care guidelines.
ICU = Intensive Care Unit

Immune effector cell-associated neurotoxicity syndrome (ICANS)

Patients should be monitored for signs and symptoms of ICANS. Other causes of neurologic symptoms should be ruled out. Intensive care should be provided for severe or life-threatening neurologic toxicities. If ICANS is suspected, it should be managed 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	IMDYLLTRA dose modification	Management
Grade 1	ICE score 7-9[b] with no depressed level of consciousness.	• Withhold IMDYLLTRA until ICANS resolves, then resume IMDYLLTRA at the next scheduled dose[c].	• Supportive care.

ICANS grade[a]	Defining symptoms	IMDYLLTRA dose modification	Management
Grade 2	ICE score 3-6[b] and/or mild somnolence awaking to voice.	• Withhold IMDYLLTRA until ICANS resolves, then resume IMDYLLTRA at the next scheduled dose[c].	• Supportive care. • Dexamethasone[d] (or equivalent) 8 mg to 10 mg orally or intravenously. • If symptoms worsen, repeat dexamethasone every 12 hours or methylprednisolone[d] (or equivalent) 1 mg/kg intravenously every 12 hours. • Monitor neurologic symptoms and consider consultation with neurologist and other specialists for further evaluation and management. • Monitor patients at the physician's discretion following the next dose of IMDYLLTRA[c].
Grade 3	ICE score 0-2[b] and/or depressed level of consciousness awakening only to tactile stimulus and/or any clinical seizure focal or generalised that resolves rapidly Or Nonconvulsive seizures on EEG that resolve with intervention and/or focal or local oedema seen on neuroimaging.	• Withhold IMDYLLTRA until the ICANS resolves, then resume IMDYLLTRA at the next scheduled dose[c]. • If there is no improvement to grade ≤ 1 within 7 days, permanently discontinue IMDYLLTRA. • For recurrent grade 3 events, permanently discontinue.	• Intensive monitoring, e.g., ICU care is recommended. • Consider mechanical ventilation for airway protection. Dexamethasone[d] (or equivalent) 10 mg intravenously every 6 hours or methylprednisolone[d] (or equivalent) 1 mg/kg intravenously every 12 hours. • Consider repeat neuroimaging (CT or MRI) every 2-3 days if patient has persistent grade ≥ 3 neurotoxicity. • Monitor patients at the physician's discretion following the next dose of IMDYLLTRA[c].

ICANS grade[a]	Defining symptoms	IMDYLLTRA dose modification	Management
Grade 4	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 oedema on neuroimaging, decerebrate or decorticate posturing or papilloedema, cranial nerve VI palsy, or Cushing's triad.	• Permanently discontinue IMDYLLTRA.	• ICU care. • Consider mechanical ventilation for airway protection. • High-dose corticosteroids such as methylprednisolone[d] 1 000 mg/day in divided doses intravenously for 3 days. • Consider repeat neuroimaging (CT or MRI) every 2-3 days if patient has persistent grade ≥ 3 neurotoxicity. • 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 IMDYLLTRA after dose delays.
[d] Taper steroids per standard of care guidelines.
CT = Computed Tomography; EEG = Electroencephalogram; ICU = Intensive Care Unit; MRI = Magnetic resonance imaging

Neutropenia and other adverse reactions

Neutropenia and other adverse reactions should be managed in accordance with table 6.

Table 6. Recommended treatment interruptions of IMDYLLTRA for the management of other adverse reactions[a,b]

Adverse reactions	Severity[a]	Dose modification[b]
Neutropenia (see section 4.4)	Grades 1 and 2	No treatment interruption needed.
	Grade 3	• Interrupt IMDYLLTRA for at least 3 days and until the event improves to grade ≤ 2, then resume IMDYLLTRA. Consider using granulocyte-colony stimulating factor (G-CSF).
	Grade 4	• Interrupt IMDYLLTRA for at least 3 days and until the event improves to grade ≤ 2, then resume IMDYLLTRA. • If event lasts for > 7 days or grade 4 event reoccurs, permanently discontinue IMDYLLTRA. Consider using granulocyte-colony stimulating factor (G-CSF).
Hepatotoxicity (see section 4.4)[c]	Grade 3 Increased ALT or AST or bilirubin	• Withhold IMDYLLTRA until improved to grade ≤ 1.
	Grade 4 Increased ALT or AST or bilirubin	• Permanently discontinue IMDYLLTRA.
	AST or ALT > 3 × ULN with total bilirubin> 2 × ULN in the absence of alternative causes	• Permanently discontinue IMDYLLTRA.
Other adverse reactions (see section 4.8)	Grade 3 or 4	Withhold IMDYLLTRA until recovery to grade ≤ 1 or baseline. Consider permanently discontinuing if adverse reaction does not resolve within 28 days. • 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 IMDYLLTRA after dose delays.
[c] For patients with liver enzyme elevations at baseline, multiples of baseline values should be used for hepatotoxicity assessment.
ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal

Special populations

Elderly

No dose adjustment is necessary in elderly patients (≥ 65 years of age).

Hepatic impairment

No dose adjustment is required in patients with mild hepatic impairment (see section 5.2). Limited data is available in patients with moderate hepatic impairment. IMDYLLTRA has not been studied in patients with severe hepatic impairment. No dose recommendations can be made for patients with moderate or severe hepatic impairment.

Renal impairment

No dose adjustment is required in patients with mild or moderate renal impairment (see section 5.2). IMDYLLTRA has not been studied in patients with severe renal impairment. No dose recommendations can be made for patients with severe renal impairment to end-stage renal disease.

Paediatric population

There is no relevant use of IMDYLLTRA in the paediatric population for the treatment of small cell lung cancer.

Method of administration

IMDYLLTRA is for intravenous use.

IMDYLLTRA is to be reconstituted and then further diluted prior to administration by intravenous infusion.

For instructions on reconstitution and dilution of the medicinal product before administration, see section 6.6.

The infusion line for premedication can be used for IMDYLLTRA. An infusion line flush should be conducted between administering concomitant medicinal products and IMDYLLTRA.

Administer the entire contents of IMDYLLTRA as an intravenous infusion over 1 hour at a constant flow rate using an infusion pump, see table 7. The pump should be programmable, lockable, non-elastomeric, and have an alarm.

The infusion line is primed with sodium chloride 9 mg/mL (0.9%) solution for injection OR final prepared IMDYLLTRA.

Upon completion of the IMDYLLTRA infusion, the intravenous infusion line should be flushed over 3-5 minutes using sodium chloride 9 mg/mL (0.9%) solution for injection.

Table 7. Tarlatamab administration information

Infusion duration for 250 mL intravenous preparation	Infusion rate (mL/hour)
1 hour	250 mL/hour

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

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Cytokine release syndrome (CRS)

Administration of tarlatamab has been associated with CRS, including life-threatening or fatal events, see section 4.8. CRS may be associated with symptoms including pyrexia, hypotension, hypoxia, fatigue, tachycardia, headache, chills, nausea, and vomiting.

Patients and caregivers should be advised of the potential for CRS onset after discharge and instructed to seek immediate medical attention if any signs or symptoms occur.

Tarlatamab should be administered in a healthcare facility equipped to monitor and manage CRS. It should be ensured that patients are euvolemic prior to initiating the infusions. Patients should be closely monitored for signs and symptoms of CRS during the initiation of tarlatamab treatment. To mitigate the risk of CRS, it is important to initiate tarlatamab at the recommended starting dose in table 1.

CRS should be managed according to the recommendations in table 4.

Immune effector cell-associated neurotoxicity syndrome (ICANS)

Administration of tarlatamab has been associated with ICANS, including life-threatening or fatal events, see section 4.8. ICANS can occur up to several weeks following administration of tarlatamab. Adverse reactions 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 ICANS during tarlatamab treatment.

Patients and caregivers should be advised of the potential for ICANS onset after discharge and instructed to seek immediate medical attention if any signs or symptoms occur.

ICANS should be managed according to the recommendations in table 5.

Neutropenia

Administration of tarlatamab has been associated with neutropenia, see section 4.8. Patients should be closely monitored for signs and symptoms of neutropenia during tarlatamab treatment.

Neutropenia should be managed according to the recommendations in table 6.

Infections

Serious infections, including life-threatening and fatal infections, have been reported in patients treated with tarlatamab. The most frequent infections include pneumonia, urinary tract infection, COVID-19, upper respiratory tract infection, respiratory tract infection, candida infection, oral candidiasis and nasopharyngitis.

Patients should be monitored for signs and symptoms of infections prior to and during treatment with tarlatamab.

Hypersensitivity

Hypersensitivity reactions have been reported in patients treated with tarlatamab including rare severe events. Clinical signs and symptoms of hypersensitivity may include but are not limited to rash and bronchospasm. Patients should be monitored for signs and symptoms of hypersensitivity during treatment with tarlatamab and managed as clinically indicated. It should be considered to withhold or to permanently discontinue tarlatamab based on severity, see table 6 for management of other adverse reactions.

Hepatotoxicity

Administration of tarlatamab has been associated with elevated liver enzymes. Liver enzyme elevation can occur with or without concurrent CRS.

Liver enzymes and bilirubin should be monitored prior to treatment with tarlatamab, and as clinically indicated. Potential toxicities should be managed according to the recommendations in table 6.

Women of child bearing potential/contraception

Pregnancy status of females of child bearing potential should be verified prior to initiating treatment with tarlatamab. Females of reproductive potential have to use effective contraception during treatment and for 2 months after the last dose of tarlatamab (see section 4.6).

Excipients with known effect

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

This medicinal product contains 0.04 mg of polysorbate 80 in each 1 mg vial and 0.2 mg in each 10 mg vial. Polysorbates may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed. Initiation of tarlatamab treatment causes transient release of cytokines that may suppress CYP450 enzymes and may result in increased exposures of concomitant CYP substrates. Patients who are receiving concomitant CYP450 substrates, particularly those with a narrow therapeutic index, should be monitored for known adverse events. The dose of the concomitant medicinal product should be adjusted as needed.

4.6 Fertility, pregnancy and lactation

Women of child bearing potential/contraception

Women of child bearing potential have to use effective contraception during and for 2 months after treatment with tarlatamab.

Pregnancy

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

A reproductive toxicity study conducted in mice using the murine surrogate molecule muS757 showed transplacental transport of muS757 (see section 5.3). Based on its mechanism of action and potential development of adverse reactions (like CRS) following tarlatamab exposure, tarlatamab may cause foetal harm when administered to a pregnant woman (see section 5.1).

Tarlatamab is not recommended during pregnancy and in women of child bearing potential not using contraception.

Pregnancy status for females of child-bearing potential should be verified prior to starting treatment with tarlatamab.

Breast-feeding

It is unknown whether tarlatamab 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. Breast-feeding should be discontinued during treatment with tarlatamab and for at least 2 months after the last dose.

Fertility

There are no clinical trials to evaluate the effect of tarlatamab on fertility.

4.7 Effects on ability to drive and use machines

Due to the potential for ICANS associated neurological events following tarlatamab infusion, tarlatamab may have major influence on the ability to drive and use machines. In the event of any neurologic symptoms, patients should be advised to refrain from driving and engaging in hazardous occupations or activities, such as operating heavy or potentially dangerous machinery, until they resolve.

4.8 Undesirable effects

Summary of the safety profile

The safety of IMDYLLTRA was evaluated in 473 patients with small cell lung cancer (SCLC) who received the tarlatamab target dose of 10 mg as monotherapy in clinical trials.

The most common adverse reactions are: CRS (56.7%), decreased appetite (36.4%), pyrexia (31.9%), dysgeusia (31.3%), constipation (30.4%), anaemia (30.0%), fatigue (29.8%), nausea (24.9%), asthenia (19.0%), neutropenia (16.9%), hyponatraemia (16.7%), headache (16.3%), lymphopenia (15.6%).

The most common serious adverse reactions are CRS (19.7%) and pyrexia (4.7%).

Tabulated list of adverse reactions

Adverse reactions reported in clinical trials are listed by system organ class and by frequency. The frequencies of adverse reactions is based on pooled data from one phase 1, one phase 2, and one phase 3 clinical trials with 473 patients. The median duration of exposure was 18.0 weeks (range: 0.1 to 175.1 weeks).

Adverse reactions are listed according to the MedDRA system organ classification and by frequency. Frequency categories are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000), very rare (< 1/10 000) and not known (frequency cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 8. Adverse reactions

MedDRA system organ class	Adverse reaction	All grades	Grade ≥ 3
Blood and lymphatic system disorders	Anaemia	Very common	Common
	Neutropenia[a, c]	Very common	Common
	Lymphopenia[b]	Very common	Very common
	Thrombocytopenia	Common	Uncommon
	Leukopenia	Common	Uncommon
Gastrointestinal disorders	Constipation	Very common	Uncommon
	Nausea	Very common	Uncommon
	Vomiting	Very common	Uncommon
	Diarrhoea	Very common	Uncommon

MedDRA system organ class	Adverse reaction	All grades	Grade ≥ 3
General disorders and administration site conditions	Pyrexia	Very common	Uncommon
	Fatigue	Very common	Common
	Asthenia	Very common	Common
	Chills	Common	Not reported
Immune system disorders	Cytokine release syndrome[c]	Very common	Common
Investigations	Weight decreased	Very common	Common
	Alanine aminotransferase increased	Very common	Common
	Aspartate aminotransferase increased	Common	Common
	White blood cell count decreased	Common	Common
Metabolism and nutrition disorders	Decreased appetite	Very common	Common
	Hyponatraemia	Very common	Common
	Hypokalaemia	Very common	Common
	Hypomagnesaemia	Common	Uncommon
Musculoskeletal and connective tissue disorders	Myalgia	Common	Not reported
Nervous system disorders	Dysgeusia	Very common	Not reported
	Headache	Very common	Not reported
	Dizziness	Common	Not reported
	Immune effector cell-associated neurotoxicity syndrome[c]	Common	Uncommon
	Tremor	Common	Not reported
	Neurotoxicity	Uncommon	Not reported
	Seizure	Uncommon	Uncommon
	Ataxia	Uncommon	Uncommon
	Encephalopathy	Uncommon	Uncommon
Psychiatric disorders	Confusional state	Common	Uncommon
	Delirium	Common	Uncommon
Respiratory, thoracic and mediastinal disorders	Dyspnoea	Very common	Common
Skin and subcutaneous tissue disorders	Pruritus	Very common	Uncommon
	Rash	Common	Uncommon
Vascular disorders	Hypotension	Common	Common
	Hypertension	Common	Common

[a] Includes neutrophil count decreased.
[b] Includes lymphocyte count decreased.
[c] Additional information is provided in “Descriptions of selected adverse reactions”.

Description of selected adverse reactions

Cytokine release syndrome (CRS)

In clinical trials with pooled safety data from 473 patients with SCLC receiving the IMDYLLTRA 1 mg as first dose and 10 mg second and later dose, CRS occurred in 56.7% of patients, with grade 1 in 39.3%, grade 2 in 15.4% of patients, grade 3 in 1.7% of patients and grade 4 events in 0.2% of patients. Serious events of CRS were reported in 19.7% of patients. After the first dose of IMDYLLTRA, 41.4% of patients experienced any grade CRS, with 34.0% of patients experiencing any grade CRS after the second dose. The majority of CRS events occurred after the first two doses, with 8.5% of patients experiencing CRS following third dose or later. Following the day 1 infusion, 13.7% of patients experienced ≥ grade 2 CRS. Following the day 8 infusion, 4.4% of patients experienced ≥ grade 2 CRS. The median time from the most recent dose of IMDYLLTRA to the first onset of CRS was 15.9 hours (range: 9.0 to 26.5 hours). For those grade 1 events that progressed to grade 2 or greater, the median time from grade 1 event to grade 2 or greater events was 22.1 hours (interquartile range: 8.5 - 31.6 hours). Cytokine release syndrome led to treatment interruption and/or dose modification in 2.1% of patients and to discontinuation of tarlatamab in 0.6% of patients.

Fatal CRS cases have been reported in the post-marketing setting.

For clinical management of CRS, see section 4.4.

Immune effector cell-associated neurotoxicity syndrome (ICANS)

Tarlatamab can cause ICANS, including life-threatening or fatal events.

In clinical trials with pooled safety data from 473 patients with SCLC receiving IMDYLLTRA at 10 mg, ICANS was reported in 4.7% of patients. The median time from the first dose of IMDYLLTRA to the first onset of ICANS was 9.0 days (interquartile range: 2 to 13 days). The median time to resolution of ICANS was 4 days (interquartile range: 2 to 8 days).

For clinical management of ICANS, see section 4.4.

Neutropenia

In clinical trials with pooled safety data from 473 patients with SCLC receiving IMDYLLTRA at 10 mg, neutropenia occurred in 16.9% of patients including 8.2% of patients experiencing grade 3 or grade 4 events. The median time from the first dose of IMDYLLTRA to the first onset of neutropenia was 43 days (range: 29 to 109 days). Neutropenia leading to dose interruption occurred in 3.2% patients with none leading to treatment discontinuation. Treatment with G-CSF was required in 6% of patients.

For clinical management of neutropenia, see section 4.4.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:

Ireland
HPRA Pharmacovigilance
Website: www.hpra.ie

4.9 Overdose

Doses up to 100 mg every 2 weeks and 200 mg every 3 weeks have been evaluated in clinical trials. In the event of an overdose, the patient must be closely monitored for signs or symptoms of adverse reactions and should be treated symptomatically, and supportive measures instituted as required.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, other monoclonal antibodies and antibody drug conjugates, ATC code: L01FX33

Mechanism of action

Tarlatamab is a bispecific delta-like ligand 3 (DLL3)-directed CD3 T-cell engager that binds to DLL3 expressed on the surface of tumour cells and CD3 expressed on the surface of T-cells. The bispecific binding of tarlatamab to T-cells and DLL3-positive tumour cells triggers T-cell activation, production of inflammatory cytokines, and release of cytotoxic proteins, which results in redirected lysis of tumour cells.

Pharmacodynamic effects

The pharmacodynamic response after a single infusion of tarlatamab was characterised 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.

Immunogenicity

Anti-drug antibodies (ADA) were commonly detected. No evidence of ADA impact on pharmacokinetics, efficacy or safety was observed, however, data are still limited.

Clinical efficacy and safety

Study DeLLphi-304

The efficacy of IMDYLLTRA was studied in a phase 3 multicentre, randomised, open-label trial (Study DeLLphi-304). Eligible patients were required to have SCLC with disease progression following 1 platinum-based regimen. In regions where standard of care (SOC) first-line systemic treatment for patients diagnosed with extensive-stage disease included platinum-based chemotherapy in combination with PD-(L)1 inhibitor, patients were required to have failed PD-(L)1 inhibitor as part of their first-line systemic treatment or to be ineligible to receive PD-(L)1 inhibitor therapy. Additionally, patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0-1, and at least one measurable lesion as defined by response evaluation criteria in solid tumours (RECIST v1.1). The trial excluded patients with symptomatic brain metastases or active immunodeficiency.

A total of 509 patients were enrolled and randomised 1:1 to receive either IMDYLLTRA or SOC chemotherapy. 254 patients were randomised to IMDYLLTRA 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 in a 28-day cycle until disease progression or unacceptable toxicity. SOC chemotherapies included topotecan (n = 185), lurbinectedin (n = 47) or amrubicin (n = 23). Randomisation was stratified by prior anti-PD-(L)1 exposure (yes vs no), platinum sensitivity status (chemotherapy-free interval ≥ 180 days, < 180 to ≥ 90 days, or < 90 days), presence (previous or current) of brain metastases (yes vs no) and standard of care (topotecan/amrubicin vs lurbinectedin). Treatment continued until disease progression or unacceptable toxicity. Tumour assessments were performed every 6 weeks for the first 48 weeks and every 12 weeks thereafter.

The baseline demographics and disease characteristics of the study population were: median age of 65 years (range: 20 to 86 years); 41.3% age 65 to 74; 10.8% age 75 or older; 69% male; 57.2% White and 40.1% Asian; 32% ECOG PS of 0 and 67.2% ECOG PS of 1; 91% patients had metastatic disease at baseline; 44.8% had brain metastases at baseline; 35.2% had liver metastases at baseline. 68.8% patients were former smokers; 20.6% were current smokers, 10.6% were never smokers. All patients received at least 1 line of prior platinum-based chemotherapy (range: 1 to 3 lines); 97.6% of patients had received 1 prior treatment line; 70.7% received prior anti-PD-(L)1 therapy; 223 patients (43.8%) had chemotherapy-free interval < 90 days after end of first-line platinum therapy, while 286 patients (56.2%) had chemotherapy-free interval ≥ 90 days.

The primary efficacy outcome measure was overall survival (OS). Key secondary efficacy outcomes were progression-free survival (PFS) based on investigator assessment per response evaluation criteria in solid tumours (RECIST v1.1) and select patient-reported outcomes. Additional endpoints included overall response rate (ORR) based on investigator assessment per RECIST v1.1.

Patients received a median of 5 cycles of IMDYLLTRA treatment (range: 1 to 19 cycles), and a median of 4 cycles of SOC treatment (range: 1 to 21 cycles).

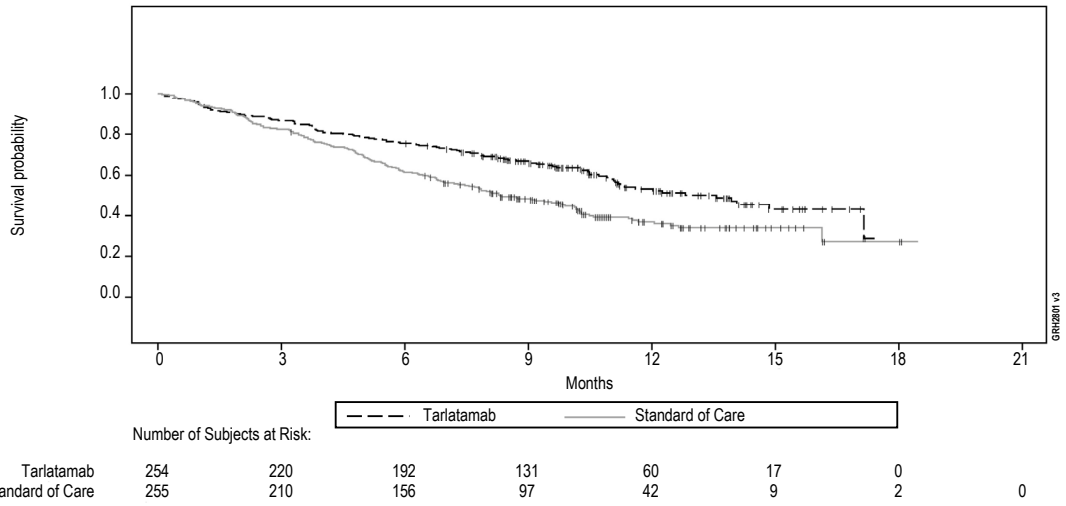
Efficacy results are summarised in table 9 and figure 1. The median (95% CI) follow-up time for OS was 11.2 months (10.4, 12.1) in the tarlatamab group and 11.7 months (10.6, 12.3) in the SOC chemotherapy group. The median (95% CI) follow-up time for PFS was 11.0 (8.5, 11.2) months for tarlatamab and 9.7 (8.4, 11.1) months for SOC chemotherapy.

Table 9. Efficacy results for patients with SCLC in Study DeLLphi-304

Efficacy parameter	IMDYLLTRA (N = 254)	Standard of care (N = 255)
Overall survival (OS)		
Deaths (%)	111 (43.7)	152 (59.6)
Median[a] in months (95% CI)	13.6 (11.1, NE)	8.3 (7.0, 10.2)
Hazard ratio[b] (95% CI)	0.60 (0.47, 0.77)	
p-value (stratified log-rank)	< 0.001	
Progression-free survival (PFS)[c]		
Events (%)	191 (75.2)	205 (80.4)
Median[a] in months (95% CI)	4.2 (3.0, 4.4)	3.2 (2.9, 4.2)
Hazard ratio[b] (95% CI)	0.72 (0.59, 0.88)	
p-value (stratified log-rank)	< 0.001	
Overall response rate (ORR)[c]		
ORR, %	35.0	20.4

[a] per Kaplan-Meier estimates.
[b] Hazard ratio based on the stratified Cox proportional hazard model.
[c] PFS, ORR based on investigator assessment per RECIST v1.1.
CI = Confidence interval; N = number; NE = not estimable

Figure 1. Kaplan-Meier plot for overall survival (ITT analysis set)



Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with tarlatamab in all subsets of the paediatric population in treatment of small cell lung cancer (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Tarlatamab population pharmacokinetic (PK) analyses in adult subjects (n = 702) with previously treated advanced SCLC were performed to characterise the time course of tarlatamab serum concentrations after intravenous administration, to quantify inter-individual variability and to evaluate effects of subject specific covariates on the PK parameters of tarlatamab.

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 1 mg to 100 mg Q2W (10 times the recommended dose). Approximate steady state in serum tarlatamab exposures were achieved by cycle 2 day 15.

Distribution

The typical value (inter-subject CV%) for central volume of distribution is 3.23 L (38%) and steady state volume of distribution is 8.19 L as estimated by population PK analysis.

Biotransformation

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

Elimination

The systemic clearance (inter-subject CV%) was 0.728 L/day (34%) and terminal elimination half-life was approximately 10.6 days in subjects with SCLC as estimated by population PK analysis.

Special populations

No clinically meaningful differences in the clearance of tarlatamab were observed based on age (range: 20-86 years), bodyweight (range: 35-149 kg), 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). Limited data is available in patients with moderate hepatic impairment and no data is available in patients with severe hepatic or severe renal impairment.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology and repeated dose toxicity.

Genotoxicity and carcinogenicity

No genotoxicity or carcinogenicity studies have been conducted with tarlatamab.

Impairment of fertility

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

Reproductive and developmental toxicity

A reproductive toxicity study conducted in mice using the murine surrogate molecule muS757 showed transplacental transport of muS757 and did not induce embryo-foetal toxicity or teratogenicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder
Glutamic acid
Sucrose
Polysorbate 80 (E433)
Sodium hydroxide (for pH-adjustment)

Solution (stabiliser)
Citric acid monohydrate (E330)
Lysine hydrochloride
Polysorbate 80 (E433)
Sodium hydroxide (for pH-adjustment)
Water for injections

6.2 Incompatibilities

No known incompatibilities.

6.3 Shelf life

Unopened vial

4 years.

Diluted solution for intravenous infusion (infusion bag)

Chemical and physical in-use stability has been demonstrated for 28 days at 2°C to 8°C and 8 hours at 20°C to 25°C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user and would normally

not be longer than 24 hours at 2°C to 8°C, unless the method of reconstitution and dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store and transport refrigerated (2°C to 8°C).

Do not freeze.

Store in the original packaging in order to protect from light.

For storage conditions after reconstitution and dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

IMDYLLTRA consists of two packaging configurations. Each IMDYLLTRA pack contains 1 vial of powder for concentrate for solution for infusion and 2 vials of solution (stabiliser).

IMDYLLTRA 1 mg powder for concentrate and solution for solution for infusion

- 1 mg tarlatamab powder in a Type 1 glass vial with an elastomeric stopper, aluminium seal and a grey flip-off cap
- 7 mL solution in a Type 1 glass vial with an elastomeric stopper, aluminium seal and a white flip-off cap

IMDYLLTRA 10 mg powder for concentrate and solution for solution for infusion

- 10 mg tarlatamab powder in a Type 1 glass vial with an elastomeric stopper, aluminium seal and an orange flip-off cap
- 7 mL solution in a Type 1 glass vial with an elastomeric stopper, aluminium seal and a white flip-off cap

6.6 Special precautions for disposal and other handling

Aseptic preparation

Strictly observe aseptic technique when preparing the solution for infusion since tarlatamab vials do not contain antimicrobial preservatives.

Other instructions

- **Reconstitution of IMDYLLTRA is with water for injections. Do not use the solution (stabiliser) to reconstitute IMDYLLTRA.** The solution (stabiliser) is used to coat the infusion bag prior to addition of reconstituted IMDYLLTRA to prevent adsorption of IMDYLLTRA to infusion bags and infusion line.
- Infusion 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.
- Infusion 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. Compatibility testing of vial adaptor CSTDs with IMDYLLTRA has not been performed.

Preparation of the solution for infusion

Reconstitution of tarlatamab

Table 10. Required amount of water for injections to reconstitute IMDYLLTRA[a]

IMDYLLTRA vial strength	Amount of water for injections needed to reconstitute IMDYLLTRA	Final concentration
1 mg	1.3 mL	0.9 mg/mL
10 mg	4.4 mL	2.4 mg/mL

[a] Each vial contains an 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 labelled vial strength.

1. Transfer required amount of water for injections (refer to table 10) into the tarlatamab vial to provide a final tarlatamab concentration of 0.9 mg/mL (1 mg vial) or 2.4 mg/mL (10 mg vial). Direct the water along the walls of the IMDYLLTRA vial and not directly on the lyophilised powder.
   - **Do not use the solution (stabiliser) to reconstitute IMDYLLTRA.**
2. Gently swirl contents. **Do not shake.**
3. Visually inspect that the solution is clear to slightly opalescent, colourless to slightly yellow. **Do not** use if solution is cloudy or has particulates.

Preparation of IMDYLLTRA infusion bag

Table 11. Preparation guide for 1-hour infusion

IMDYLLTRA vial strength	IMDYLLTRA dose	Volume of sodium chloride 9 mg/mL (0.9%) solution for injection to withdraw from infusion bag	Volume of solution (stabiliser) to add to infusion bag	Volume of reconstituted IMDYLLTRA to add to infusion 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.

1. Use an infusion bag pre-filled with 250 mL sodium chloride 9 mg/mL (0.9%) solution for injection.
2. Withdraw the required volume of sodium chloride 9 mg/mL (0.9%) solution for injection from the pre-filled infusion bag and discard (refer to table 11). Disregard any overfill in the infusion bag.
3. Add solution (stabiliser).
   - To coat the infusion bag, transfer 13 mL of the solution (stabiliser) to the infusion bag containing sodium chloride 9 mg/mL (0.9%) solution for injection.
   - Gently mix the contents of the bag to avoid foaming. **Do not shake.**
4. Add reconstituted IMDYLLTRA.
   - Transfer the required volume of reconstituted IMDYLLTRA into the stabilised infusion bag containing sodium chloride 9 mg/mL (0.9%) solution for injection and the solution (stabiliser). Refer to table 11.
   - Gently mix the contents of the bag to avoid foaming. **Do not shake.**
5. Remove the air from the infusion bag using an empty syringe to avoid foaming.
6. Prime infusion line with sodium chloride 9 mg/mL (0.9%) solution for injection or final prepared product from the infusion bag.

The storage time per section 6.3 includes total time permitted from point of reconstitution of first vial to the end of administration. After removal from refrigeration, allow the infusion bag to reach room temperature and complete administration of the diluted IMDYLLTRA infusion solution within the allowable room temperature storage time (including infusion time). If the prepared tarlatamab infusion bag is not administered within the time frames and temperatures indicated, it must be discarded; it should not be refrigerated again.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Amgen Europe B.V.
Minervum 7061
4817 ZK Breda
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/26/2033/001
EU/1/26/2033/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

May 2026

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.