SUMMARY OF PRODUCT CHARACTERISTICS

▼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 milligram powder for concentrate and solution for infusion.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Single use vial of powder contains 1 milligram tarlatamab.

Reconstitution with 1.3mL of sterile water for injection results in a final tarlatamab concentration of 0.9mg/mL.

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

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for concentrate and 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 for the treatment of adult patients with small cell lung cancer (SCLC) with disease progression on or after platinum-based chemotherapy.

4.2 Posology and method of administration

Treatment with IMDYLLTRA should be initiated and supervised by physicians experienced in the treatment of small cell lung cancer.

IMDYLLTRA should only be administered by a qualified healthcare professional with appropriate medical support to manage severe reactions such as cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) (see Section 4.4).

Posology

Pre-treatment medicinal products should be administered prior to each dose of IMDYLLTRA on Day 1 and Day 8 of the dosing schedule (see below).

Recommended dosing Schedule

The recommended dosage and 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.

Table 1. IMDYLLTRA recommended dosage and schedule.

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

Administer IMDYLLTRA as a 1-hour intravenous infusion in an appropriate healthcare setting. Ensure patients are well hydrated prior to administration of IMDYLLTRA. Premedicate with dexamethasone 8 mg IV 1 hour prior to first two doses (Day 1 and Day 8). Consider IV fluids for patients after infusion of IMDYLLTRA (Day 1 and Day 8).

Monitor patients during the infusion and for at least 16 hours after the first infusion (Day 1).

On Day 8, monitor patients for 6-8 hours post infusion and at subsequent infusions monitor patients for 2-4 hours post infusion at the discretion of the healthcare professional.

On Day 1 and Day 8, recommend patients to remain within 1 hour of an appropriate healthcare setting, such as the treatment hospital, for 24 hours starting from each IMDYLLTRA infusion, accompanied by a caregiver.

Inform both the patient and the caregiver on the signs and symptoms of Cytokine Release Syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) prior to discharge.

Duration of treatment

Administer IMDYLLTRA until disease progression or unacceptable toxicity.

Dose modifications and Adverse Reaction Management

If a dose of IMDYLLTRA is delayed because of an adverse event, therapy will be restarted based on the recommendations listed in Table 6. See Table 2 and Table 3 for recommended actions for the management of CRS and ICANS respectively and Table 4 for neutropenia and other adverse reactions.

Cytokine Release Syndrome (CRS)

Diagnose CRS based on clinical presentation. Evaluate for and treat other causes of fever, hypoxia, and hypotension. If CRS is suspected, manage according to the recommendations in Table 2. Patients who experience Grade 2 or higher CRS (e.g., hypotension not responsive to fluids, or hypoxia requiring supplemental oxygen) should be monitored for signs and symptoms of CRS including fever, hypotension and hypoxia using pulse oximetry or cardiac telemetry as indicated. 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 2 provides the guidelines for grading and dosage modification and management of cytokine release syndrome.

Table 2. Guidelines for Grading, Dosage Modification and Management of Cytokine Release Syndrome[a]

CRS Grade	Defining Symptoms	IMDYLLTRA Dosage 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 treatment (e.g., paracetamol) for fever. • Consider dexamethasone[c] 4 mg (or equivalent) to 10 mg PO or IV.
Grade 2	Symptoms require and respond to moderate intervention. Fever ≥38°C, Hypote	Withhold IMDYLLTRA until event resolves, then resume IMDYLLTRA at the next scheduled	• Recommend hospitalisation with monitoring for fever, hypotension and hypoxia using pulse oximetry or cardiac telemetry as indicated. • Administer symptomatic

CRS Grade	Defining Symptoms	IMDYLLTRA Dosage Modification	Management
	nsion responsive to fluids not requiring vasopressors, and/or Hypoxia requiring low flow nasal cannula or blow-by.	dose[b].	treatment (e.g., paracetamol) for fever. • Administer supplemental oxygen and intravenous fluids when indicated. • Consider dexamethasone[c] (or equivalent) 8 mg PO or IV.[i] • Consider tocilizumab (or equivalent). 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 with: Haemodynamic instability requiring a vasopressor (with or without vasopressin) or Worsening hypoxia or respiratory distress requiring high flow nasal canula (> 6 L/min oxygen) or face mask.	Withhold 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: • Recommend intensive monitoring, e.g., ICU care. • Administer dexamethasone[c] (or equivalent) 8 mg IV every 8 hours up to 3 doses. • Vasopressor support as needed. • High flow oxygen support as needed. • Recommend tocilizumab (or equivalent) • Prior to the next dose, administer concomitant medications as recommended for Day 1 and Day 8 (see Table 1). 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	IMDYLLTRA Dosage Modification	Management
Grade 4	Life-threatening symptoms defined as temperature ≥38°C with: Haemodynamic instability requiring multiple vasopressors (excluding vasopressin). Worsening hypoxia or respiratory distress despite oxygen administration requiring positive pressure.	Permanently discontinue IMDYLLTRA.	• ICU care. • Grade 3 treatment.

[a] CRS based on American Society for Transplantation and Cellular Therapy (ASTCT) Consensus Grading (2019).

[b] See section 4.2, Table 5 for recommendations on restarting IMDYLLTRA 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 3.

Table 3. Guidelines for Grading, Dose Modification and Management of Immune Effector Cell-Associated Neurotoxicity Syndrome[a]

ICANS Grade[a]	Defining Symptoms	IMDYLLTRA Dosage Modifications	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.
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 to 10 mg PO or IV. • If symptoms worsen, repeat dexamethasone every 12 hours or methylprednisolone[d] (or equivalent) 1 mg/kg IV 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	• 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 or Grade 3 toxicity reoccurs within 7 days of restart, permanently discontinue IMDYLLTRA. • For recurrent	• Recommend intensive monitoring, e.g., ICU care. • Consider mechanical ventilation for airway protection. Dexamethasone[d] (or equivalent) 10 mg IV every 6 hours or methylprednisolone[d] (or equivalent) 1 mg/kg IV every 12 hours. • Consider repeat neuroimaging (CT or MRI) every 2-3 days if patient has persistent Grade ≥ 3 neurotoxicity. • Monitor patients at the physician's

ICANS Grade[a]	Defining Symptoms	IMDYLLTRA Dosage Modifications	Management
	neuroimaging.	Grade 3 events, permanently discontinue.	discretion following the next dose of IMDYLLTRA[c].
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 papilledema, 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] 1000 mg/day in divided doses IV 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 6 for recommendations on restarting IMDYLLTRA after dose delays (see section 4.2).
[d] Taper steroids per standard of care guidelines.

Table 4. Recommended Treatment Interruptions of IMDYLLTRA for the Management of Cytopenias, and Other Adverse Reactions

Adverse Reactions	Severity[b]	Dosage Modification[a]

Cytopenias (see section 4.4)	Grade 3 neutropenia	Withhold IMDYLLTRA until recovery to Grade ≤ 2. Consider administration of granulocyte colony stimulating factor (G-CSF).
	Grade 4 neutropenia	Withhold IMDYLLTRA until recovery to Grade ≤ 2. Consider administration of granulocyte colony stimulating factor (G-CSF). Permanently discontinue if recover to Grade ≤ 2 does not occur within 3 weeks.
	Recurrent Grade 4 neutropenia	Permanently discontinue IMDYLLTRA.
	Febrile neutropenia	Withhold IMDYLLTRA until neutropenia recovers to Grade ≤ 2 and fever resolves.
	Haemoglobin <8 g/dL	Withhold IMDYLLTRA until haemoglobin is ≥8 g/dL.
	Grade 3 or Grade 4 decreased platelet count	Withhold IMDYLLTRA until platelet count is Grade ≤ 2 and no evidence of bleeding. Permanently discontinue if recovery to Grade ≤ 2 does not occur within 3 weeks.
	Recurrent Grade 4 decreased platelet count	Permanently discontinue IMDYLLTRA.
Elevated Liver Tests (see section 4.4)	Grade 3 Increased ALT or AST or bilirubin	Withhold IMDYLLTRA until adverse events improve 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] Refer to Table 6 for recommendations on restarting IMDYLLTRA after dose delay.
[b] Severity based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 5.0.

Recommended Concomitant Medications for IMDYLLTRA Administration for Day 1 and Day 8

Administer concomitant medications for IMDYLLTRA administration as presented in Table 5 to reduce the risk of cytokine release syndrome (see section 4.4).

Table 5. Concomitant Medications for IMDYLLTRA Administration for Day 1 and Day 8

Treatment Day	Medication	Administration
Day 1 and Day 8	Administer 8 mg of dexamethasone intravenously (or equivalent)	Within 1 hour prior to IMDYLLTRA administration
	Administration of 1 liter of normal saline intravenously is recommended per standard of care guidelines	Immediately after completion of IMDYLLTRA infusion

Restarting IMDYLLTRA After Dosage Delay

If a dose of IMDYLLTRA is delayed, restart therapy based on the recommendations listed in Table 6 and resume the dosing schedule accordingly (see Table 1).
Administer required concomitant medications as indicated in section 4.2.

Table 6. Recommendations for Restarting Therapy with IMDYLLTRA After Dosage Delay

Last Dose Administered	Time Since the Last Dose Administered	Action [a]
Day 1 1 mg	14 days or less	Administer IMDYLLTRA 10 mg, then continue with the planned dosage schedule
	Greater than 14 days	Restart IMDYLLTRA 1 mg, then

		continue with the planned dosage schedule.
Day 8 10 mg	21 days or less	Administer IMDYLLTRA 10 mg, then continue with the planned dosage schedule
	Greater than 21 days	Restart IMDYLLTRA 1 mg, then continue with the planned dosage schedule.
Day 15 and every 2 weeks thereafter 10 mg	28 days or less	Administer IMDYLLTRA 10 mg, then continue with the planned dosage schedule
	Greater than 28 days	Restart IMDYLLTRA 1 mg, then continue with the planned dosage schedule.

[a] Administer recommended concomitant medications before and after Day 1 and Day 8 of IMDYLLTRA infusions and monitor patients accordingly (see section 4.2, Table 1 and Table 5).

Special populations

Elderly

In clinical studies, no overall differences in IMDYLLTRA pharmacokinetics, safety or efficacy were observed between elderly patients (≥ 65 years of age) and younger patients. No dose adjustment is necessary in elderly patients (≥ 65 years of age).

Hepatic Impairment

Based on population pharmacokinetic analyses, no dose adjustment is required in patients with mild hepatic impairment. IMDYLLTRA has not been studied in patients with moderate or severe hepatic impairment.

Renal impairment

Based on population pharmacokinetic analyses, no dose adjustment is required in patients with mild or moderate renal impairment. IMDYLLTRA has not been studied in patients with severe renal impairment.

Paediatric population

The safety and efficacy of IMDYLLTRA in children aged ≤ 18 years of age have not yet been established.

Method of administration

IMDYLLTRA is for intravenous use.

IV line for premedication can be used for IMDYLLTRA. IV line flush should be conducted between administering concomitant medication and IMDYLLTRA.

Administer the entire contents of IMDYLLTRA 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). IV tubing is primed with 0.9% Sodium Chloride for Injection, OR final prepared IMDYLLTRA. Upon completion of the IMDYLLTRA infusion, the IV administration line should be flushed over 3-5 minutes using 0.9% Sodium Chloride for Injection.

IMDYLLTRA should be infused over 1 hour at an infusion rate of 250mL/hour, see Table 7.

Table 7. IMDYLLTRA Administration Information

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

For instructions on the handling and preparation of the medicinal product before administration, see section 6.6.

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 IMDYLLTRA has been associated with cytokine release syndrome (CRS) which may be serious or life-threatening (see section 4.8). CRS may be associated with symptoms including pyrexia, hypotension, fatigue, hypoxia, tachycardia, headache, chills, nausea, and vomiting. The majority of these events did not lead to IMDYLLTRA discontinuation in clinical trials.

Potentially life-threatening complications of CRS may include cardiac dysfunction, acute respiratory distress syndrome, neurologic toxicity, renal and/or hepatic failure, and disseminated intravascular coagulation (DIC).

Administer IMDYLLTRA in a healthcare setting equipped to monitor and manage CRS. Ensure patients are euvolemic prior to initiating the infusions. Section 4.2. Patients should be closely monitored for signs and symptoms of CRS during the initiation of IMDYLLTRA treatment. To mitigate the risk of CRS, it is important to initiate IMDYLLTRA at the recommended starting dose in Table 1. CRS should be managed according to the recommendations in Table 2.

At the first sign of CRS, immediately interrupt IMDYLLTRA infusion, evaluate the patient for hospitalisation and institute supportive care based on severity. Management of these events may require the dose to be either modified or permanently discontinued (see section 4.2). Counsel patients to seek medical attention should signs or symptoms of CRS occur.

Immune effector cell-associated neurotoxicity syndrome (ICANS)

Administration of IMDYLLTRA has been associated with ICANS which may be serious or life-threatening. ICANS can occur up to several weeks following administration of IMDYLLTRA. 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 ICANS during IMDYLLTRA treatment. ICANS should be managed according to the recommendations in Table 3.

CNS metastases

There is limited experience of IMDYLLTRA in patients with central nervous system (CNS) involvement. The risk/benefit of IMDYLLTRA has not been established in patients with active brain metastases.

The overall safety profile was similar for patients with or without a history of active CNS metastases.

Hypersensitivity

Hypersensitivity reactions have been reported in patients treated with IMDYLLTRA 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 IMDYLLTRA and manage as clinically indicated. Withhold or consider permanent discontinuation of IMDYLLTRA based on severity (see sections 4.2).

Cytopenias

IMDYLLTRA can cause cytopenias including neutropenia, thrombocytopenia, and anaemia. Monitor patients for signs and symptoms of cytopenias. Perform complete blood counts prior to treatment with IMDYLLTRA, as clinically

indicated. Based on the severity of cytopenias, temporarily withhold, or permanently discontinue IMDYLLTRA as clinically indicated.

Elevated Liver Tests

IMDYLLTRA can cause transient elevation of liver enzymes. Liver enzyme elevation can occur with or without concurrent CRS. Monitor liver enzymes and bilirubin prior to treatment with IMDYLLTRA, as clinically indicated. Withhold IMDYLLTRA or permanently discontinue based on severity as clinically indicated.

4.5 Interaction with other medicinal products and other forms of interaction

No formal drug interaction studies have been conducted with IMDYLLTRA. Initiation of IMDYLLTRA 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 e.g., sirolimus and tacrolimus, monitor for known adverse events. Adjust the dose of the concomitant drug as needed.

4.6 Fertility, pregnancy and lactation

Pregnancy

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

Breast-feeding

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

Fertility

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

4.7 Effects on ability to drive and use machines

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

Summary of the safety profile

The safety of IMDYLLTRA, based on pooled data from Study DeLLphi-300, and Study DeLLphi-301 and Study DeLLphi-304, was evaluated in 473 patients with small cell lung cancer (SCLC) who received 10 mg as monotherapy. The median duration of exposure to IMDYLLTRA was 18 weeks (range: 6 to 38).

The most common adverse reactions were cytokine release syndrome (56.7%), pyrexia (31.9%), dysgeusia (31.3%), decreased appetite (36.4%), constipation (30.4%), fatigue (29.8%), anaemia (30.0%), and asthenia (19.0%).

Tabulated list of adverse reactions

Adverse reactions reported in IMDYLLTRA clinical studies are displayed in Table 8 below. Frequency is provided by MedDRA category: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 and < 1/1,000), very rare (< 10,000). Within each system organ class, adverse reactions are presented in order of decreasing seriousness.

Table 8. Adverse reactions

MedDRA system organ class	Very Common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥ 1/1,000 to < 1/100)
Blood and lymphatic systems disorders	Anaemia Neutropenia[a, c] Lymphopenia[b]		
Gastrointestinal disorders	Constipation Nausea		
General disorders and administration site conditions	Pyrexia Fatigue Asthenia		
Immune system disorders	Cytokine release syndrome[b]		
Metabolism and nutrition disorders	Decreased appetite Hyponatraemia		
Nervous system disorders	Dysgeusia Headache	Immune effector cell-associated neurotoxicity syndrome[c] Tremor	Neurotoxicity Seizure Ataxia Encephalopathy

Psychiatric disorders		Confusional state Delirium	
Respiratory, thoracic, and mediastinal disorders	Dyspnoea		
Investigations	Weight decreased		

[a] Includes neutropenia and neutrophil count decreased.

[b] Includes lymphopenia and 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 for 473 patients with SCLC enrolled in Study DeLLphi-300, Study DeLLphi-301 and Study DeLLphi-304, receiving the IMDYLLTRA 10 mg 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. No patients had Grade 5 events. 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% 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 to 26.5 hours).

In patients treated with IMDYLLTRA at 10 mg enrolled in Study DeLLphi-304 (n=252), CRS occurred in 56.3% of patients, including Grade 1 in 42.5%, Grade 2 in 12.7 % and Grade 3 in 1.2% of patients. No patients had Grade 4 or Grade 5 events. Most patients experienced CRS after the first two doses of IMDYLLTRA with 6.3% experiencing CRS after the third dose or later. Following the Day 1 infusion, 11.5% of patients experienced ≥ Grade 2 CRS. Following the Day 8 infusion, 4.8% of patients experienced ≥ Grade 2 CRS. For those Grade 1 events that progressed to Grade 2 or greater, the median time from Grade 1 event to Grade 2 events was 22.3 hours (range: 6.5 – 40.1 hours).

ICANS

In clinical trials with pooled safety data for 473 patients with SCLC enrolled in Study DeLLphi-300, Study DeLLphi-301 and Study DeLLphi-304 receiving IMDYLLTRA 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 (range: 2 to 13 days). The median time to resolution of ICANS was 4 days (range: 2 to 8 days).

Neutropenia

In clinical trials with pooled safety data for 473 patients with SCLC enrolled in Study DeLLphi-300, Study DeLLphi-301 and Study DeLLphi-304 receiving IMDYLLTRA 10 mg, neutropenia occurred in 16.9% including 8.2% of patients experiencing Grade 3 and 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 and/or reduction of tarlatamab occurred in 34.9% patients with none leading to treatment discontinuation.

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, Study DeLLphi-301 and Study DeLLphi-304, the incidence of anti-tarlatamab antibody development was 7.7% (34/444) in patients receiving the dose of 10 mg. In Studies DeLLphi-301 and DeLLphi-304 which employed the neutralising assay, 7.5% (27/359) of the patients developed anti-tarlatamab antibody, including 3.1% (11/359) of patients developed anti-tarlatamab neutralising antibodies. Positive anti-tarlatamab antibody status had no clinically relevant impact on efficacy, safety and pharmacokinetics.

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

Yellow Card Scheme

Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store

4.9 Overdose

There is no clinical experience with overdose with IMDYLLTRA. 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: Other monoclonal antibodies and antibody drug conjugates, ATC code: L01FX33.

Mechanism of action

Tarlatamab is a bispecific 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, 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 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.

Clinical efficacy and safety

The efficacy of IMDYLLTRA was demonstrated in patients enrolled 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 trials excluded patients with symptomatic brain metastases or active immunodeficiency.

A total of 509 patients were enrolled and randomized 1:1 to receive either IMDYLLTRA or SOC chemotherapy. 254 patients were randomised to IMDYLLTRA at an initial dose of 1 mg on Day 1 followed by 10 mg on Days 8, 15, and every 2 weeks thereafter until disease progression or unacceptable toxicity. SOC chemotherapies included topotecan, lurbinectedin or amrubicin. 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); 52.1% age 65 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); 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 included 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 were overall response rate (ORR) and duration of response (DOR) 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).

The trial demonstrated a statistically significant and clinically meaningful improvement in OS, stratified hazard ratio [HR] = 0.60 [95% CI: 0.47, 0.77] with a 40% reduced risk of death for patients randomised to IMDYLLTRA as compared with SOC at the prespecified interim analysis, when 263 events were observed (76% of the planned number of events for final analysis). The trial also demonstrated a statistically significant and clinically meaningful improvement in PFS, HR = 0.72 [95% CI: 0.59, 0.88] resulting in a 28% reduced risk of disease progression or death in patients randomised to IMDYLLTRA compared with patients randomised to SOC. Efficacy results are summarised in table 9 and figures 1 and 2.

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%	4.2 (3.0, 4.4)	3.2 (2.9, 4.2)

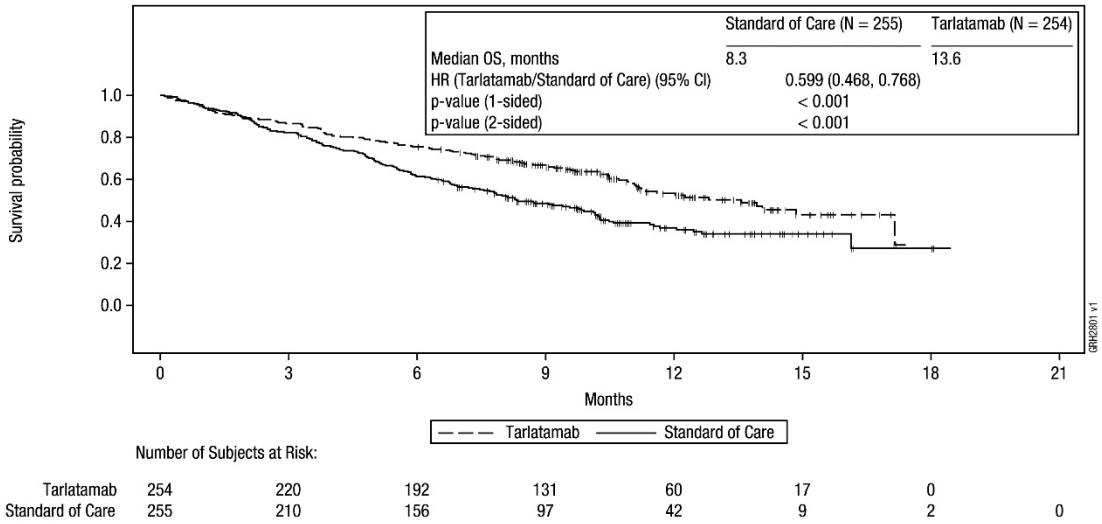
CI)		
Hazard ratio[b] (95% CI)	0.72 (0.59, 0.88)	
p-value (stratified log-rank)	< 0.001	
Overall response rate (ORR)[c]		
ORR, % (95% CI)	35.0 (29.2, 41.3)	20.4 (15.6, 25.9)
Complete response, n (%)	3 (1.2)	0 (0.0)
Partial response, n (%)	86 (33.9)	52 (20.4)
Duration of response (DOR)[c]		
Median[a] in months (95% CI) Min, Max (+ for censored)	6.9 (4.5, 12.4) 1.9, 15.3+	5.5 (4.2, 5.7) 1.3+, 12.5+
Responders with duration ≥ 6 months[d], %	46.1	26.9
Responders with duration ≥ 12 months[d], %	13.5	1.9

[a] per Kaplan-Meier estimates.
[b] Hazard ratio based on the stratified Cox proportional hazard model.
[c] PFS, ORR, DOR based on investigator assessment per RECIST v1.1.
[d] Based on observed duration of response.
[+] Denotes ongoing response. At the time of analysis, 47% (42/89) of patients randomised to IMDYLLTRA and 15% (8/52) of patients randomised to SOC had ongoing responses.
CI = Confidence interval

109 patients in the tarlatamab arm and 114 patients in the SOC arm had a chemotherapy-free interval (CFI) < 90 days at baseline. The hazard ratio for OS was 0.60 (95% CI: 0.43, 0.84) with a median OS of 10.9 months (95% CI: 8.7, 12.3) and 6.4 months (95% CI: 5.0, 7.9) in the tarlatamab and SOC arm, respectively.

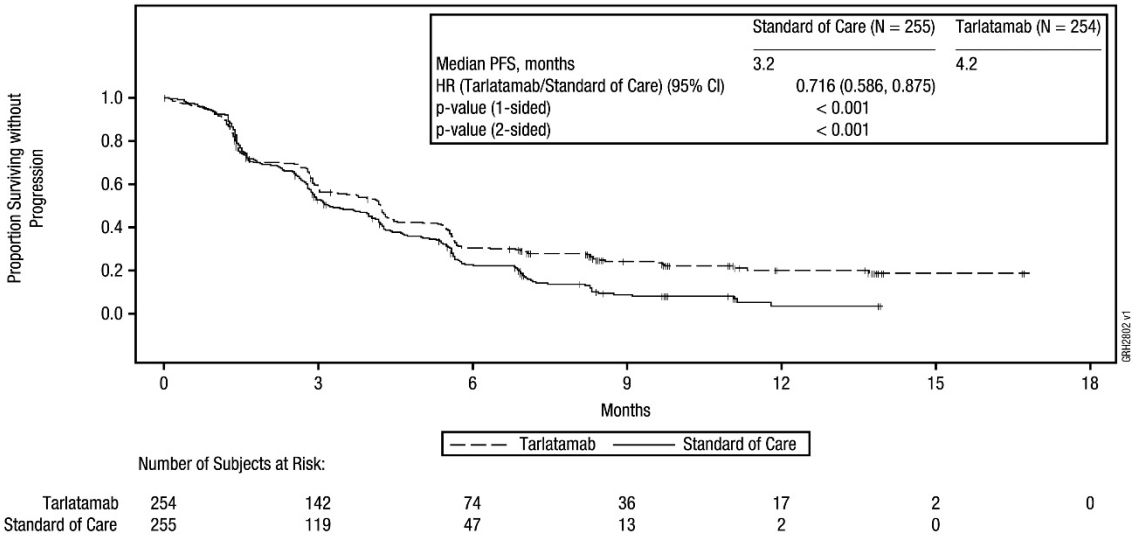
145 patients in the tarlatamab arm and 141 patients in the SOC arm had a CFI ≥ 90 days at baseline. The hazard ratio for OS was 0.65 (95% CI: 0.45, 0.93) with a median OS of 17.1 months (95% CI: 13.6, NE) and 10.6 months (95% CI: 8.7, NE) in the tarlatamab and SOC arm, respectively.

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



HR = Hazard ratio; ITT = Intent-to-treat; N = Number; OS = Overall survival

Figure 2. Kaplan-Meier plot for progression-free survival (ITT analysis set)



Number of Subjects at Risk:

Tarlatamab	254	142	74	36	17	2	0
Standard of Care	255	119	47	13	2	0	

HR = Hazard ratio; ITT = Intent-to-treat; N = Number; PFS = Progression-free survival

Patient-reported outcomes

Patient-reported outcomes were collected using EORTC QLQ-C30 and EORTC QLQ LC13. Compliance rates were comparable between groups and were above 69% throughout 18 weeks from baseline.

Tarlatamab demonstrated statistically significant and clinically meaningful improvements in dyspnoea and cough. Dyspnoea, derived from EORTC QLQ-C30 and EORTC QLQ-LC13, showed a mean difference of –9.14 (95% CI: –12.64 to –5.64; $p < 0.001$) at week 18 in favour of tarlatamab. For cough, measured by the EORTC QLQ-LC13, patients receiving tarlatamab had 2.041 times higher odds (95% CI: 1.174–3.549; $p = 0.012$) of achieving a clinically meaningful improvement compared with standard of care (SOC).

Paediatric population

The Medicines and Healthcare products Regulatory Agency has waived the obligation to submit the results of studies with IMDYLLTRA in all subsets of the paediatric population in SCLC (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

The peak serum concentration (C_{max}), trough serum concentrations (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 dosage). Approximate steady state in serum tarlatamab exposures were achieved by Day 15.

Distribution

The mean value (CV%) for volume of distribution at steady state based on individual parameters is 8.53 L (33%).

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 estimated 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.

Pharmacokinetics in special populations

No clinically meaningful differences in the clearance of tarlatamab were observed based on age, bodyweight, sex, race, mild or moderate renal impairment (eGFR $\geq$ 30 mL/min), or mild hepatic impairment (total bilirubin $\leq$ 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

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 toxicity

There are no available data from the use of tarlatamab in pregnant women. Based on its mechanism of action, tarlatamab may cause foetal harm when administered to a pregnant woman. In a murine embryo-foetal 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 foetal external, visceral, or skeletal malformations or variations.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder

L-glutamic acid

Sucrose

Polysorbate 80

Sodium hydroxide

IV Solution stabiliser (IVSS)

Citric acid monohydrate (E330)

Lysine hydrochloride

Polysorbate 80

Sodium hydroxide (for pH adjustment)

Water for injections

6.2 Incompatibilities

No known incompatibilities.

6.3 Shelf life

Unopened vial
48 months.

6.4 Special precautions for storage

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

Do not freeze.

Store the vials 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:

- **1 mg** packaging contains 1 vial of 1 mg tarlatamab and 2 vials of 7 mL IV Solution Stabiliser
- **10 mg** packaging contains 1 vial of 10 mg tarlatamab and 2 vials of 7 mL IV Solution Stabiliser

Sterile Water for Injection, (not included) should be used to reconstitute IMDYLLTRA.

The IV Solution Stabiliser is used to coat the intravenous bag prior to addition of reconstituted IMDYLLTRA to prevent adsorption of IMDYLLTRA to IV bags and IV tubing.

IMDYLLTRA should be reconstituted without the use of IV Solution Stabiliser (IVSS).

6.6 Special precautions for disposal

Aseptic preparation

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

Other instructions

IMDYLLTRA is compatible with polyolefin, PVC or ethyl vinyl acetate (EVA) infusion bags at the specified administration conditions.

IV line and catheter materials composed of polyolefin, PVC and polyurethane have been shown to be compatible with IMDYLLTRA at the specified administration conditions.

The use of Closed System Transfer Device (CSTD) is not required when preparing IMDYLLTRA and currently Amgen cannot provide guidance on, nor recommend for or against, their use.

The empty IV bag and IV tubing should be disposed of in accordance with local requirements.

Table 11. Required amount of Sterile Water for Injection (SWFI) to Reconstitute IMDYLLTRA[a]

IMDYLLTRA vial Strength (mg)	Amount of Sterile Water for Injection, needed to reconstitute IMDYLLTRA (mL)	Final Concentration (mg/mL)
1 mg	1.3 mL	0.9 mg/mL
10 mg	4.4 mL	2.4 mg/mL

[a] Vial contains overfull to ensure delivery at the stated concentration of labelled vial strength.

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

IMDYLLTRA vial

Reconstituted IMDYLLTRA

1. Transfer required amount of Sterile Water for Injection (refer to table 11) into the IMDYLLTRA vial to provide a final IMDYLLTRA 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 IMDYLLTRA vial and not directly on the lyophilized powder.
    - **IV Solution Stabiliser should not be used to reconstitute IMDYLLTRA.**
2. Gently swirl contents. **Do not shake.**
3. Inspect that the solution is clear to slightly opalescent, colourless to slightly yellow. **Do not** use if solution is cloudy or has particulates.

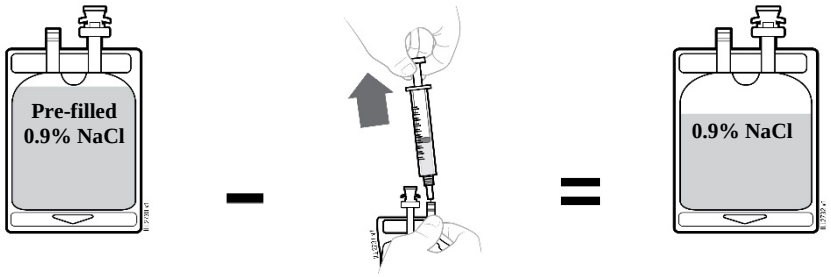
Preparation of IMDYLLTRA

Table 12. Preparation Guide for 1-hour infusion[a]

IMDYLLTRA Vial Strength (mg)	IMDYLLTRA Dose (mg)	Volume of 0.9% NaCl to withdraw from IV bag (mL)	Volume of IV Solution Stabiliser (IVSS) to add to IV bag (mL)	Volume of reconstituted IMDYLLTRA to add to IV bag (mL)
1	1	14	13	1.1
10	10	17	13	4.2

[a] the final concentrations for the different strength vials are NOT the same following reconstitution.

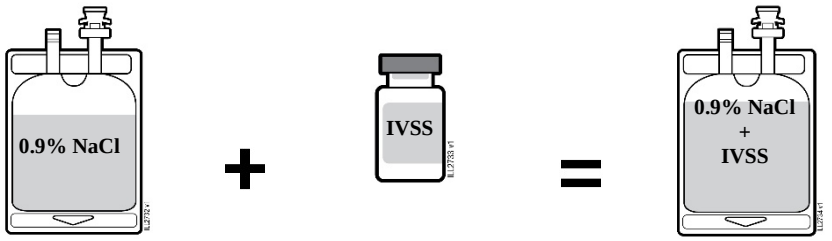
1. Withdraw 0.9% Sodium Chloride for Injection.



250 mL IV Bag

a. 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.

2. Add IV Solution Stabiliser (IVSS).



Stabilised

a. Transfer 13 mL of IVSS to the IV bag containing 0.9% Sodium Chloride for Injection.

b. Gently mix the contents of the bag to avoid foaming. **Do not shake.**

3. Add reconstituted IMDYLLTRA.

Stabilised | Reconstituted IMDYLLTRA | Completed 1-Hour Infusion

a. Transfer the required volume of reconstituted IMDYLLTRA into the stabilised IV bag containing 0.9% Sodium Chloride for Injection and IVSS. Refer to Table 11.

b. Gently mix the contents of the bag to avoid foaming. **Do not shake.**

4. Remove the air from the IV bag.

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

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

Disposal

The release of pharmaceuticals into the environment should be minimised. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

PLGB 13832/0083

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Date of latest renewal: 18 September 2025

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23/12/2025