▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at https://www.tga.gov.au/reporting-problems.

WARNING:

CYTOKINE RELEASE SYNDROME AND NEUROLOGIC TOXICITY INCLUDING IMMUNE EFFECTOR CELL-ASSOCIATED NEUROTOXICITY SYNDROME.

Cytokine release syndrome (CRS), including serious or life-threatening reactions, can occur in patients receiving Imdelltra. Initiate treatment with Imdelltra using the step-up dosing schedule to reduce the incidence and severity of CRS. Withhold Imdelltra until CRS resolves or permanently discontinue based on severity (see section 4.2.5 Management of severe adverse reactions and section 4.4 Special warnings and precautions for use).

Neurologic toxicity, including immune effector cell-associated neurotoxicity syndrome (ICANS), including serious or life-threatening reactions, can occur in patients receiving Imdelltra. Monitor patients for signs and symptoms of neurologic toxicity, including ICANS, during treatment and treat promptly. Withhold Imdelltra until ICANS resolves or permanently discontinue based on severity (see section 4.2.5 Management of severe adverse reactions and section 4.4 Special warnings and precautions for use).

AUSTRALIAN PRODUCT INFORMATION – IMDELLTRA® (TARLATAMAB)

1. NAME OF THE MEDICINE

Tarlatamab

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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

For the full list of excipients, see section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Imdelltra has **provisional approval** in Australia for the treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC) with disease progression on or after platinum-based chemotherapy.

The decision to approve this indication has been made on the basis of overall response rate and duration of response in a single arm trial. Continued approval of this indication depends on verification and description of benefit in confirmatory trials.

4.2 Dose and method of administration

4.2.1 Important safety information

- Treatment with Imdelltra should be initiated and supervised by physicians experienced in the treatment of small cell lung cancer.
- Administer Imdelltra according to the step-up dosing schedule in Table 1 to reduce the incidence and severity of cytokine release syndrome (CRS) (see section 4.2.2 Dosage (dose and interval)).
- For Cycle 1, administer recommended concomitant medications in Table 2 before and after Cycle 1 Imdelltra infusions to reduce the risk of CRS reactions (see section 4.2.2 Dosage (dose and interval)).
- Imdelltra should only be administered by a qualified healthcare professional with appropriate medical support to manage severe reactions such as CRS and neurologic toxicity including immune effector cell-associated neurotoxicity syndrome (ICANS) (see section 4.2.5 Management of severe adverse reactions and section 4.4 Special warnings and precautions for use).
- Due to the risk of CRS and neurologic toxicity, including ICANS, monitor patients from the start of the Imdelltra infusion for 16 hours on Cycle 1 Day 1 in an appropriate healthcare setting (see section 4.2.2 Dosage (dose and interval) and

section 4.4 Special warnings and precautions for use).

- Recommend that patients remain within 1-hour of an appropriate healthcare setting for a total of 24 hours from start of the infusion with Imdelltra following Cycle 1 Day 1 and Cycle 1 Day 8 doses, accompanied by a caregiver.
- Instruct patients and/or caregiver on signs and symptoms of CRS and ICANS prior to discharge (see section 4.4 Special warnings and precautions for use).
- Prior to administration of Imdelltra evaluate complete blood count, liver enzymes and bilirubin before each dose, and as clinically indicated (see section 4.4 Special warnings and precautions for use).
- Ensure patients are well hydrated prior to administration of Imdelltra.

4.2.2 Dosage (dose and interval)

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

Table 1. Recommended Dosage Schedule of Imdelltra

Dosing Schedule	Day	Dose of Imdelltra	Administration Instructions	Recommended Monitoring
Step-up Dosing Schedule Cycle 1	Day 1[a]	Step-up dose[a] 1 mg	Administer Imdelltra as a 1-hour intravenous infusion in an appropriate healthcare setting.	Monitor patients from the start of the Imdelltra infusion for 16 hours on Cycle 1 Day 1 in an appropriate healthcare setting. Recommend that patients remain within 1-hour of an appropriate healthcare setting for a total of 24 hours from start of the infusion with Imdelltra, accompanied by a caregiver.
	Day 8[a]	10 mg[a]		

Dosing Schedule	Day	Dose of Imdelltra	Administration Instructions	Recommended Monitoring
	Day 15	10 mg		Observe patients for 6-8 hours post Imdelltra infusion[b].
Cycle 2	Day 1 and 15	10 mg		Observe patients for 6-8 hours post Imdelltra infusion[b].
Cycles 3 and 4	Day 1 and 15	10 mg		Observe patients for 3-4 hours post Imdelltra infusion[b].
Cycle 5 and subsequent infusions	Day 1 and 15	10 mg		Observe patients for 2 hours post Imdelltra infusion[b].

[a] Administer recommended concomitant medications before and after Cycle 1 Imdelltra infusions as described in Table 2.
[b] Extended monitoring in a healthcare setting is not required unless the patient experiences Grade ≥ 2 CRS, ICANS or neurological toxicity during prior treatments. See Tables 4 and 5 for monitoring recommendations.
Note: see Table 3 for recommendation on restarting Imdelltra after dose delays.

Recommended concomitant medications for Imdelltra administration for days 1, 8 and 15

Administer recommended concomitant medications for Imdelltra administration as presented in Table 2 to reduce the risk of cytokine release syndrome (see section 4.4 Special warnings and precautions for use, Cytokine release syndrome).

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

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

4.2.3 Restarting Imdelltra after dosage delay

If a dose of Imdelltra is delayed, restart therapy based on the recommendations listed in Table 3 and resume the dosing schedule accordingly (see section 4.2.4 Dosage adjustment and adverse reaction management). Administer recommended concomitant

medications as indicated in section 4.2.2 Dosage (dose and interval).

Table 3. Recommendations for Restarting Therapy with Imdelltra After Dosage Delay

Last Dose Administered	Time Since the Last Dose Administered	Action[a]
1 mg Day 1	2 weeks or less (≤ 14 days)	Administer Imdelltra 10 mg, then resume with the planned dosage schedule.
	Greater than 2 weeks (> 14 days)	Administer Imdelltra step-up dose 1 mg. If tolerated, increase to 10 mg 1 week later. Then resume with the planned dosage schedule.
10 mg Day 8	3 weeks or less (≤ 21 days)	Administer Imdelltra 10 mg, then resume with the planned dosage schedule.
	Greater than 3 weeks (> 21 days)	Administer Imdelltra step-up dose 1 mg. If tolerated, increase to 10 mg 1 week later. Then resume with the planned dosage schedule.
10 mg Day 15 and every 2 weeks thereafter	4 weeks or less (≤ 28 days)	Administer Imdelltra 10 mg, then resume with the planned dosage schedule.
	Greater than 4 weeks (> 28 days)	Administer Imdelltra step-up dose 1 mg. If tolerated, increase to 10 mg 1 week later. Then resume with the planned dosage schedule.

[a] Administer required concomitant medications before and after Day 1 and Day 8 of Imdelltra infusions and monitor patients accordingly (see section 4.2.2 Dosage (dose and interval), Tables 1 and 2).

4.2.4 Dosage adjustment and adverse reaction management

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

Hepatic Impairment

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

Renal Impairment

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

4.2.5 Management of severe adverse reactions

Cytokine Release Syndrome (CRS)

Diagnose CRS based on clinical presentation (see section 4.4 Special warnings and precautions for use, Cytokine release syndrome (CRS)). Evaluate for and treat other causes of fever, hypoxia, and hypotension. If CRS is suspected, manage according to the recommendations in Table 4. Patients who experience Grade 2 or higher CRS (e.g., hypotension not responsive to fluids, or hypoxia requiring supplemental oxygen) should be monitored with continuous cardiac telemetry and pulse oximetry. For severe or life-threatening CRS, recommend anti-IL-6 therapy, for example, tocilizumab and admission in an intensive-care unit (ICU) for supportive therapy.

Perform laboratory testing to monitor for disseminated intravascular coagulation (DIC), haematology parameters, as well as pulmonary, cardiac, renal, and hepatic function.

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

CRS Grade	Defining Symptoms	Imdelltra Dosage Modification	Management[a]
Grade 1	Symptoms require symptomatic treatment only (e.g., fever ≥ 38°C without hypotension or hypoxia).	Withhold Imdelltra until event resolves, then resume Imdelltra at the next scheduled dose[b]	Administer symptomatic treatment (e.g., paracetamol/acetaminophen) for fever.
Grade 2	Symptoms require and respond to moderate intervention. Fever ≥ 38°C,	Withhold Imdelltra until event resolves, then resume Imdelltra at the next scheduled dose[b]	Recommend hospitalisation with cardiac telemetry and pulse oximetry. Administer symptomatic treatment (e.g., acetaminophen) for fever.

CRS Grade	Defining Symptoms	Imdelltra Dosage Modification	Management[a]
	Hypotension responsive to fluids not requiring vasopressors, and/or Hypoxia requiring low-flow nasal cannula or blow-by.		Administer supplemental oxygen and IV fluids when indicated. Consider dexamethasone[c] (or equivalent) 8 mg IV. Consider tocilizumab (or equivalent). When resuming treatment at the next planned dose, monitor patients 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) and/or Worsening hypoxia or respiratory distress requiring high flow nasal cannula (> 6 L/min oxygen) or face mask.	Withhold Imdelltra until the event resolves, then resume Imdelltra at the next scheduled dose[b]. For recurrent Grade 3 events, permanently discontinue Imdelltra.	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 Days 1, 8 and 15 (see Table 2). When resuming treatment at the next planned dose, monitor patients at the physician's discretion in an appropriate healthcare setting[b].

Product Information – Imdelltra

CRS Grade	Defining Symptoms	Imdelltra Dosage Modification	Management[a]
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 Imdelltra.	ICU care. Per Grade 3 treatment.

[a] CRS based on American Society for Transplantation and Cellular Therapy (ASTCT) Consensus Grading (2019).
[b] See section 4.2.3, Table 3 for recommendations on restarting Imdelltra after dose delays.
[c] Taper steroids per standard of care guidelines.

Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)

At the first sign of neurologic toxicity, including ICANS, withhold Imdelltra and consider neurology evaluation. 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, including ICANS (see section 4.4 Special warnings and precautions for use). Manage ICANS and neurologic toxicity according to the recommendations in Table 5 and consider further management per current practice guidelines.

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

ICANS Grade[a]	Defining Symptoms	Imdelltra Dosage Modifications	Management
Grade 1[a]	ICE score 7-9[b] with no depressed level of consciousness.	Withhold Imdelltra until ICANS resolves, then resume Imdelltra at the next scheduled dose[c].	Supportive care.
Grade 2[a]	ICE score 3-6[b] and/or mild somnolence awaking to voice.	Withhold Imdelltra until ICANS resolves, then resume Imdelltra at the next scheduled dose[c].	Supportive care. Dexamethasone[d] (or equivalent) 10 mg IV. Repeat every 6 hours or methylprednisolone 1 mg/kg IV every 12 hours if symptoms worsen. Monitor neurologic symptoms and consider consultation with neurologist and other specialists for further evaluation and management. Monitor patients at the physician's discretion following the next dose of Imdelltra[c].
Grade 3[a]	ICE score 0-2[b] and/or depressed level of consciousness awakening only to tactile stimulus and/or any clinical seizure focal or generalised that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention and/or focal or local oedema on neuroimaging.	Withhold Imdelltra until the ICANS resolves, then resume Imdelltra at the next scheduled dose[c]. If there is no improvement to Grade ≤ 1 within 7 days, permanently discontinue Imdelltra. For recurrent Grade 3 events, permanently discontinue.	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 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 discretion following the next dose of Imdelltra[c]

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ICANS Grade[a]	Defining Symptoms	Imdelltra Dosage Modifications	Management
Grade 4[a]	ICE score 0[b] (patient is unarousable and	Permanently discontinue Imdelltra.	ICU care.
	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.		Consider mechanical ventilation for airway protection. High-dose corticosteroids[d]. 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 Imdelltra after dose delays (Section 4.2.3).
[d] Taper steroids per standard of care guidelines.

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

Adverse Reactions	Severity[b]	Dosage Modification[a]
Cytopenias (see section 4.4 Special warnings and precautions for use).	Grade 3 or Grade 4 Neutropenia	Withhold Imdelltra until recovery to ≤ Grade 2. Consider administration of granulocyte colony stimulating factor (G-CSF). Permanently discontinue if

Product Information – Imdelltra

Adverse Reactions	Severity[b]	Dosage Modification[a]
		recovery to ≤ Grade 2 does not occur within 3 weeks.
	Recurrent Grade 4 Neutropenia	Permanently discontinue Imdelltra
	Febrile neutropenia	Withhold Imdelltra until neutropenia recovers to ≤ Grade 2 and fever resolves.
	Haemoglobin < 8 g/dL	Withhold Imdelltra until haemoglobin is ≥ 8 g/dL.
	Grade 3 or Grade 4 Decreased platelet count	Withhold Imdelltra until platelet count is ≤ Grade 2 and no evidence of bleeding. Permanently discontinue if recovery to ≤ Grade 2 does not occur within 3 weeks.
	Recurrent Grade 4 Decreased platelet count	Permanently discontinue Imdelltra.
Infections (see section 4.4 Special warnings and precautions for use).	All Grades	Withhold Imdelltra in the step-up phase in patients until infection resolves.
	Grade 3	Withhold Imdelltra during the treatment phase until infection improves to ≤ Grade 1[a].
	Grade 4	Permanently discontinue Imdelltra.
Hepatotoxicity (see section 4.4 Special warnings and precautions for	Grade 3 Increased ALT or AST or bilirubin	Withhold Imdelltra until adverse events improve to ≤ Grade 1.

Adverse Reactions	Severity[b]	Dosage Modification[a]
use).	Grade 4 Increased ALT or AST or bilirubin	Permanently discontinue Imdelltra.
	AST or ALT > 3 × ULN with total bilirubin > 2 × ULN in the absence of alternative causes	Permanently discontinue Imdelltra.
Other Adverse Reactions (see section 4.8 Adverse effects (Undesirable effects))	Grade 3 or 4	Withhold Imdelltra 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 3 for dose restarting guidance (Section 4.2.3).
[b] Severity based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 5.0.

4.2.6 Method of Administration

Reconstitution and preparation

Call 1800 803 638 if you have questions about the reconstitution and preparation of Imdelltra.

Material Compatibility Information

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

of vial adaptor CSTDs with Imdelltra.

Reconstitution of Imdelltra

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

Do not use IV Solution Stabiliser to reconstitute Imdelltra. The IV Solution Stabiliser is used to coat the intravenous bag prior to addition of reconstituted Imdelltra to prevent adsorption of Imdelltra to IV bags and IV tubing.

Table 7. Required Amount of Sterile Water for Injections to Reconstitute Imdelltra[a]

Imdelltra Vial Strength	Amount of Sterile Water for Injections needed to Reconstitute Imdelltra	Resulting Concentration
1 mg	1.3 mL	0.9 mg/mL
10 mg	4.4 mL	2.4 mg/mL

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

1. Transfer required amount of Sterile Water for Injections (refer to Table 7) into the Imdelltra vial to provide a final Imdelltra concentration of 0.9 mg/mL (1 mg vial) or 2.4 mg/mL (10 mg vial). Direct Sterile Water for Injections along the walls of the Imdelltra vial and not directly on the lyophilised powder.
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.

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

Preparation of Imdelltra infusion bag

Table 8. Preparation Guide for 1-hour Infusion

Imdelltra Vial Strength	Imdelltra Dose	Volume of 0.9% NaCl to Withdraw from IV Bag	Volume of IV Solution Stabiliser (IVSS) to Add to IV Bag	Volume of Reconstituted Imdelltra to Add to IV Bag
1 mg	1 mg	14 mL	13 mL	1.1 mL
10 mg	10 mg	17 mL	13 mL	4.2 mL

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

Withdraw 0.9% Sodium Chloride for Injection

Withdraw the required volume from a pre-filled 250 mL 0.9% Sodium Chloride bag. Refer to Table 8. Disregard any overfill in the IV bag.

Add IV Solution Stabiliser (IVSS)

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

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

Add Reconstituted Imdelltra

Transfer the required volume of reconstituted Imdelltra into the stabilised IV bag containing 0.9% Sodium Chloride for Injection and IVSS. Refer to Table 8.

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

Remove air from the IV bag

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

Prime IV tubing with 0.9% Sodium Chloride for Injection or Final Prepared Product

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

Administration

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

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

Table 9. Imdelltra Administration Information

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

- IV tubing is primed with 0.9% Sodium Chloride for Injection OR final prepared Imdelltra.
- For the infusion rate per infusion duration, refer to Table 9.
- The empty IV bag and IV tubing should be disposed of in accordance with local requirements.

Consider IV fluids for patients after infusion of Imdelltra (Day 1 and Day 8).

Product is for single use in one patient only. Discard any residue.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Cytokine Release Syndrome (CRS)

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

Administer Imdelltra following the recommended step-up dosing and administer concomitant medications before and after Cycle 1 Imdelltra infusions as described in Table 2 to reduce the risk of CRS (see section 4.2.2 Dosage (dose and interval)).

Administer Imdelltra in a healthcare facility equipped to monitor and manage CRS.

Ensure patients are euvolemic prior to initiating the infusions. Closely monitor patients for signs and symptoms of CRS during the initiation of Imdelltra treatment. At the first sign of CRS, immediately discontinue Imdelltra infusion, evaluate the patient for hospitalisation and institute supportive care based on severity. Withhold or permanently discontinue Imdelltra based on severity (see section 4.2.5 Management of severe adverse reactions). Counsel patients to seek medical attention should signs if symptoms of CRS occur.

Immune Effector Cell-associated Neurotoxicity Syndrome (ICANS)

Administration of Imdelltra has been associated with ICANS which may be serious or life-threatening. ICANS can occur up to several weeks following administration of Imdelltra. Adverse events that may be associated with ICANS include headache, encephalopathy, confusion, delirium, seizure, ataxia, neurotoxicity, and tremor.

The onset of ICANS can be concurrent with CRS, following resolution of CRS, or in the absence of CRS. Clinical signs and symptoms of ICANS may include but are not limited to confusional state, depressed level of consciousness, disorientation, somnolence, lethargy, and bradyphrenia.

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

Patients should be closely monitored for signs and symptoms of ICANS during Imdelltra treatment. At the first sign of ICANS, immediately evaluate the patient and provide supportive therapy based on severity. Withhold Imdelltra or permanently discontinue based on severity (see section 4.2.5 Management of severe adverse reactions).

Patient card and patient guide

Counsel patients to seek medical attention should signs or symptoms of CRS and/or ICANS occur. A Patient Card to inform patients of CRS and ICANS associated with Imdelltra is available. The Patient Card should be kept with the patient at all times whilst on treatment.

Cytopenias

Imdelltra can cause cytopenias including neutropenia, thrombocytopenia, and anaemia. In the pooled safety population, decreased neutrophils occurred in 12% including 6%

Grade 3 or 4 of Imdelltra-treated patients. The median time to onset for Grade 3 or 4 neutropenia was 29.5 days (range: 2 to 213). Decreased platelets occurred in 33% including 3.2% Grade 3 or 4. The median time to onset for Grade 3 or 4 decreased platelets was 50 days (range: 3 to 420). Decreased haemoglobin occurred in 58% including 5% Grade 3 or 4. Febrile neutropenia occurred in 0.5% of patients treated with Imdelltra. Monitor patients for signs and symptoms of cytopenias. Perform complete blood counts prior to treatment with Imdelltra, before each dose, and as clinically indicated. Based on the severity of cytopenias, temporarily withhold, or permanently discontinue Imdelltra (see section 4.2.5 Management of severe adverse reactions).

Infections

Imdelltra can cause serious infections, including life-threatening and fatal infections. In the pooled safety population, infections including opportunistic infections occurred in 41% of patients who received Imdelltra. Grade 3 or 4 infections occurred in 13% of patients. The most frequent infections were COVID-19 (9%, majority during the COVID-19 pandemic), urinary tract infection (10%), pneumonia (9%), respiratory tract infection (3.2%), and Candida infection (3.2%). Monitor patients for signs and symptoms of infection prior to and during treatment with Imdelltra and treat as clinically indicated. Withhold or permanently discontinue Imdelltra based on severity (see section 4.2.5 Management of severe adverse reactions).

Hepatotoxicity

Imdelltra can cause hepatotoxicity. In the pooled safety population, elevated ALT occurred in 42% with Grade 3 or 4 ALT elevation occurring in 2.1% of Imdelltra-treated patients. Elevated AST occurred in 44% of patients, with Grade 3 or 4 AST elevation occurring in 3.2%. Elevated bilirubin occurred in 15% of patients, with Grade 3 or 4 total bilirubin elevations occurring in 1.6% of patients. Liver enzyme elevation can occur with or without concurrent CRS. Monitor liver enzymes and bilirubin prior to treatment with Imdelltra, before each dose, and as clinically indicated. Withhold Imdelltra or permanently discontinue based on severity (see section 4.2.5 Management of severe adverse reactions).

Hypersensitivity

Hypersensitivity reactions have been reported in patients treated with Imdelltra including rare severe events. Clinical signs and symptoms of hypersensitivity may include but are

not limited to rash and bronchospasm. Monitor patients for signs and symptoms of hypersensitivity during treatment with Imdelltra and manage as clinically indicated.

Withhold or consider permanent discontinuation of Imdelltra based on severity (see section 4.2.4 Dosage adjustment and adverse reaction management).

Embryo-Fetal Toxicity

Based on its mechanism of action, Imdelltra may cause fetal harm when administered to a pregnant woman. Advise patients of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with Imdelltra and for 2 months after the last dose (see section 4.6 Fertility, pregnancy and lactation).

Use in the elderly

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

Paediatric use

Safety and effectiveness of Imdelltra in paediatric patients have not been established.

Effects on laboratory tests

No data available.

4.5 Interaction with other medicines and other forms of interaction

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

4.6 Fertility, pregnancy and lactation

Effects on fertility

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

Use in pregnancy

Australian Pregnancy Category: C

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

Use in lactation

No peri- and post-natal reproductive toxicity studies have been conducted with tarlatamab. It is unknown whether Imdelltra is secreted in human milk. Because many medicinal products, including antibodies, can be secreted in human milk, a risk to the newborns/infants cannot be excluded. Because of the potential for serious adverse reactions in a breastfed child, advise patients not to breastfeed during treatment with Imdelltra and for 2 months after the last dose. A decision must be made whether to discontinue breast-feeding or to discontinue Imdelltra treatment taking into account the benefit of breast-feeding for the child and the benefit of Imdelltra treatment for the woman.

4.7 Effects on ability to drive and use machines

Studies of the effects of Imdelltra on the ability to drive and use machines have not been performed. However, due to the potential for ICANS associated neurological events, following Imdelltra infusion, advise patients to refrain from driving and engaging in hazardous occupations or activities, such as operating heavy or potentially dangerous machinery, in the event of any neurologic symptoms until they resolve.

4.8 Adverse effects (Undesirable effects)

Summary of safety profile

The safety of Imdelltra was evaluated in 160 patients with extensive-stage SCLC who

received 10 mg as monotherapy. The median duration of exposure to Imdelltra was 14.14 weeks (range: 0.1 to 93.4). The most common adverse reactions were cytokine release syndrome (53.8%), pyrexia (38.8%), dysgeusia (31.3%), decreased appetite (33.8%), constipation (29.4%), fatigue (28.1%), anaemia (26.9%), and asthenia (23.8%).

Tabulated list of adverse events

Adverse reactions

Study DeLLphi-300 and Study DeLLphi-301 at 10 mg as monotherapy

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

Table 10. Adverse Reactions Reported in Imdelltra 10 mg Pooled Clinical Studies

System Organ Class	Adverse Reaction Preferred Term	Frequency	Overall Subject Incidence (treatment arm) (N = 160) n (%)
Blood and lymphatic system disorders	Anaemia	Very common	43 (26.9)
	Neutropenia	Common	14 (8.8)
Gastrointestinal disorders	Constipation	Very common	47 (29.4)
	Nausea	Very common	31 (19.4)
General disorders and administration site conditions	Pyrexia	Very common	62 (38.8)
	Asthenia	Very common	38 (23.8)
	Fatigue	Very common	45 (28.1)
Immune system disorders	Cytokine release syndrome	Very common	86 (53.8)
Investigations	Neutrophil count decreased	Common	8 (5.0)
Metabolism and nutrition disorders	Decreased appetite	Very common	54 (33.8)
	Hyponatremia	Very common	25 (15.6)
Nervous system	Dysgeusia	Very common	50 (31.3)

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

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

Description of selected adverse reactions

Cytokine Release Syndrome (CRS)

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

In patients treated with Imdelltra at 10 mg enrolled in Study DeLLphi-301 (n = 133), CRS occurred in 52.6% of patients, including Grade 1 in 31.6%, Grade 2 in 20.3% and Grade 3

in 0.8% of patients. No patients had Grade 4 or Grade 5 events. Most patients experienced CRS after the first two doses of Imdelltra with 9.8% experiencing CRS after the third dose or later. Following the Day 1 infusion, 16.5% of patients experienced ≥ Grade 2 CRS. Following the Day 8 infusion, 3.0% of patients experienced ≥ Grade 2 CRS. For those Grade 1 events that progressed to Grade 2 or greater, the median time from Grade 1 event to Grade 2 events was 22.1 hours.

Immune Effector Cell-associated Neurotoxicity Syndrome (ICANS)

In clinical trials with pooled safety data from 160 patients with SCLC enrolled in Study DeLLphi-300 and Study DeLLphi-301 receiving Imdelltra 10 mg, ICANS was reported in 9.4% of patients. The median time from the first dose of Imdelltra to the first onset of ICANS was 3 days (range: 1 to 154 days). The median time to resolution of ICANS was 33 days (range: 1 to 93 days).

Neutropenia

In clinical trials with pooled safety data for 160 patients with SCLC enrolled in Study DeLLphi-300 and Study DeLLphi-301 receiving Imdelltra 10 mg, neutropenia occurred in 14.4% of patients including Grade 3 or higher events in 6.3% of patients, and Grade 4 events in 2.5% of patients. The median time from the first dose of Imdelltra to the first onset of neutropenia was 43 days (range: 3 to 244 days). Neutropenia leading to dose interruption occurred in 0.6% patients with none leading to treatment discontinuation.

Immunogenicity

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

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

Reporting of suspected adverse effects

Reporting suspected adverse reactions after registration 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 at https://www.tga.gov.au/reporting-problems.

4.9 Overdose

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

For advice on the management of overdose contact the Poisons Information Centre on 131126.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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, 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.

Clinical trials

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

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

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

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

days for 27/69 (39.1%) subjects and ≥ 90 days for 42/69 (60.9%) subjects.

ORR and DOR were generally similar to the total population in the subgroups that had < 90 or ≥ 90 days to progression after first-line platinum therapy. Efficacy results are summarised in Table 11.

Table 11. Efficacy Results for Patients with SCLC Who Received Imdelltra 10 mg

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

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

5.2 Pharmacokinetic properties

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

Distribution

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

Metabolism

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

Excretion

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

Special populations

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

5.3 Preclinical safety data

Genotoxicity

No genotoxicity studies have been conducted with tarlatamab.

Carcinogenicity

No carcinogenicity studies have been conducted with tarlatamab.

Impairment of Fertility

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Imdelltra

Glutamic acid

Sucrose

Polysorbate 80

Sodium hydroxide

IV Solution Stabiliser (IVSS)

Citric acid monohydrate

Lysine hydrochloride

Polysorbate 80

Sodium hydroxide

Water for injections

6.2 Incompatibilities

No known incompatibilities.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

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

The information in Table 12 indicates the storage time for the prepared Imdelltra infusion bag. Store lyophilised Imdelltra and IV Solution Stabiliser vials for a maximum of 24 hours at room temperature in the original carton to protect from light.

Table 12. Maximum Storage Time

	Room Temperature 23°C to 25°C	Refrigerated 2°C to 8°C
Prepared Imdelltra Infusion Bag	8 hours*	7 days*

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

6.5 Nature and contents of container

Imdelltra consists of two packaging configurations:

- 1 mg package contains 1 vial of 1 mg Imdelltra and 2 vials of 7 mL IV Solution Stabiliser.
- 10 mg package contains 1 vial of 10 mg Imdelltra and 2 vials of 7 mL IV Solution Stabiliser.

6.6 Special precautions for disposal

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

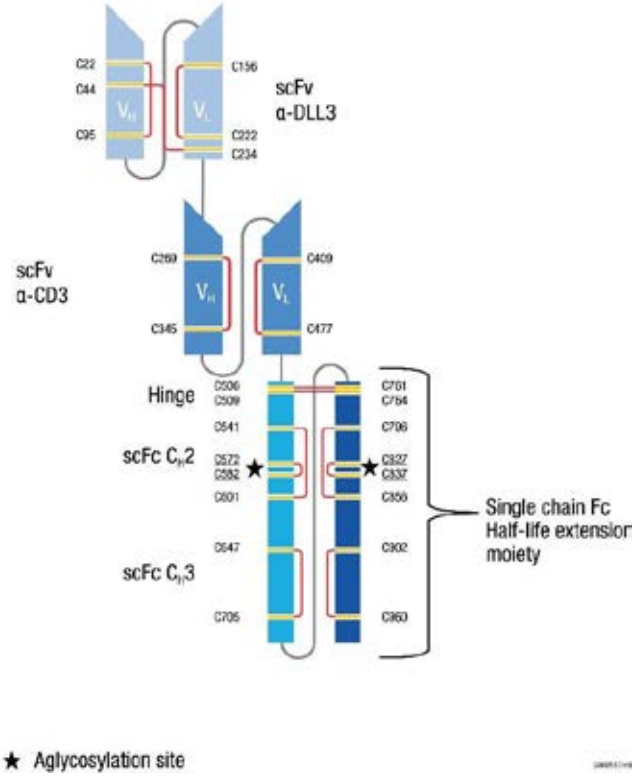
6.7 Physicochemical properties

Imdelltra is a bispecific T-cell engager molecule that selectively binds to DLL3

(expressed on tumour cells) and CD3 (expressed on T-cells). Imdelltra is produced using recombinant DNA technology in Chinese hamster ovary (CHO) cells. Imdelltra consists of 982 amino acids and has a molecular weight of approximately 105 kilodaltons.

Chemical structure

The domain structure of tarlatamab is shown in the figure below.



CAS number

2307488-83-9

7. MEDICINE SCHEDULE (POISONS STANDARD)

SCHEDULE 4 – PRESCRIPTION ONLY MEDICINE

8. SPONSOR

Amgen Australia Pty Ltd

Level 11, 10 Carrington St

Sydney NSW 2000

Ph: 1800 803 638

www.amgenmedinfo.com.au

Email: medinfo.JAPAC@amgen.com

9. DATE OF FIRST APPROVAL

Date of first inclusion in the Australian Register of Therapeutic Goods: {DD month YYYY}

10. DATE OF REVISION

Not applicable.

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information