▼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

TECVAYLI 10 mg/mL solution for injection
TECVAYLI 90 mg/mL solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

TECVAYLI 10 mg/mL solution for injection
One 3 mL vial contains 30 mg of teclistamab (10 mg/mL).

TECVAYLI 90 mg/mL solution for injection
One 1.7 mL vial contains 153 mg of teclistamab (90 mg/mL).

Teclistamab is a humanised immunoglobulin G4-proline, alanine, alanine (IgG4-PAA) bispecific antibody directed against the B cell maturation antigen (BCMA) and CD3 receptors, produced in a mammalian cell line (Chinese hamster ovary [CHO]) using recombinant DNA technology.

Excipient with known effect
Each 3 mL vial contains 1.2 mg (0.4 mg/mL) of polysorbate 20.
Each 1.7 mL vial contains 0.68 mg (0.4 mg/mL) of polysorbate 20.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection).

The solution is colourless to light yellow, with a pH of 5.2 and osmolarity of approximately 296 mOsm/L (10 mg/mL solution for injection), and approximately 357 mOsm/L (90 mg/mL solution for injection).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

TECVAYLI is indicated

- in combination with daratumumab for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least one prior therapy.

- as monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma, who have received at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody and have demonstrated disease progression on the last therapy.

4.2 Posology and method of administration

Treatment with TECVAYLI should be initiated and supervised by physicians experienced in the treatment of multiple myeloma.

TECVAYLI should be administered by a healthcare professional with adequately trained medical personnel and appropriate medical equipment to manage severe reactions, including cytokine release syndrome (CRS) (see section 4.4).

Posology

Pre-treatment medicinal products should be administered prior to each dose of TECVAYLI in the step-up dosing schedule (see below).

TECVAYLI step-up dosing schedule should not be administered in patients with active infection (see Table 4 and section 4.4).

Treatment with TECVAYLI should be initiated according to the step-up dosing schedule in Tables 1 and 2 to reduce the incidence and severity of cytokine release syndrome. Due to the risk of cytokine release syndrome, patients should be instructed to remain within proximity of a healthcare facility, and monitored for signs and symptoms daily for 48 hours after administration of all doses within the TECVAYLI step-up dosing schedule (see section 4.4).

Failure to follow the recommended doses or dosing schedule for initiation of therapy, or re-initiation of therapy after dose delays, may result in increased frequency and severity of adverse reactions related to mechanism of action, particularly cytokine release syndrome (see section 4.4).

Recommended dosing schedule for combination therapy with daratumumab

TECVAYLI dosing schedule in Table 1 is for combination therapy with daratumumab.

Table 1: TECVAYLI dosing schedule for combination therapy with daratumumab

Dosing schedule[a]	**Week/Day**	**Dose[b]**	
	Day 1	Daratumumab dosing only	
Step-up dosing schedule[c]	Day 2[d]	Step-up dose 1	0.06 mg/kg
	Day 4[e]	Step-up dose 2	0.3 mg/kg
	Day 8[f]	First treatment dose	1.5 mg/kg
Weekly dosing schedule[c]	Weeks 3 to 8[g]	Subsequent treatment doses	1.5 mg/kg
Q2W (every two weeks) dosing schedule[c]	Weeks 9 to 24[h]	Subsequent treatment doses	3 mg/kg
Q4W (every four weeks) dosing schedule[c]	Week 25 onwards[h]	Subsequent treatment doses	3 mg/kg

[a] TECVAYLI must be administered at least 3 hours after daratumumab for the first treatment dose and thereafter, TECVAYLI must be administered at least 15 minutes after daratumumab.
[b] Dose is based on actual body weight and must be administered subcutaneously.
[c] See Table 3 for recommendations on restarting TECVAYLI after dose delays.
[d] Step-up dose 1 must be administered 20 hours or more after daratumumab.
[e] Step-up dose 2 may be given between 2 to 7 days after Step-up dose 1,
[f] First treatment dose may be given between 2 to 7 days after Step-up dose 2. This is the first full treatment dose (1.5 mg/kg).
[g] Maintain a minimum of 5 days between 1.5 mg/kg treatment doses.
[h] Maintain a minimum of 12 days between 3 mg/kg treatment doses.

For dosing and administration instructions of daratumumab, see section 5.1 and please refer to the daratumumab solution for subcuteaneous injection Summary of Product Characteristics for monotherapy, except that dexamethasone (or equivalent) premedication should not be administered after the TECVAYLI step-up dosing schedule.

Recommended dosing schedule for monotherapy

The recommended dosing schedule for TECVAYLI is provided in Table 2. The recommended doses of TECVAYLI are 1.5 mg/kg by subcutaneous injection (SC) weekly, preceded by step-up doses of 0.06 mg/kg and 0.3 mg/kg. In patients who have a complete response or better for a minimum of

6 months, a reduced dosing frequency of 1.5 mg/kg SC every two weeks may be considered (see section 5.1).

Table 2: TECVAYLI dosing schedule for monotherapy

Dosing schedule	Day	Dose[a]	
All patients			
Step-up dosing schedule[b]	Day 1	Step-up dose 1	0.06 mg/kg SC single dose
	Day 3[c]	Step-up dose 2	0.3 mg/kg SC single dose
	Day 5[d]	First treatment dose	1.5 mg/kg SC single dose
Weekly dosing schedule[b]	One week after first treatment dose and weekly thereafter[e]	Subsequent treatment doses	1.5 mg/kg SC once weekly
Patients who have a complete response or better for a minimum of 6 months			
Q2W (every two weeks) dosing schedule[b]	Consider reducing the dosing frequency to 1.5 mg/kg SC every two weeks		

[a] Dose is based on actual body weight and should be administered subcutaneously.

[b] See Table 3 for recommendations on restarting TECVAYLI after dose delays.

[c] Step-up dose 2 may be given between two to seven days after Step-up dose 1.

[d] First treatment dose may be given between two to seven days after Step-up dose 2. This is the first full treatment dose (1.5 mg/kg).

[e] Maintain a minimum of five days between weekly treatment doses.

Refer to Tables 11, 12, 13 and 14 to determine the dosage based on predetermined weight ranges (see section 6.6).

Duration of treatment

Patients should be treated with TECVAYLI until disease progression or unacceptable toxicity.

Pre-treatment medicinal products

The following pre-treatment medicinal products must be administered 1 to 3 hours before each dose of the TECVAYLI step-up dosing schedule (see Tables 1 and 2) to reduce the risk of cytokine release syndrome (see sections 4.4 and 4.8).

- Corticosteroid (oral or intravenous dexamethasone 16 mg)
- Antihistamine (oral or intravenous diphenhydramine 50 mg, or equivalent)
- Antipyretics (oral or intravenous paracetamol 650 to 1 000 mg, or equivalent)

Administration of pre-treatment medicinal products may also be required prior to administration of subsequent doses of TECVAYLI for the following patients:

- Patients who repeat doses within the TECVAYLI step-up dosing schedule due to dose delays (Table 3), or
- Patients who experienced CRS following the previous dose (Table 4).

Prophylactic therapy
Prophylactic therapy for infections is outlined in section 4.4.

Restarting TECVAYLI after dose delay

If a dose of TECVAYLI is delayed, therapy should be restarted based on the recommendations listed in Table 3 and TECVAYLI resumed according to the dosing schedule (see Tables 1 and 2). Pre-treatment medicinal products should be administered as indicated in Table 3.

Table 3: Recommendations for restarting therapy with TECVAYLI after dose delay

Last dose administered	Duration of delay from the last dose administered	Action
Step-up dose 1	More than 1 week (> 7 days)	Restart TECVAYLI step-up dosing schedule at Step-up dose 1 (0.06 mg/kg)[a].
Step-up dose 2	More than 1 week to less than or equal to 4 weeks (8 days to ≤ 28 days)	Repeat Step-up dose 2 (0.3 mg/kg)[a] and continue TECVAYLI step-up dosing schedule.
	More than 4 weeks (>28 days)	Restart TECVAYLI step-up dosing schedule at Step-up dose 1 (0.06 mg/kg)[a].
Any treatment doses	More than 1 week to less than or equal to 9 weeks (8 days to ≤ 63 days)	Continue TECVAYLI at last treatmentdose and schedule.
	More than 9 weeks to less than or equal to 16 weeks (64 days to ≤ 112 days)	Restart TECVAYLI step-up dosing schedule at Step-up dose 2 (0.3 mg/kg)[a].
	More than 16 weeks (>112 days)	Restart TECVAYLI step-up dosing schedule at Step-up dose 1 (0.06 mg/kg)[a].

[a] Pre-treatment medicinal products should be administered prior to TECVAYLI dose.

Dose modifications

Treatment with TECVAYLI should be initiated according to the step-up dosing schedule in Tables 1 and 2.

Monotherapy: Dose reductions of TECVAYLI are not recommended.

Combination therapy: Dose reductions of TECVAYLI during the step-up dosing and the first 1.5 mg/kg treatment dose are not recommended. Recommendations to manage toxicities in subsequent treatment dosing are described in section 4.4.

Refer to the daratumumab solution for subcutaneous injection Summary of Product Characteristics for information about dose modifications for daratumumab.

Dose delays may be required to manage toxicities related to TECVAYLI (see section 4.4). Recommendations on restarting TECVAYLI after a dose delay are provided in Table 3.

Recommended actions after adverse reactions following administration of TECVAYLI are listed in Table 4.

Table 4: Recommended actions taken after adverse reactions following administration of TECVAYLI

Adverse reactions	Grade	Actions
Cytokine release syndrome[a] (see section 4.4)	Grade 1 • Temperature ≥38 °C[b]	• Withhold TECVAYLI until adverse reaction resolves. • See Table 5 for management of cytokine release syndrome.

	Grade 2
	• Temperature ≥38 °C[b] with either:
	  • Hypotension responsive to fluids and not requiring vasopressors, or
	  • Oxygen requirement of low-flow nasal cannula[c] or blow-by
	
	Grade 3 (Duration: less than 48 hours)
	• Temperature ≥38 °C[b] with either:
	  • Hypotension requiring one vasopressor with or without vasopressin, or
	  • Oxygen requirement of high-flow nasal cannula[c], facemask, non-rebreather mask, or Venturi mask
		• Withhold TECVAYLI until adverse reaction resolves.
		• See Table 5 for management of cytokine release syndrome.
		• Administer pre-treatment medicinal products prior to next dose of TECVAYLI.
		• Monitor patient daily for 48 hours following the next dose of TECVAYLI. Instruct patients to remain within proximity of a healthcare facility during daily monitoring.

	Grade 3 (Recurrent or duration: more than 48 hours)
	• Temperature ≥38 °C[b] with either:
	  • Hypotension requiring one vasopressor with or without vasopressin, or
	  • Oxygen requirement of high-flow nasal cannula[c], facemask, non-rebreather mask, or Venturi mask.
	
	Grade 4
	• Temperature ≥38 °C[b] with either:
	  • Hypotension requiring multiple vasopressors (excluding vasopressin), or
	  • Oxygen requirement of positive pressure (e.g., continuous positive airway pressure [CPAP], bilevel positive airway pressure [BiPAP], intubation, and mechanical ventilation).
		• Permanently discontinue therapy with TECVAYLI.
		• See Table 5 for management of cytokine release syndrome.

Immune effector cell-associated neurotoxicity syndrome (ICANS)[d] (see section 4.4)	Grade 1	• Withhold TECVAYLI until adverse reaction resolves. • See Table 6 for management of immune effector cell-associated neurotoxicity syndrome.
	Grade 2 Grade 3 (First occurrence)	• Withhold TECVAYLI until adverse reaction resolves. • See Table 6 for management of immune effector cell-associated neurotoxicity syndrome. • Monitor patient daily for 48 hours following the next dose of TECVAYLI. Instruct patients to remain within proximity of a healthcare facility during daily monitoring.
	Grade 3 (Recurrent) Grade 4	• Permanently discontinue therapy with TECVAYLI. • See Table 6 for management of immune effector cell-associated neurotoxicity syndrome.
Infections (see section 4.4)	All Grades	• Do not administer TECVAYLI step-up dosing schedule in patients with active infection. TECVAYLI step-up dosing schedule may proceed upon resolution of active infection.
	Grade 3 Grade 4	• Withhold subsequent treatment doses of TECVAYLI (i.e., doses administered after TECVAYLI step-up dosing schedule) until no evidence of an active infection.
Haematologic toxicities (see sections 4.4 and 4.8)	Absolute neutrophil count less than 0.5×10^9/L	• Withhold TECVAYLI until absolute neutrophil count is 0.5×10^9/L or higher.
	Febrile neutropenia	• Withhold TECVAYLI until absolute neutrophil count is 1.0×10^9/L or higher, and fever resolves.
	Haemoglobin less than 8 g/dL	• Withhold TECVAYLI until haemoglobin is 8 g/dL or higher.

	Monotherapy: Platelet count less than 25 000/µL Platelet count between 25 000/µL and 50 000/µL with bleeding Combination therapy: Platelet count less than 50 000/µL	Monotherapy • Withhold TECVAYLI until platelet count is 25 000/µL or higher and no evidence of bleeding. Combination therapy • Withhold TECVAYLI until platelet count is 50 000/µL or higher and no evidence of bleeding.
Other adverse reactions (see section 4.8)[e]	Grade 3 Grade 4	• Withhold TECVAYLI until adverse reaction improves to Grade 2 or better.

[a] Based on American Society for Transplantation and Cellular Therapy (ASTCT) grading for CRS (Lee et al 2019).

[b] Attributed to CRS. Fever may not always be present concurrently with hypotension or hypoxia as it may be masked by interventions such as antipyretics or anticytokine therapy (e.g., tocilizumab or corticosteroids).

[c] Low-flow nasal cannula is ≤6 L/min, and high-flow nasal cannula is >6 L/min.

[d] Based on ASTCT grading for ICANS.

[e] Based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.03.

Special populations

Paediatric population

There is no relevant use of TECVAYLI in the paediatric population for the treatment of multiple myeloma.

Elderly

No dosage adjustment is necessary (see section 5.2).

Renal impairment

No dosage adjustment is recommended for patients with mild or moderate renal impairment (see section 5.2).

Hepatic impairment

No dosage adjustment is recommended for patients with mild hepatic impairment (see section 5.2).

Method of administration

TECVAYLI is for subcutaneous injection only.

For instructions on handling 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)

Cytokine release syndrome, including life-threatening or fatal reactions, may occur in patients receiving TECVAYLI.

Clinical signs and symptoms of CRS may include but are not limited to fever, hypoxia, chills, hypotension, tachycardia, headache, and elevated liver enzymes. Potentially life-threatening complications of CRS may include cardiac dysfunction, adult respiratory distress syndrome, neurologic toxicity, renal and/or hepatic failure, and disseminated intravascular coagulation (DIC).

Treatment should be initiated with TECVAYLI according to the step-up dosing schedule to reduce risk of CRS. Pre-treatment medicinal products (corticosteroids, antihistamine and antipyretics) should be administered prior to each dose of the TECVAYLI step-up dosing schedule to reduce risk of CRS (see section 4.2).

The following patients should be instructed to remain within proximity of a healthcare facility and monitored daily for 48 hours:

- If the patient has received any dose within the TECVAYLI step-up dosing schedule (for CRS).
- If the patient has received TECVAYLI after experiencing Grade 2 or higher CRS.

Patients who experience CRS following their previous dose should be administered pre-treatment medicinal products prior to the next dose of TECVAYLI.

Patients should be counselled to seek medical attention should signs or symptoms of CRS occur. At the first sign of CRS, patients should be immediately evaluated for hospitalisation. Treatment with supportive care, tocilizumab and/or corticosteroids should be instituted, based on severity as indicated in Table 5 below. The use of myeloid growth factors, particularly granulocyte macrophage-colony stimulating factor (GM-CSF), has the potential to worsen CRS symptoms and should be avoided during CRS. Treatment with TECVAYLI should be withheld until CRS resolves as indicated in Table 4 (see section 4.2).

Management of cytokine release syndrome

CRS should be identified based on clinical presentation. Patients should be evaluated and treated for other causes of fever, hypoxia, and hypotension.

If CRS is suspected, TECVAYLI should be withheld until the adverse reaction resolves (see Table 4). CRS should be managed according to the recommendations in Table 5. Supportive care for CRS (including but not limited to anti-pyretic agents, intravenous fluid support, vasopressors, supplemental oxygen, etc.) should be administered as appropriate. Laboratory testing to monitor for disseminated intravascular coagulation (DIC), haematology parameters, as well as pulmonary, cardiac, renal, and hepatic function should be considered.

Table 5: Recommendations for management of cytokine release syndrome with tocilizumab and corticosteroids

Grade[e]	Presenting symptoms	Tocilizumab[a]	Corticosteroids[b]
Grade 1	Temperature ≥38 °C[c]	May be considered	May be considered
Grade 2	Temperature ≥38 °C[c] with either: • Hypotension responsive to fluids and not requiring vasopressors, or • Oxygen requirement of low-flow nasal cannula[d] or blow-by	Administer tocilizumab[b] 8 mg/kg intravenously over 1 hour (not to exceed 800 mg). Repeat tocilizumab every 8 hours as needed, if not responsive to intravenous fluids or increasing supplemental oxygen. Limit to a maximum of 3 doses in a 24-hour period; maximum total of 4 doses.	If no improvement within 24 hours of starting tocilizumab, administer methylprednisolone 1 mg/kg intravenously twice daily, or dexamethasone 10 mg intravenously every 6 hours. Continue corticosteroid use until the event is Grade 1 or less, then taper over 3 days.
Grade 3	Temperature ≥38 °C[c] with either: • Hypotension requiring one vasopressor with or without vasopressin, or • Oxygen requirement of high-flow nasal cannula[d], facemask, non-rebreather mask, or Venturi mask	Administer tocilizumab 8 mg/kg intravenously over 1 hour (not to exceed 800 mg). Repeat tocilizumab every 8 hours as needed, if not responsive to intravenous fluids or increasing supplemental oxygen. Limit to a maximum of 3 doses in a 24-hour period; maximum total of 4 doses.	If no improvement, administer methylprednisolone 1 mg/kg intravenously twice daily, or dexamethasone 10 mg intravenously every 6 hours. Continue corticosteroid use until the event is Grade 1 or less, then taper over 3 days.
Grade 4	Temperature ≥38 °C[c] with either: • Hypotension requiring multiple vasopressors (excluding vasopressin), or • Oxygen requirement of positive pressure (e.g., continuous positive airway pressure [CPAP], bilevel positive airway pressure [BiPAP], intubation, and mechanical ventilation)	Administer tocilizumab 8 mg/kg intravenously over 1 hour (not to exceed 800 mg). Repeat tocilizumab every 8 hours as needed if not responsive to intravenous fluids or increasing supplemental oxygen. Limit to a maximum of 3 doses in a 24-hour period; maximum total of 4 doses.	As above, or administer methylprednisolone 1 000 mg intravenously per day for 3 days, per physician discretion. If no improvement or if condition worsens, consider alternate immunosuppressants[b].

[a] Refer to tocilizumab prescribing information for details.

[b] Treat unresponsive CRS per institutional guidelines.

[c] Attributed to CRS. Fever may not always be present concurrently with hypotension or hypoxia as it may be masked by interventions such as antipyretics or anticytokine therapy (e.g., tocilizumab or corticosteroids).

[d] Low-flow nasal cannula is ≤6 L/min, and high-flow nasal cannula is >6 L/min.

[e] Based on ASTCT grading for CRS (Lee et al 2019).

Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)

Serious, life-threatening or fatal Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) occurred following treatment with TECVAYLI.

Patients should be monitored for signs or symptoms of ICANS during treatment and treated promptly.

Patients should be counselled to seek medical attention should signs or symptoms of ICANS occur. At the first sign of ICANS, patients should be immediately evaluated and treated based on severity. Patients who experience Grade 2 or higher ICANS or first occurrence of Grade 3 ICANS with the previous dose of TECVAYLI should be instructed to remain within proximity of a healthcare facility and monitored for signs and symptoms daily for 48 hours.

For ICANS, treatment with TECVAYLI should be withheld as indicated in Table 4 (see section 4.2).

Due to the potential for ICANS, patients should be advised not to drive or operate heavy machinery during the TECVAYLI step-up dosing schedule and for 48 hours after completing the TECVAYLI step-up dosing schedule and in the event of new onset of any neurological symptoms (see section 4.7).

Management of ICANS

At the first sign of ICANS, neurology evaluation should be considered. Other causes of neurologic symptoms should be ruled out. TECVAYLI should be withheld until adverse reaction resolves (see Table 4). Intensive care and supportive therapy should be provided for severe or life-threatening ICANS. General management for ICANS with or without concurrent CRS is summarised in Table 6.

Table 6: Guidelines for management of immune effector cell-associated neurotoxicity syndrome (ICANS)

<table>
<tr><th>Grade</th><th>Presenting symptoms[a]</th><th>Concurrent CRS</th><th>No Concurrent CRS</th></tr>
<tr><td rowspan="2">Grade 1</td><td rowspan="2">ICE score 7-9[b]

Or, depressed level of consciousness[c]: awakens spontaneously.</td><td>Management of CRS per Table 5.

Monitor neurologic symptoms and consider neurology consultation and evaluation, per physician discretion.</td><td>Monitor neurologic symptoms and consider neurology consultation and evaluation, per physician discretion.</td></tr>
<tr><td colspan="2">Consider non-sedating, anti-seizure medicinal products (e.g., levetiracetam) for seizure prophylaxis.</td></tr>
<tr><td rowspan="2">Grade 2</td><td rowspan="2">ICE score 3-6[b]

Or, depressed level of consciousness[c]: awakens to voice.</td><td>Administer tocilizumab per Table 5 for management of CRS.
If no improvement after starting tocilizumab, administer dexamethasone[d] 10 mg intravenously every 6 hours if not already taking other corticosteroids. Continue dexamethasone use until resolution to Grade 1 or less, then taper.</td><td>Administer dexamethasone[d] 10 mg intravenously every 6 hours.

Continue dexamethasone use until resolution to Grade 1 or less, then taper.</td></tr>
<tr><td colspan="2">Consider non-sedating, anti-seizure medicinal products (e.g., levetiracetam) for seizure prophylaxis. Consider neurology consultation and other specialists for further evaluation, as needed.</td></tr>
</table>

<table>
<tr><td rowspan="2">Grade 3</td><td rowspan="2">ICE score 0-2[b]

Or, depressed level of consciousness[c]: awakens only to tactile stimulus, or

seizures[c], either:
• any clinical seizure, focal or generalised that resolves rapidly, or
• non-convulsive seizures on electroencephalogram (EEG) that resolve with intervention, or

raised intracranial pressure: focal/local oedema on neuroimaging[c].</td><td>Administer tocilizumab per Table 5 for management of CRS.
In addition, administer dexamethasone[d] 10 mg intravenously with the first dose of tocilizumab, and repeat dose every 6 hours. Continue dexamethasone use until resolution to Grade 1 or less, then taper.</td><td>Administer dexamethasone[d] 10 mg intravenously every 6 hours.

Continue dexamethasone use until resolution to Grade 1 or less, then taper.</td></tr>
<tr><td colspan="2">Consider non-sedating, anti-seizure medicinal products (e.g., levetiracetam) for seizure prophylaxis. Consider neurology consultation and other specialists for further evaluation, as needed.</td></tr>
</table>

<table>
<tr><td rowspan="2">Grade 4</td><td>ICE score 0[b]

Or, depressed level of consciousness[c] either:
• patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse, or
• stupor or coma, or

seizures[c], either:
• life-threatening prolonged seizure (>5 minutes), or
• repetitive clinical or electrical seizures without return to baseline in between, or

motor findings[c]:
• deep focal motor weakness such as hemiparesis or paraparesis, or

raised intracranial pressure / cerebral oedema[c], with signs/symptoms such as:
• diffuse cerebral oedema on neuroimaging, or
• decerebrate or decorticate posturing, or
• cranial nerve VI palsy, or
• papilloedema, or
• cushing's triad</td><td>Administer tocilizumab per Table 5 for management of CRS.

As above, or consider administration of methylprednisolone 1 000 mg per day intravenously with first dose of tocilizumab, and continue methylprednisolone 1 000 mg per day intravenously for 2 or more days.</td><td>As above, or consider administration of methylprednisolone 1 000 mg per day intravenously for 3 days; if improves, then manage as above.</td></tr>
<tr><td colspan="2">Consider non-sedating, anti-seizure medicinal products (e.g., levetiracetam) for seizure prophylaxis. Consider neurology consultation and other specialists for further evaluation, as needed. In case of raised intracranial pressure/cerebral oedema, refer to institutional guidelines for management.</td></tr>
</table>

[a] Management is determined by the most severe event, not attributable to any other cause.

[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** (name 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] Attributable to no other cause.

[d] All references to dexamethasone administration are dexamethasone or equivalent.

Infections

Severe, life-threatening, or fatal infections have been reported in patients receiving TECVAYLI (see section 4.8). New or reactivated viral infections occurred during therapy with TECVAYLI.

Patients should be monitored for signs and symptoms of infection prior to and during treatment with TECVAYLI and treated appropriately. Infection precautions (including vaccinations), and antimicrobials (e.g., prevention of pneumocystis jirovecii pneumonia), including antibiotic or antiviral

(e.g., prevention of herpes zoster reactivation) prophylaxis, should be administered according to local institutional guidelines. The rate of infections is higher during the initial months of therapy and decreases over time with TECVAYLI.

TECVAYLI step-up dosing schedule should not be administered in patients with active infection. For subsequent doses, TECVAYLI should be withheld as indicated in Table 4 (see section 4.2).

Progressive Multifocal Leukoencephalopathy (PML), which can be fatal, has also been reported in patients receiving TECVAYLI. Patients should be monitored for any new onset of or changes in pre-existing neurological signs or symptoms. If PML is suspected, treatment with TECVAYLI should be withheld and appropriate diagnostic testing initiated. If PML is confirmed, TECVAYLI must be discontinued.

Hepatitis B virus reactivation

Hepatitis B virus reactivation can occur in patients treated with medicinal products directed against B cells, and in some cases, may result in fulminant hepatitis, hepatic failure, and death.

Patients with evidence of positive HBV serology should be monitored for clinical and laboratory signs of HBV reactivation while receiving TECVAYLI, and for at least six months following the end of TECVAYLI treatment.

In patients who develop reactivation of HBV while on TECVAYLI, treatment with TECVAYLI should be withheld as indicated in Table 4 and manage per local institutional guidelines (see section 4.2).

Hypogammaglobulinaemia

Hypogammaglobulinaemia has been reported in patients receiving TECVAYLI (see section 4.8).

Immunoglobulin levels should be monitored during treatment with TECVAYLI. Intravenous or subcutaneous immunoglobulin therapy should be used to maintain the serum IgG levels ≥400 mg/dL. Infection precautions, and antimicrobials, including antibiotic or antiviral prophylaxis, should be used according to local institutional guidelines.

Vaccines

Immune response to vaccines may be reduced when taking TECVAYLI.

The safety of immunisation with live viral vaccines during or following TECVAYLI treatment has not been studied. Vaccination with live virus vaccines is not recommended for at least 4 weeks prior to the start of treatment, during treatment and at least 4 weeks after treatment.

Neutropenia

Neutropenia and febrile neutropenia have been reported in patients who received TECVAYLI (see section 4.8).

Complete blood cell counts should be monitored at baseline and periodically during treatment. Supportive care should be provided per local institutional guidelines.

Patients with neutropenia should be monitored for signs of infection.

Treatment with TECVAYLI should be withheld as indicated in Table 4 (see section 4.2).

Tumour flare

Tumour flare has been reported in patients receiving TECVAYLI (see section 4.8). Manifestations included localised pain and symptoms of nerve and spinal compression due to transient tumour enlargement. Tumour flare does not imply treatment failure or tumour progression. Monitoring and evaluation of tumour flare is recommended in patients treated with TECVAYLI and should be managed as clinically indicated.

Excipients

Sodium
This medicinal product contains less than 1 mmol (23 mg) sodium per dose, that is to say essentially 'sodium-free'.
Polysorbate
This medicinal product contains 0.4 mg of polysorbate 20 in each mL, which is equivalent to 1.2 mg per 3 mL vial and 0.68 mg per 1.7 mL vial. Polysorbates may cause hypersensitivity reactions.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed with TECVAYLI.

The initial release of cytokines associated with the start of TECVAYLI treatment could suppress CYP450 enzymes. The highest risk of interaction is expected to be from initiation of TECVAYLI step-up schedule up to 7 days after the first treatment dose or during a CRS event. During this time period, toxicity or medicinal product concentrations (e.g., cyclosporine) should be monitored in patients who are receiving concomitant CYP450 substrates with a narrow therapeutic index. The dose of the concomitant medicinal product should be adjusted as needed.

4.6 Fertility, pregnancy and lactation

Women of child-bearing potential/Contraception in males and females

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

Women of child-bearing potential should use effective contraception during treatment and for five months after the final dose of TECVAYLI. In clinical studies, male patients with a female partner of child-bearing potential used effective contraception during treatment and for three months after the last dose of teclistamab.

Pregnancy

There are no available data on the use of teclistamab in pregnant women or animal data to assess the risk of teclistamab in pregnancy. Human IgG is known to cross the placenta after the first trimester of pregnancy. Therefore, teclistamab, a humanised IgG4-based antibody, has the potential to be transmitted from the mother to the developing foetus. TECVAYLI is not recommended for women who are pregnant. TECVAYLI is associated with hypogammaglobulinaemia, therefore, assessment of immunoglobulin levels in newborns of mothers treated with TECVAYLI should be considered.

Breast-feeding

It is not known whether teclistamab is excreted in human or animal milk, affects breast-fed infants or affects milk production. Because of the potential for serious adverse reactions in breast-fed infants from TECVAYLI, patients should be advised not to breast-feed during treatment with TECVAYLI and for at least five months after the last dose.

Fertility

There are no data on the effect of teclistamab on fertility. Effects of teclistamab on male and female fertility have not been evaluated in animal studies.

4.7 Effects on ability to drive and use machines

TECVAYLI has major influence on the ability to drive and use machines.

Due to the potential for ICANS, patients receiving TECVAYLI are at risk of depressed level of consciousness (see section 4.8). Patients should be instructed to avoid driving and operating heavy or potentially dangerous machinery during and for 48 hours after completion of TECVAYLI step-up dosing schedule and in the event of new onset of any neurological symptoms (Tables 1 and 2) (see section 4.2 and section 4.4).

4.8 Undesirable effects

Summary of safety profile

The most frequent adverse reactions of any grade in patients were hypogammaglobulinaemia, neutropenia, cytokine release syndrome, upper respiratory tract infection, musculoskeletal pain, diarrhoea, anaemia, cough, fatigue, injection site reaction, thrombocytopenia, pneumonia, COVID-19, lymphopenia, pyrexia, pain, nausea, headache and hypokalaemia.

Serious adverse reactions were reported in 65% of patients who received TECVAYLI, including pneumonia (22%), COVID-19 (14%), cytokine release syndrome (11%), upper respiratory tract infection (7%), sepsis (6%), pyrexia (3.5%), febrile neutropenia (3.1%), diarrhoea (2.3%) and musculoskeletal pain (2.3%).

Tabulated list of adverse reactions

The adverse reaction frequencies are based on all-cause adverse event frequencies, from patients with multiple myeloma exposed to teclistamab, when after thorough assessment, a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility.

The safety data of TECVAYLI was evaluated in 739 adult patients with relapsed or refractory multiple myeloma including 165 patients from MajesTEC-1 and 291 patients from MajesTEC-9 who received subcutaneous (SC) TECVAYLI as monotherapy, with a median duration of treatment of 9 (Range 0.20 to 41) months and 13 (Range 0.10 to 28) months respectively and 283 patients from MajesTEC-3 who received SC TECVAYLI in combination with SC daratumumab with a median duration of treatment of 32 (Range 0.03 to 43) months.

Table 7 summarises adverse reactions reported in patients in MajesTEC-1, MajesTEC-9 and MajesTEC-3 studies and postmarketing.

Adverse reactions are listed in Table 7 by system organ class and by frequency. Frequency categories are defined as follows: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1 000 to <1/100); rare (≥1/10 000 to <1/1 000); very rare (<1/10 000) and not known (frequency cannot be estimated from the available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 7: Adverse reactions in multiple myeloma patients treated with TECVAYLI in clinical trials and postmarketing.

System Organ Class	Adverse Reaction	Frequency (all grades)	N=739	
			Any Grade (%)	Grade 3 or 4 (%)
Infections and infestations	Upper respiratory tract infection[1]	Very common	60	9
	Pneumonia[2]	Very common	34	24
	COVID-19[3]	Very common	31	13
	Urinary tract infection[4]	Very common	15	4.1
	Sepsis[5]	Common	9	6
	Cellulitis	Common	2	1.1
	Progressive multifocal leukoencephalopathy	Uncommon	0.1	0.1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Tumour flare*	Not known		
Blood and lymphatic system disorders	Neutropenia	Very common	71	65
	Anaemia[6]	Very common	44	23
	Thrombocytopenia	Very common	34	17
	Lymphopenia	Very common	26	24
	Leukopenia	Very common	19	10
	Febrile neutropenia	Common	4.9	4.6
Immune system disorders	Hypogammaglobulinaemia[7]	Very common	76	3.8
	Cytokine release syndrome	Very common	65	0.4
Metabolism and nutrition disorders	Hypokalaemia	Very common	20	7
	Decreased appetite	Very common	14	0.7
	Hypophosphataemia	Common	9	2.4
	Hyponatraemia	Common	7	2
	Hyperkalaemia	Common	3.5	0.8
	Hyperamylasaemia	Common	3.2	0.9
Nervous system disorders	Headache	Very common	21	0.9
	Neuropathy peripheral[8]	Very common	15	0.4
	Encephalopathy[9]	Common	6	0.5
	Immune effector cell-associated neurotoxicity syndrome	Common	2.7	0.3
Vascular disorders	Haemorrhage[10]	Very common	10	1.8
	Hypertension[11]	Very common	10	4.9
	Hypotension	Common	7	1.1
Respiratory, thoracic and mediastinal disorders	Cough[12]	Very common	40	0.5
	Dyspnoea[13]	Very common	11	2.4
	Hypoxia	Common	3.9	1.8

Gastrointestinal disorders	Diarrhoea[14]	Very common	45	4.2
	Nausea	Very common	22	0.4
	Constipation	Very common	16	0.1
	Vomiting	Very common	16	0.5
	Abdominal pain[15]	Very common	12	0.5
Musculoskeletal and connective tissue disorders	Musculoskeletal pain[16]	Very common	45	3.4
	Muscle spasms	Common	6	0
General disorders and administration site conditions	Injection site reaction[17]	Very common	37	0.1
	Fatigue[18]	Very common	37	3.2
	Pyrexia	Very common	25	0.7
	Pain[19]	Very common	24	0.9
	Oedema[20]	Very common	12	0.3
Investigations	Transaminase elevation[21]	Very common	16	2.8
	Weight decreased	Very common	13	2
	Gamma-glutamyltransferase increased	Common	10	2.3
	Lipase increased	Common	8	1.1

Note: Adverse events are graded according to the NCI-CTCAE Version 5.0, with the exception of ICANS and CRS, which were graded by ASTCT consensus grading system (Lee et al 2019).

[1] Upper respiratory tract infection includes Acute sinusitis, Adenoviral upper respiratory infection, Bacterial rhinitis, Bronchiolitis, Bronchitis, Bronchitis bacterial, Bronchitis chronic, Bronchitis haemophilus, Bronchitis viral, Chronic sinusitis, Herpes simplex bronchitis, Nasopharyngitis, Pharyngitis, Pharyngitis streptococcal, Respiratory syncytial virus infection, Respiratory tract infection, Respiratory tract infection bacterial, Respiratory tract infection fungal, Respiratory tract infection viral, Rhinitis, Rhinovirus infection, Sinobronchitis, Sinusitis, Sinusitis bacterial, Tracheitis, Tracheobronchitis, Upper respiratory fungal infection, Upper respiratory tract infection, Upper respiratory tract infection bacterial, Viral rhinitis, Viral sinusitis and Viral upper respiratory tract infection.

[2] Pneumonia includes Atypical pneumonia, Candida pneumonia, Coronavirus pneumonia, Enterobacter pneumonia, Lower respiratory tract infection, Lower respiratory tract infection bacterial, Lower respiratory tract infection viral, Metapneumovirus pneumonia, Pneumocystis jirovecii pneumonia, Pneumonia, Pneumonia adenoviral, Pneumonia bacterial, Pneumonia chlamydial, Pneumonia cryptococcal, Pneumonia cytomegaloviral, Pneumonia escherichia, Pneumonia fungal, Pneumonia haemophilus, Pneumonia influenzal, Pneumonia klebsiella, Pneumonia legionella, Pneumonia moraxella, Pneumonia mycoplasmal, Pneumonia parainfluenzae viral, Pneumonia pneumococcal, Pneumonia pseudomonal, Pneumonia respiratory syncytial viral, Pneumonia staphylococcal, Pneumonia streptococcal, Pneumonia viral and Stenotrophomonas maltophilia pneumonia.

[3] COVID-19 includes COVID-19 and COVID-19 pneumonia.

[4] Urinary tract infection includes Cystitis, Cystitis escherichia, Cystitis haemorrhagic, Cystitis klebsiella, Escherichia urinary tract infection, Genitourinary tract infection, Klebsiella urinary tract infection, Pyelonephritis, Pyelonephritis acute, Pyuria, Urinary tract candidiasis, Urinary tract infection, Urinary tract infection bacterial, Urinary tract infection enterococcal, Urinary tract infection fungal and Urinary tract infection staphylococcal.

[5] Sepsis includes Abdominal sepsis, Acinetobacter bacteraemia, Bacillus bacteraemia, Bacteraemia, Bacterial sepsis, Campylobacter bacteraemia, Campylobacter sepsis, Citrobacter bacteraemia, Corynebacterium bacteraemia, Device related bacteraemia, Enterococcal bacteraemia, Enterococcal sepsis, Escherichia bacteraemia, Escherichia sepsis, Haemophilus sepsis, Klebsiella sepsis, Meningococcal sepsis, Neutropenic sepsis, Pseudomonal bacteraemia, Pseudomonal sepsis, Pulmonary sepsis, Sepsis, Septic shock, Staphylococcal bacteraemia, Staphylococcal sepsis, Streptococcal sepsis and Urosepsis.

[6] Anaemia includes Anaemia, Iron deficiency anaemia, Leukoerythroblastic anaemia and Microcytic anaemia

[7] Hypogammaglobulinaemia includes patients with adverse events of hypogammaglobulinaemia, hyperglobulinaemia, immunoglobulins decreased; and/or patients with laboratory IgG levels below 400 mg/dL following treatment with TECVAYLI.

[8] Neuropathy peripheral includes Dysaesthesia, Hypoaesthesia, Hypoaesthesia oral, Neuralgia, Neuropathy peripheral, Paraesthesia, Paraesthesia oral, Peripheral motor neuropathy, Peripheral sensory neuropathy and Sciatica.

[9] Encephalopathy includes Amnesia, Brain fog, Cognitive disorder, Confusional state, Depressed level of consciousness, Lethargy, Memory impairment and Somnolence.

[10] Haemorrhage includes Anal haemorrhage, Conjunctival haemorrhage, Epistaxis, Eye haemorrhage, Eyelid bleeding, Eyelid haematoma, Gastrointestinal haemorrhage, Gingival bleeding, Haematochezia, Haematoma, Haematuria, Haemoperitoneum, Haemoptysis, Haemorrhoidal haemorrhage, Haemorrhoids, Hepatic haemorrhage, Lower gastrointestinal haemorrhage, Melaena, Mouth haemorrhage, Post procedural haemorrhage, Postmenopausal haemorrhage, Pulmonary alveolar haemorrhage, Rectal haemorrhage, Subdural haematoma, Upper gastrointestinal haemorrhage and Vitreous haemorrhage.

[11] Hypertension includes Blood pressure increased, Essential hypertension, Hypertension, Hypertensive crisis, Mean arterial pressure increased and Systolic hypertension.

[12] Cough includes Allergic cough, Cough, Productive cough and Upper-airway cough syndrome.

[13] Dyspnoea includes Acute respiratory failure, Dyspnoea, Dyspnoea exertional and Respiratory failure.

[14] Diarrhoea includes Bacterial diarrhoea, Diarrhoea and Viral diarrhoea.

[15] Abdominal pain includes Abdominal discomfort, Abdominal pain, Abdominal pain lower, Abdominal pain upper, Epigastric discomfort and Gastrointestinal pain.

[16] Musculoskeletal pain includes Arthralgia, Back pain, Bone pain, Musculoskeletal chest pain, Musculoskeletal pain, Myalgia, Neck pain, Pain in extremity and Sacral pain.

[17] Injection site reaction includes Administration site pruritus, Administration site reaction, Application site erythema, Injection site bruising, Injection site cellulitis, Injection site discolouration, Injection site discomfort, Injection site eczema, Injection site erythema, Injection site haematoma, Injection site hyperaesthesia, Injection site induration, Injection site inflammation, Injection site irritation, Injection site oedema, Injection site pain, Injection site paraesthesia, Injection site pruritus, Injection site rash, Injection site reaction, Injection site swelling, Injection site vesicles and Injection site warmth.

[18] Fatigue includes Asthenia, Fatigue and Malaise.

[19] Pain includes Axillary pain, Breast pain, Cancer pain, Chest pain, Ear pain, Eye pain, Facial pain, Flank pain, Gingival pain, Groin pain, Laryngeal pain, Non-cardiac chest pain, Oesophageal pain, Oral pain, Oropharyngeal pain, Pain, Pain in jaw, Pain of skin, Pelvic pain, Perineal pain, Periorbital pain, Sinus pain, Spinal pain, Testicular pain, Toothache and Tumour pain.

[20] Oedema includes Eyelid oedema, Face oedema, Localised oedema, oedema, oedema peripheral, Periorbital oedema, Peripheral swelling, Skin oedema, Swelling, Swelling face and Testicular swelling.

[21] Transaminase elevation includes Alanine aminotransferase increased, Aspartate aminotransferase, Aspartate aminotransferase increased, Hypertransaminasaemia and Transaminase increased.

[*] Based on post-marketing experience.

Description of selected adverse reactions

Cytokine release syndrome

In clinical trials (monotherapy and combination therapy; N=739) , CRS was reported in 65% of patients following treatment with TECVAYLI. Twenty-seven percent of patients experienced more than one CRS event. Most patients experienced CRS during the initial step-up dosing schedule (Step-up Dose 1 (37%), Step-up Dose 2 (33%), or the initial treatment dose (21%)). CRS events were Grade 1 (47%) and Grade 2 (17%) or Grade 3 (0.4%). The median time to onset of CRS was 2 (Range: 1 to 9) days after the most recent dose, and the median duration of CRS was 2 (Range: 1 to 22) days.

The most frequent signs and symptoms associated with CRS were fever (65%), hypotension (13%), hypoxia (8%), chills (6%) and headache (4%).

In clinical trials , tocilizumab, corticosteroids and tocilizumab in combination with corticosteroids were used to treat CRS in 33%, 6% and 3% of CRS events, respectively.

ICANS

In clinical trials (monotherapy and combination therapy; N=739), ICANS was reported in 2.7% of patients receiving TECVAYLI at the recommended dose. Grade 3 or Grade 4 ICANS occurred in 0.2% of patients. The most frequent clinical manifestations of ICANS were confusional state (1.2%) and dysgraphia (0.8%). The onset of ICANS can be concurrent with CRS, following resolution of CRS, or in the absence of CRS. The observed time to onset of ICANS ranged from 1 to 11 days after the most recent dose.

Infections

In clinical trials (monotherapy and combination therapy; N=739), in patients who received TECVAYLI at the recommended dose, serious infections occurred in 46% of patients, Grade 3 or Grade 4 infections in 49% of patients and fatal infections in 7%.

Elderly

In monotherapy clinical trials (MajesTEC-1 and MajesTEC-9), 186 patients were less than 65 years of age, 165 patients were 65 to less than 75 years of age, and 105 patients were 75 years of age or older. Serious adverse events occurred in 65% of patients less than 65 years of age, compared with 63% in those aged 65 to less than 75 years of age and 52% in those 75 years of age or older.

In the combination therapy clinical trial (MajesTEC-3), 141 patients were less than 65 years of age, 112 patients were 65 to less than 75 years of age, and 30 patients were 75 years of age or older. Serious adverse events occurred in 63% of patients less than 65 years of age, compared with 77% in those aged 65 to less than 75 years of age and 83% in those 75 years of age or older.

In monotherapy and combination therapy clinical trials (MajesTEC-1, MajesTEC-9 and MajesTEC-3), infections (Grade 3 or 4) occurred in 42% of patients under 65 years of age, compared with 47% in those aged 65 to less than 75 years of age, and 38% in those 75 years of age or older. Fatal infections occurred in 7% of patients under 65 years of age, compared with 6% in those aged 65 to less than 75 years of age, and 8% in those 75 years of age or older.

Reporting of suspected adverse reactions

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

Ireland
HPRA Pharmacovigilance
Website: www.hpra.ie

4.9 Overdose

Symptoms and signs

The maximum tolerated dose of teclistamab has not been determined. In clinical studies, doses of up to 6 mg/kg have been administered.

Treatment

In the event of an overdose, the patient should be monitored for any signs or symptoms of adverse reactions, and appropriate symptomatic treatment should be instituted immediately.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other monoclonal antibodies and antibody drug conjugates, ATC code: L01FX24

Mechanism of action

Teclistamab is a full-size, IgG4-PAA bispecific antibody that targets the CD3 receptor expressed on the surface of T cells and B cell maturation antigen (BCMA), which is expressed on the surface of malignant multiple myeloma B-lineage cells, as well as late-stage B cells and plasma cells. With its dual binding sites, teclistamab is able to draw $CD3^+$ T cells in close proximity to $BCMA^+$ cells, resulting in T cell activation and subsequent lysis and death of $BCMA^+$ cells, which is mediated by secreted perforin and various granzymes stored in the secretory vesicles of cytotoxic T cells. This effect occurs without regard to T cell receptor specificity or reliance on major histocompatibility complex (MHC) Class 1 molecules on the surface of antigen presenting cells.

Pharmacodynamic effects

Within the first month of treatment, activation of T-cells, redistribution of T-cells, reduction of B-cells and induction of serum cytokines were observed.

Within one month of treatment with teclistamab, the majority of responders had reduction in soluble BCMA, and a greater reduction in soluble BCMA was observed in subjects with deeper responses to teclistamab.

Immunogenicity

Anti-drug antibodies (ADA) were very rarely detected. No evidence of ADA impact on pharmacokinetics, efficacy or safety was observed.

Clinical efficacy

Combination therapy with daratumumab- MajesTEC-3

The efficacy of TECVAYLI in combination with daratumumab (Tec-Dara) versus the control arm of either daratumumab, pomalidomide and dexamethasone (DPd) or daratumumab, bortezomib and dexamethasone (DVd) in patients with relapsed or refractory multiple myeloma, was evaluated in a randomised, open-label, multi-centre study (MajesTEC-3). The study included patients who had previously received one to three prior therapies including a proteasome inhibitor (PI) and lenalidomide. Patients who had received only one prior therapy must have been refractory to lenalidomide. The study excluded patients who had disease refractory to a prior anti-CD38 monoclonal antibody therapy, or who had received any prior BCMA-directed therapy and patients with central nervous system/meningeal involvement by multiple myeloma or other severe neurologic conditions. Patients with low cardiac ejection fraction or patients with rarer forms of plasma cell neoplasms, such as plasma cell leukaemia, primary systemic light-chain amyloidosis, Waldenstrom macroglobulinaemia, or POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, skin changes) syndrome were also excluded.

Patients received TECVAYLI administered subcutaneously consisting of initial step-up doses of 0.06 mg/kg and 0.3 mg/kg, followed by a treatment dose schedule of 1.5 mg/kg weekly through Week 8, then 3 mg/kg once every two weeks through Week 24, and then 3 mg/kg once every four weeks thereafter until disease progression or unacceptable toxicity. Daratumumab was administered subcutaneously at a dose of 1800 mg weekly in Week 1 to Week 8, and then 1800 mg once every two weeks through Week 24, and then once every four weeks thereafter until disease progression or unacceptable toxicity (see section 4.2).

A total of 587 patients were randomised: 291 to the Tec-Dara arm and 296 to the control arm (269 to DPd and 27 to DVd). Randomisation was stratified by investigator's choice of DPd or DVd, stage of disease at screening per International Staging System (ISS) (I vs II vs III), prior anti-CD38 monoclonal antibody exposure (yes vs no), and number of prior lines of therapy (1 vs 2 or 3). The baseline disease characteristics were similar between the Tec-Dara arm and the control arm. The median age was 64 (range: 25 to 88) years with 10% aged ≥75 years; 55% were male, 65% were White, 6% were Black or African American, and 22% were Asian. The ISS was 62.5% in Stage I, 29.5% in Stage II, and 8.0% in Stage III. High-risk cytogenetics (presence of del(17p). t(4;14) or t(14; 16)) were present in 35.9% of patients. Additionally, 14% of patients had soft tissue plasmacytomas.

The median number of prior lines of therapy was 2 (range: 1 to 3), with 37.8% of patients who received one prior line of the therapy. All patients received prior lenalidomide and 99.8% received a prior proteasome inhibitor; 83.6% were refractory to lenalidomide. Additionally, 5.3% of patients received a prior anti-CD38 monoclonal antibody.

MajesTEC-3 demonstrated a statistically significant improvement in the Tec-Dara arm compared with the control arm in Progression-Free Survival (PFS) and overall survival (OS). Efficacy results were determined by the Independent Review Committee (IRC) assessment using International Myeloma Working Group (IMWG) 2016 criteria (see Table 8 and Figures 1 and 2).

Table 8: Efficacy results for MajesTEC-3

	Tec-Dara Arm (N=291)	**Control Arm (N=296)**
Progression-free survival (PFS)[a]		
Number of events, n (%)	44 (15.1)	187 (63.2)
Median, months (95% CI)	NR (NE, NE)	18.10 (14.6, 22.8)
Hazard ratio (95% CI)[b] ;p-value[c]	0.17 (0.12, 0.23); <0.0001	
24-month PFS rate, % (95% CI)	85.2 (80.4, 88.9)	42.2 (36.3, 48.0)
36-month PFS rate, % (95% CI)	83.4 (78.2, 87.4)	29.7 (23.6, 36.0)
Complete response or better (sCR+CR)[a], n (%)	238 (81.8)	95 (32.1)
95% CI (%)	(76.9, 86.0)	(26.8, 37.7)
Odds ratio (95% CI)[d]; p-value[e]	9.56 (6.47, 14.14); <0.0001	
Overall response (sCR+CR+VGPR+PR)[a], n (%)	259 (89.0)	223 (75.3)
95% CI (%)	(84.8, 92.4)	(70.0, 80.1)
Odds ratio (95% CI)[d]; p-value[e]	2.65 (1.68, 4.18); <0.0001	

MRD negativity[f,g], n/N (%)	153/262 (58.4)	46/269 (17.1)
95% CI (%)	(52.2, 64.4)	(12.8, 22.1)
Odds ratio (95% CI)[d]; p-value[h]	6.78 (4.53, 10.15); <0.0001	
Overall survival (OS)[a]		
Number of events, n (%)	46 (15.8)	98 (33.1)
Median, months (95% CI)	NR (NE, NE)	NR (41.40, NE)
Hazard ratio (95% CI)[b]; p-value[c]	0.46 (0.32, 0.65); <0.0001	
24-month survival rate, % (95% CI)	86.5 (81.9, 90.0)	76.4 (71.1, 80.9)
36-month survival rate, % (95% CI)	83.3 (78.3, 87.2)	65.0 (58.8, 70.5)

CI=confidence interval; NE=not estimable; NR=not reached; MRD = minimal residual disease; Control arm= DPd or DVd
Median duration of follow-up = 34.5 months
[a] Based on intent-to-treat analysis set
[b] Stratified Cox proportional hazard model. For all stratified analyses, stratification was based on ISS staging (I vs. II or III) and number of prior lines (1 vs. 2 or 3), as randomised
[c] Stratified log-rank test
[d] Mantel-Haenszel estimate of the common odds ratio for stratified tables is used
[e] Cochran Mantel-Haenszel Chi-Squared test
[f] Based on MRD next-generation sequencing (NGS) primary analysis set, defined as all randomised patients in the study except for those recruited in China.
[g] Based on a threshold of 10^{-5} using a next generation sequencing assay (clonoSEQ).
[h] Fisher's exact test

In MajesTEC-3, in patients who had received a prior anti-CD38 monoclonal antibody (n=15), the ORR was 93.3% (95% CI: 68.1, 99.8).

In responders, the median time to response was 1.2 months (range: 0.9 to 25.0 months) in the Tec-Dara arm and 1.2 months (range: 0.7 to 6.3 months) in the control arm.

Figure 1: Kaplan-Meier Curve of PFS in MajesTEC-3

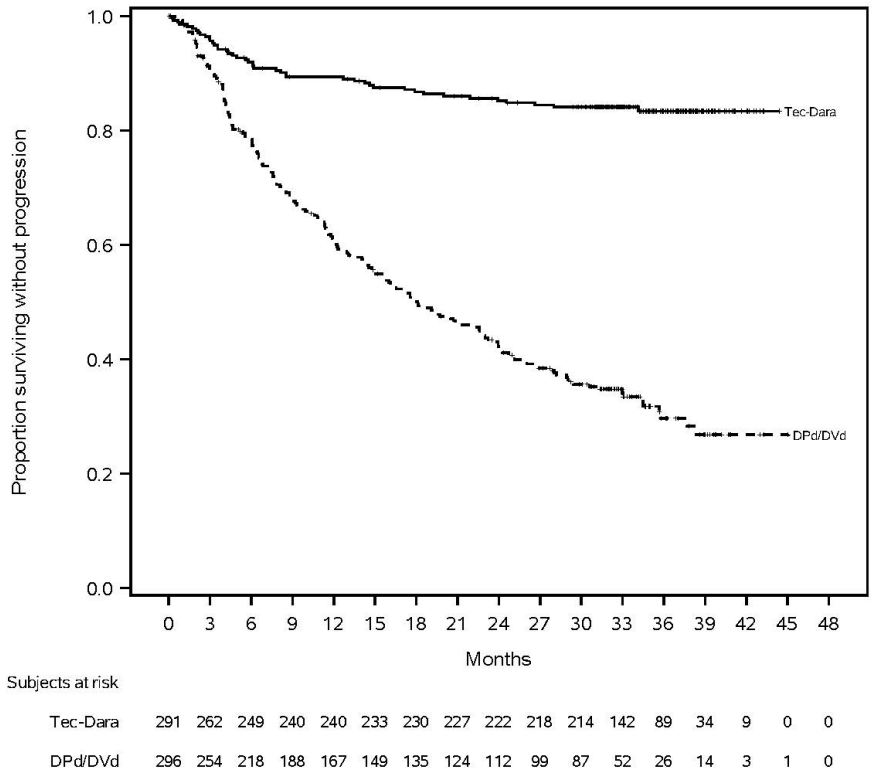
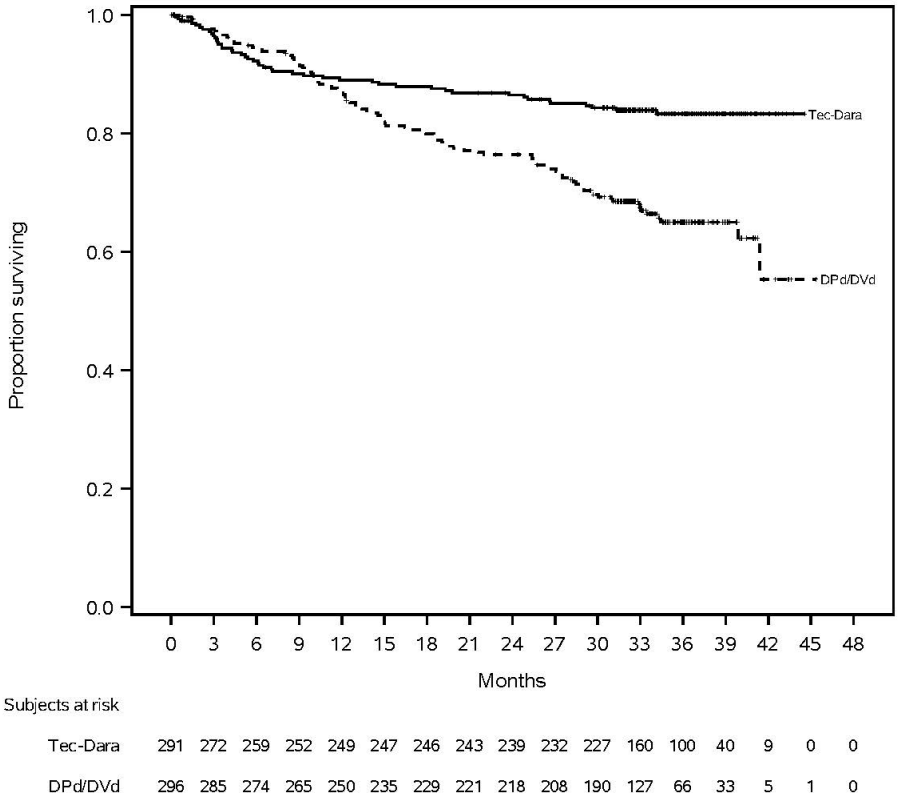


Figure 2: Kaplan-Meier Curve of OS in MajesTEC-3



Monotherapy- MajesTEC-1
The efficacy of TECVAYLI monotherapy was evaluated in patients with relapsed or refractory multiple myeloma in a single-arm, open-label, multi-centre, Phase 1/2 study (MajesTEC-1). The study included patients who had previously received at least three prior therapies, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody. The study excluded patients who experienced stroke or seizure within the past 6 months, and patients with Eastern Cooperative Oncology Group performance score (ECOG PS) ≥2, plasma cell leukaemia, known active CNS involvement or exhibited clinical signs of meningeal involvement of multiple myeloma, or active or documented history of autoimmune disease with the exception of vitiligo, Type 1 diabetes and prior autoimmune thyroiditis.

Patients received initial step-up doses of 0.06 mg/kg and 0.3 mg/kg of TECVAYLI administered subcutaneously, followed by the treatment dose of TECVAYLI 1.5 mg/kg, administered subcutaneously once weekly thereafter, until disease progression or unacceptable toxicity. Patients who had a complete response (CR) or better for a minimum of 6 months were eligible to reduce dosing frequency to 1.5 mg/kg subcutaneously every two weeks until disease progression or unacceptable toxicity (see section 4.2). The median duration between Step-up Dose 1 and Step-up Dose 2 was 2.9 (Range: 2-7) days. The median duration between Step-up Dose 2 and the initial treatment dose was 3.1 (Range: 2-9) days. Patients were hospitalised for monitoring for at least 48 hours after administration of each dose of the TECVAYLI Step-up dosing schedule.

The efficacy population included 165 patients. The median age was 64 (Range: 33-84) years with 15% of subjects ≥75 years of age; 58% were male; 81% were White, 13% were Black, 2% were Asian. The International Staging System (ISS) at study entry was 52% in Stage I, 35% in Stage II and 12% in Stage III. High-risk cytogenetics (presence of del(17p), t(4;14) or t(14;16)) were present in 26% of patients. Seventeen percent of patients had extramedullary plasmacytomas.

The median time since initial diagnosis of multiple myeloma to enrolment was 6 (Range: 0.8-22.7) years. The median number of prior therapies was 5 (Range: 2-14), with 23% of patients who received

3 prior therapies. Eighty-two percent of patients received prior autologous stem cell transplantation, and 4.8% of patients received prior allogeneic transplantation. Seventy-eight percent of patients were triple-class refractory (refractory to proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody).

Efficacy results were based on overall response rate, as determined by the Independent Review Committee (IRC) assessment, using International Myeloma Working Group (IMWG) 2016 criteria (see Table 9).

Table 9: Efficacy results for MajesTEC-1

	All Treated (N=165)
Overall response rate (ORR: sCR, CR, VGPR, PR) n(%)	104 (63.0%)
95% CI (%)	(55.2%, 70.4%)
Stringent complete response (sCR)	54 (32.7%)
Complete response (CR)	11 (6.7%)
Very good partial response (VGPR)	32 (19.4%)
Partial response (PR)	7 (4.2%)
Duration of Response (DOR) (months)	
Number of Responders DOR (Months): Median (95% CI)	104 18.4 (14.9, NE)[1]
Time to First Response (months)	
Number of responders Median Range	104 1.2 (0.2; 5.5)
MRD negativity rate[2] in all treated patients, n (%) [N=165]	44 (26.7%)
95% CI (%)	(20.1%, 34.1%)
MRD negativity rate[2,3] in patients achieving CR or sCR, n (%) [N=65]	30 (46.2%)
95% CI (%)	(33.7%, 59.0%)

1 NE=not estimable

2 MRD-negativity rate is defined as the proportion of participants who achieved MRD negative status (at 10^{-5}) at any timepoint after initial dose, and prior to progressive disease (PD) or subsequent anti-myeloma therapy.

3 Only MRD assessments (10^{-5} testing threshold) within 3 months of achieving CR/sCR until death/progression/subsequent therapy (exclusive) are considered.

Results of an updated efficacy analysis after a median follow-up of 30.6 months among responders (n=104) showed a higher proportion of patients with CR (7.3%) and sCR (38.8%) compared with the primary analysis. MRD negativity rates also increased in all treated patients (29.1%) and in patients achieving CR or sCR (51.3%). The median DOR was 24.0 (17.0, NE) months.

The median follow-up after schedule change was 12.6 (Range: 1.0 to 24.7) months in patients who switched to 1.5 mg/kg subcutaneously every two weeks.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with TECVAYLI in all subsets of the paediatric population in multiple myeloma (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Teclistamab exhibited approximately dose-proportional pharmacokinetics following subcutaneous administration across a dose range of 0.08 mg/kg to 3 mg/kg in monotherapy. Following the recommended dose of teclistamab monotherapy, 90% of steady state exposure was achieved after 12 weekly treatment doses. The mean accumulation ratio between the first and 13th weekly treatment dose of teclistamab 1.5 mg/kg was 4.2-fold for C_{max}, 4.1-fold for C_{trough}, and 5.3-fold for C_{avg}.

The pharmacokinetic characteristics of teclistamab were consistent whether used as monotherapy or in combination with daratumumab.

The C_{max}, C_{trough}, and C_{avg} of teclistamab are presented in Table 10.

Table 10: Pharmacokinetic parameters of teclistamab for the recommended dose in patients with relapsed or refractory multiple myeloma

	C_{max} (µg/mL)	C_{trough} (µg/mL)	C_{avg} (µg/mL)
Teclistamab Monotherapy			
Steady state of 1.5 mg/kg weekly dosing[a]	23.8 (55%)	21.1 (63%)	22.8 (57%)
Teclistamab in Combination with Daratumumab			
First 1.5 mg/kg dose	6.36 (54%)	5.79 (59%)	4.96 (55%)
End of 1.5 mg/kg weekly dosing[b]	19.6 (54%)	17.3 (62%)	18.6 (56%)
End of 3.0 mg/kg Q2W dosing[c]	29.9 (55%)	19.8 (85%)	26.2 (62%)
Steady state of 3.0 mg/kg Q4W dosing[d]	20.2 (52%)	5.82 (152%)	13.7 (67%)

C_{avg}=average serum teclistamab concentration over a dosing interval; C_{max}=maximum serum teclistamab concentration; C_{trough}=serum teclistamab concentration prior to next dose; Q2W=every 2 weeks; Q4W=every 4 weeks

[a] steady-state exposure for the 13th weekly dose.

[b] exposure for the 7th weekly dose.

[c] exposure for the 8th Q2W dose.

[d] steady-state exposure for the 5th Q4W dose.

Note: Data are presented as geometric mean (CV %).

Absorption

The mean bioavailability of teclistamab was 72% when administered subcutaneously. The median (range) T_{max} of teclistamab after the first and 13th weekly treatment doses in monotherapy were 139 (19 to 168) hours and 72 (24 to 168) hours, respectively.

Distribution

The mean volume of distribution was 5.63 L (29% coefficient of variation (CV)).

Elimination

Teclistamab clearance decreases over time, with a mean (CV%) maximal reduction from baseline to the 13th weekly treatment dose in monotherapy of 40.8% (56%). The geometric mean (CV%) clearance is 0.472 L/day (64%) at the 13th weekly treatment dose in monotherapy. Patients who discontinue teclistamab after the 13th weekly treatment dose in monotherapy are expected to have a 50% reduction from C_{max} in teclistamab concentration at a median (5th to 95th percentile) time of 15 (7 to 33) days after T_{max} and a 97% reduction from C_{max} in teclistamab concentration at a median time of 69 (32 to 163) days after T_{max}.

Population pharmacokinetic analysis showed that soluble BCMA did not impact teclistamab serum concentrations.

Special populations

The pharmacokinetics of TECVAYLI in paediatric patients aged 17 years and younger have not been investigated.

Results of population pharmacokinetic analyses indicate that age (24 to 84 years) and sex did not influence the pharmacokinetics of teclistamab.

Renal impairment

No formal studies of TECVAYLI in patients with renal impairment have been conducted.

Results of population pharmacokinetic analyses indicate that mild renal impairment (60 mL/min ≤ estimated glomerular filtration rate (eGFR) <90 mL/min) or moderate renal impairment (30 mL/min ≤ eGFR <60 mL/min) did not significantly influence the pharmacokinetics of teclistamab. Limited data are available from patients with severe renal impairment.

Hepatic impairment

No formal studies of TECVAYLI in patients with hepatic impairment have been conducted.

Results of population pharmacokinetic analyses indicate that mild hepatic impairment (total bilirubin >1 to 1.5 times upper limit of normal (ULN) and any aspartate aminotransferase (AST), or total bilirubin ≤ULN and AST>ULN) did not significantly influence the pharmacokinetics of teclistamab. Limited data are available in patients with moderate hepatic impairment and no data are available in patients with severe hepatic impairment.

5.3 Preclinical safety data

Carcinogenicity and mutagenicity

No animal studies have been performed to assess the carcinogenic or genotoxic potential of teclistamab.

Reproductive toxicology and fertility

No animal studies have been conducted to evaluate the effects of teclistamab on reproduction and foetal development. In the 5-week repeat-dose toxicity study in cynomolgus monkeys, there were no notable effects in the male and female reproductive organs at doses up to 30 mg/kg/week (approximately 22 times the maximum recommended human dose, based on AUC exposure) intravenously for five weeks.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

EDTA disodium salt dihydrate
Glacial acetic acid
Polysorbate 20 (E432)
Sodium acetate trihydrate
Sucrose
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Unopened vial

2 years

After opening

Chemical and physical in-use stability after opening the vial, including storage in prepared syringes, has been demonstrated for 8 days at 2 °C to 8 °C and 24 hours at ambient temperature (15 °C to 30 °C).

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 °C to 8 °C, unless preparation has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store in a refrigerator (2 °C - 8 °C).
Do not freeze.
Store in the original carton in order to protect from light.

6.5 Nature and contents of container

3 mL solution for injection in a Type 1 glass vial with an elastomeric closure, and aluminium seal with a flip-off button containing 30 mg of teclistamab (10 mg/mL).
Pack size of 1 vial.

1.7 mL solution for injection in a Type 1 glass vial with an elastomeric closure, and aluminium seal with a flip-off button containing 153 mg of teclistamab (90 mg/mL).
Pack size of 1 vial.

6.6 Special precautions for disposal and other handling

It is very important that the instructions for preparation and administration provided in this section are strictly followed to minimise potential dosing errors with TECVAYLI 10 mg/mL and TECVAYLI 90 mg/mL vials.

TECVAYLI should be administered via subcutaneous injection only. Do not administer TECVAYLI intravenously.

TECVAYLI should be administered by a healthcare professional with adequately trained medical personnel and appropriate medical equipment to manage severe reactions, including cytokine release syndrome (see section 4.4).

TECVAYLI 10 mg/mL and TECVAYLI 90 mg/mL vials are for single use only.

TECVAYLI vials of different concentrations should not be combined to achieve treatment dose.

Aseptic technique should be used to prepare and administer TECVAYLI.

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

Preparation of TECVAYLI

- Verify the prescribed dose for each TECVAYLI injection. To minimise errors, use the following tables to prepare TECVAYLI injection.
    - Use Table 11 to determine the total dose, injection volume and number of vials required, based on patient's actual body weight for Step-up dose 1 using TECVAYLI 10 mg/mL vial.

Table 11: Injection volumes of TECVAYLI (10 mg/mL) for Step-up dose 1 (0.06 mg/kg)

	Body weight (kg)	Total dose (mg)	Volume of injection (mL)	Number of vials (1 vial=3 mL)
Step-Up dose 1 (0.06 mg/kg)	35-39.9	2.2	0.22	1
	40-44.9	2.5	0.25	1
	45-49.9	2.8	0.28	1
	50-59.9	3.3	0.33	1
	60-69.9	3.9	0.39	1
	70-79.9	4.5	0.45	1
	80-89.9	5.1	0.51	1
	90-99.9	5.7	0.57	1
	100-109.9	6.3	0.63	1
	110-119.9	6.9	0.69	1
	120-129.9	7.5	0.75	1
	130-139.9	8.1	0.81	1
	140-149.9	8.7	0.87	1
	150-160	9.3	0.93	1

- Use Table 12 to determine the total dose, injection volume and number of vials required based on patient's actual body weight for Step-up dose 2 using TECVAYLI 10 mg/mL vial.

Table 12: Injection volumes of TECVAYLI (10 mg/mL) for Step-up dose 2 (0.3 mg/kg)

	Body weight (kg)	Total dose (mg)	Volume of injection (mL)	Number of vials (1 vial=3 mL)
Step-up dose 2 (0.3 mg/kg)	35-39.9	11	1.1	1
	40-44.9	13	1.3	1
	45-49.9	14	1.4	1
	50-59.9	16	1.6	1
	60-69.9	19	1.9	1
	70-79.9	22	2.2	1
	80-89.9	25	2.5	1
	90-99.9	28	2.8	1
	100-109.9	31	3.1	2
	110-119.9	34	3.4	2
	120-129.9	37	3.7	2
	130-139.9	40	4.0	2
	140-149.9	43	4.3	2
	150-160	47	4.7	2

- Use Table 13 to determine the total dose, injection volume and number of vials required based on patient's actual body weight for the 1.5 mg/kg treatment dose using TECVAYLI 90 mg/mL vial.

Table 13: Injection volumes of TECVAYLI (90 mg/mL) for treatment dose (1.5 mg/kg)

	Body weight (kg)	Total dose (mg)	Volume of injection (mL)	Number of vials (1 vial=1.7 mL)
Treatment dose (1.5 mg/kg)	35-39.9	56	0.62	1
	40-44.9	64	0.71	1
	45-49.9	71	0.79	1
	50-59.9	83	0.92	1
	60-69.9	99	1.1	1
	70-79.9	108	1.2	1
	80-89.9	126	1.4	1
	90-99.9	144	1.6	1
	100-109.9	153	1.7	1
	110-119.9	171	1.9	2
	120-129.9	189	2.1	2
	130-139.9	198	2.2	2
	140-149.9	216	2.4	2
	150-160	234	2.6	2

- Use Table 14 to determine the total dose, injection volume and number of vials required based on patient's actual body weight for the 3 mg/kg treatment dose using TECVAYLI 90 mg/mL vial.

Table 14: Injection volumes of TECVAYLI (90 mg/mL) for treatment dose (3 mg/kg)

	Body weight (kg)	Total dose (mg)	Volume of injection (mL)	Number of vials (1 vial=1.7 mL)
Treatment dose (3 mg/kg)	35-39.9	108	1.2	1
	40-44.9	126	1.4	1
	45-49.9	144	1.6	1
	50-59.9	162	1.8	2
	60-69.9	198	2.2	2
	70-79.9	225	2.5	2
	80-89.9	252	2.8	2
	90-99.9	288	3.2	2
	100-109.9	315	3.5	3
	110-119.9	342	3.8	3
	120-129.9	378	4.2	3
	130-139.9	405	4.5	3
	140-149.9	432	4.8	3
	150-160	468	5.2	4

- Remove the appropriate TECVAYLI vial from refrigerated storage (2 °C – 8 °C) and equilibrate to ambient temperature (15 °C – 30 °C), as needed, for at least 15 minutes. Do not warm TECVAYLI in any other way.
- Once equilibrated, gently swirl the vial for approximately 10 seconds to mix. Do not shake.
- Withdraw the required injection volume of TECVAYLI from the vial(s) into an appropriately sized syringe using a transfer needle.
  - Each injection volume should not exceed 2.0 mL. Divide doses requiring greater than 2.0 mL equally into multiple syringes.
- TECVAYLI is compatible with stainless steel injection needles and polypropylene and polycarbonate syringe material.
- Replace the transfer needle with an appropriately sized needle for injection.
- Visually inspect TECVAYLI for particulate matter and discolouration prior to administration. Do not use if the solution is discoloured, or cloudy, or if foreign particles are present.
  - TECVAYLI solution for injection is colourless to light yellow.

Administration of TECVAYLI

- Inject the required volume of TECVAYLI into the subcutaneous tissue of the abdomen (preferred injection site). Alternatively, TECVAYLI may be injected into the subcutaneous tissue at other sites (e.g., thigh).
- If multiple injections are required (either as monotherapy or as combination therapy), TECVAYLI injections should be at least 2 cm apart.
- Do not inject into tattoos or scars or areas where the skin is red, bruised, tender, hard or not intact.

7. MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1675/001 (10 mg/ml)
EU/1/22/1675/002 (90 mg/ml)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23 August 2022
Date of latest renewal: 12 June 2026

10. DATE OF REVISION OF THE TEXT

20 August 2026

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