1. NAME OF THE MEDICINAL PRODUCT

TECVAYLI 10 mg/mL
TECVAYLI 90 mg/mL

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).

Patient safety information card

The marketing of TECVAYLI is subject to a risk management plan (RMP) including a 'Patient safety information card'. The 'Patient safety information card', emphasizes important safety information that the patient should be aware of before and during treatment.
Please explain to the patient the need to review the card before starting treatment.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

TECVAYLI is indicated 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 3 and section 4.4).

Recommended dosing schedule

The recommended dosing schedule for TECVAYLI is provided in Table 1. 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).

Treatment with TECVAYLI should be initiated according to the step-up dosing schedule in Table 1 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).

Table 1: TECVAYLI dosing schedule

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 maintenance dose	1.5 mg/kg SC single dose
Weekly dosing schedule[b]	One week after first maintenance dose and weekly thereafter[e]	Subsequent maintenance doses	1.5 mg/kg SC once weekly
Patients who have a complete response or better for a minimum of 6 months			
Biweekly (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 2 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 maintenance dose may be given between two to seven days after Step-up dose 2. This is the first full maintenance dose (1.5 mg/kg).[e] Maintain a minimum of five days between weekly maintenance doses.

Refer to Tables 9, 10 and 11 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 Table 1) 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 acetaminophen 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 2), or
- Patients who experienced CRS following the previous dose (Table 3).

Prevention of herpes zoster reactivation

Prior to starting treatment with TECVAYLI, antiviral prophylaxis should be considered for the prevention of herpes zoster virus reactivation, per local institutional guidelines.

Restarting TECVAYLI after dose delay

If a dose of TECVAYLI is delayed, therapy should be restarted based on the recommendations listed in Table 2 and TECVAYLI resumed according to the dosing schedule (see Table 1). Pre-treatment medicinal products should be administered as indicated in Table 2. Patients should be monitored accordingly (see section 4.2).

Table 2: 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 maintenance doses	8 days to 28 days	Continue TECVAYLI at last maintenance dose and schedule .
	More than 28 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 and patients monitored accordingly.

Dose modifications

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

Dose reductions of TECVAYLI are not recommended.

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 2.

Recommended actions after adverse reactions following administration of TECVAYLI are listed in Table 3.

Table 3: 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 4 for management of cytokine release syndrome. • Administer pre-treatment medicinal products prior to next dose of TECVAYLI.

	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 4 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 4 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 5 for management of immune effector cell-associated neurotoxicity syndrome.
	Grade 2 Grade 3 (First occurrence)	• Withhold TECVAYLI until adverse reaction resolves. • See Table 5 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 5 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 maintenance doses of TECVAYLI (i.e., doses administered after TECVAYLI step-up dosing schedule) until infection improves to Grade 2 or better.
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.
	Platelet count less than 25 000/µL Platelet count between 25 000/µL and 50 000/µL with bleeding	• Withhold TECVAYLI until platelet count is 25 000/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 4 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 3 (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 3). CRS should be managed according to the recommendations in Table 4. 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 4: 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	Not applicable
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).

Neurologic toxicities, including ICANS

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

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

Patients should be counselled to seek medical attention should signs or symptoms of neurologic toxicity occur. At the first sign of neurologic toxicity, including 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 and other neurologic toxicities, treatment with TECVAYLI should be withheld as indicated in Table 3 (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 neurologic toxicities

At the first sign of neurologic toxicity, including 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 3). Intensive care and supportive therapy should be provided for severe or life-threatening neurologic toxicities. General management for neurologic toxicity (e.g., ICANS with or without concurrent CRS) is summarised in Table 5.

Table 5: Guidelines for management of immune effector cell-associated neurotoxicity syndrome (ICANS)

Grade	Presenting symptoms[a]	Concurrent CRS	No Concurrent CRS
Grade 1	ICE score 7-9[b] Or, depressed level of consciousness[c]: awakens spontaneously.	Management of CRS per Table 4. Monitor neurologic symptoms and consider neurology consultation and evaluation, per physician discretion.	Monitor neurologic symptoms and consider neurology consultation and evaluation, per physician discretion.
		Consider non-sedating, anti-seizure medicinal products (e.g., levetiracetam) for seizure prophylaxis.	
Grade 2	ICE score 3-6[b] Or, depressed level of consciousness[c]: awakens to voice.	Administer tocilizumab per Table 4 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.	Administer dexamethasone[d] 10 mg intravenously every 6 hours. Continue dexamethasone use until resolution to Grade 1 or less, then taper.
		Consider non-sedating, anti-seizure medicinal products (e.g., levetiracetam) for seizure prophylaxis. Consider neurology consultation and other specialists for further evaluation, as needed.	
Grade 3	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	Administer tocilizumab per Table 4 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.	Administer dexamethasone[d] 10 mg intravenously every 6 hours. Continue dexamethasone use until resolution to Grade 1 or less, then taper.

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

Or, depressed level of consciousnessc 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 4 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. Prophylactic antimicrobials should be administered according to local institutional guidelines.

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 3 (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 3 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 was used to treat hypogammaglobulinaemia in 39% of patients. Patients should be treated according to local institutional guidelines, including infection precautions, antibiotic or antiviral prophylaxis, and administration of immunoglobulin replacement.

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 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 3 (see section 4.2).

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 maintenance 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 (Table 1) (see section 4.2 and section 4.4).

4.8 Undesirable effects

The most frequent adverse reactions of any grade in patients were hypogammaglobulinaemia (75%), cytokine release syndrome (72%), neutropenia (71%), anaemia (55%), musculoskeletal pain (52%), fatigue (41%), thrombocytopenia (40%), injection site reaction (38%), upper respiratory tract infection (37%), lymphopenia (35%), diarrhoea (28%), pneumonia (28%), nausea (27%), pyrexia (27%), headache (24%), cough (24%), constipation (21%) and pain (21%).

Serious adverse reactions were reported in 65% patients who received TECVAYLI, including pneumonia (16%), COVID-19 (15%), cytokine release syndrome (8%), sepsis (7%), pyrexia (5%), musculoskeletal pain (5%), acute kidney injury (4.8%), diarrhoea (3.0%), cellulitis (2.4%), hypoxia (2.4%), febrile neutropenia (2.4%), and encephalopathy (2.4%).

Tabulated list of adverse reactions

The safety data of TECVAYLI was evaluated in MajesTEC-1, which included 165 adult patients with multiple myeloma who received the recommended dosing regimen of TECVAYLI as monotherapy. The median duration of TECVAYLI treatment was 8.5 (Range: 0.2 to 24.4) months.

Table 6 summarises adverse reactions reported in patients who received TECVAYLI. The safety data of TECVAYLI was also evaluated in the all treated population (N=302) with no additional adverse reactions identified.

Adverse reactions observed during clinical studies are listed below by frequency category. 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 6: Adverse reactions in patients with multiple myeloma treated with TECVAYLI in MajesTEC-1 at the recommended dose for monotherapy use

System Organ Class	Adverse Reaction	Frequency (All grades)	N=165 n (%)	
			Any Grade	Grade 3 or 4
Infections and infestations	Pneumonia[1]	Very common	46 (28%)	32 (19%)
	Sepsis[2]	Common	13 (7.9%)	11 (6.7%)
	COVID-19[3]	Very common	30 (18%)	20 (12%)
	Upper respiratory tract infection[4]	Very common	61 (37%)	4 (2.4%)
	Cellulitis	Common	7 (4.2%)	5 (3.0%)
	Urinary tract infection[5, 21]	Very common	23 (14%)	10 (6.1%)
	Progressive multifocal leukoencephalopathy[21]	Uncommon	1 (0.6%)	1 (0.6%)
Blood and lymphatic system disorders	Neutropenia	Very common	117 (71%)	106 (64%)
	Febrile neutropenia	Common	6 (3.6%)	5 (3.0%)
	Thrombocytopenia	Very common	66 (40%)	35 (21%)
	Lymphopenia	Very common	57 (35%)	54 (33%)
	Anaemia6	Very common	90 (55%)	61 (37%)
	Leukopenia	Very common	29 (18%)	12 (7.3%)
	Hypofibrinogenaemia	Common	16 (9.7%)	2 (1.2%)
Immune system disorders	Cytokine release syndrome	Very common	119 (72%)	1 (0.6%)
	Hypogammaglobulinaemia[7]	Very common	123 (75%)	3 (1.8%)

Metabolism and nutrition disorders	Hyperamylasaemia	Common	6 (3.6%)	4 (2.4%)
	Hyperkalaemia	Common	8 (4.8%)	2 (1.2%)
	Hypercalcaemia	Very common	19 (12%)	5 (3.0%)
	Hyponatraemia	Common	13 (7.9%)	8 (4.8%)
	Hypokalaemia	Very common	23 (14%)	8 (4.8%)
	Hypocalcaemia	Common	12 (7.3%)	0
	Hypophosphataemia	Very common	20 (12%)	10 (6.1%)
	Hypoalbuminaemia	Common	4 (2.4%)	1 (0.6%)
	Hypomagnesaemia	Very common	22 (13%)	0
	Decreased appetite	Very common	20 (12%)	1 (0.6%)
	Hypoglycaemia[21]	Common	4 (2.4%)	0
Nervous system disorders	Immune effector cell-associated neurotoxicity syndrome	Common	5 (3.0%)	0
	Encephalopathy[8]	Common	16 (9.7%)	0
	Neuropathy peripheral[9]	Very common	26 (16%)	1 (0.6%)
	Headache	Very common	39 (24%)	1 (0.6%)
Vascular disorders	Haemorrhage[10]	Very common	20 (12%)	5 (3.0%)
	Hypertension[11]	Very common	21 (13%)	9 (5.5%)
	Hypotension[21]	Very common	18 (11%)	4 (2.4%)
Respiratory, thoracic and mediastinal disorders	Hypoxia	Common	16 (9.7%)	6 (3.6%)
	Dyspnoea[12]	Very common	22 (13%)	3 (1.8%)
	Cough[13]	Very common	39 (24%)	0
Gastrointestinal disorders	Diarrhoea	Very common	47 (28%)	6 (3.6%)
	Abdominal pain[14, 21]	Very common	20 (12%)	2 (1.2%)
	Vomiting	Very common	21 (13%)	1 (0.6%)
	Nausea	Very common	45 (27%)	1 (0.6%)
	Constipation	Very common	34 (21%)	0
Musculoskeletal and connective tissue disorders	Musculoskeletal pain[15]	Very common	85 (52%)	14 (8.5%)
	Muscle spasms[21]	Very common	17 (10%)	0
General disorders and administration site conditions	Pyrexia	Very common	45 (27%)	1 (0.6%)
	Injection site reaction[16]	Very common	62 (38%)	1 (0.6%)
	Pain[17]	Very common	34 (21%)	3 (1.8%)

	Oedema[18]	Very common	23 (14%)	0
	Fatigue[19]	Very common	67 (41%)	5 (3.0%)
Investigations	Blood creatinine increased	Common	9 (5.5%)	0
	Transaminase elevation[20]	Common	16 (9.7%)	4 (2.4%)
	Lipase increased	Common	10 (6.1%)	2 (1.2%)
	Blood alkaline phosphatase increased	Very common	18 (11%)	3 (1.8%)
	Gamma-glutamyltransferase increased	Common	16 (9.7%)	5 (3.0%)
	Activated partial thromboplastin time prolonged	Common	13 (7.9%)	2 (1.2%)
	International normalised ratio increased	Common	10 (6.1%)	2 (1.2%)

Adverse events are coded using MedDRA Version 24.0.

Note: The output includes the diagnosis of CRS and ICANS; the symptoms of CRS or ICANS are excluded.

[1] Pneumonia includes Enterobacter pneumonia, lower respiratory tract infection, lower respiratory tract infection viral, Metapneumovirus pneumonia, Pneumocystis jirovecii pneumonia, pneumonia, Pneumonia adenoviral, Pneumonia bacterial, Pneumonia klebsiella, Pneumonia moraxella, Pneumonia pneumococcal, Pneumonia pseudomonal, Pneumonia respiratory syncytial viral, Pneumonia staphylococcal and Pneumonia viral.

[2] Sepsis includes bacteraemia, Meningococcal sepsis, neutropenic sepsis, Pseudomonal bacteraemia, Pseudomonal sepsis, sepsis and Staphylococcal bacteraemia.

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

[4] Upper respiratory tract infection includes bronchitis, nasopharyngitis, pharyngitis, respiratory tract infection, respiratory tract infection bacterial, rhinitis, rhinovirus infection, sinusitis, tracheitis, upper respiratory tract infection and viral upper respiratory tract infection.

[5] Urinary tract infection includes Cystitis, Cystitis escherichia, Cystitis klebsiella, Escherichia urinary tract infection, Urinary tract infection and Urinary tract infection bacterial.

[6] Anaemia includes anaemia, iron deficiency and iron deficiency anaemia.

[7] Hypogammaglobulinaemia includes patients with adverse events of hypogammaglobulinaemia, hypoglobulinaemia, immunoglobulins decreased, and/or patients with laboratory IgG levels below 500 mg/dL following treatment with teclistamab.

[8] Encephalopathy includes confusional state, depressed level of consciousness, lethargy, memory impairment and somnolence.

[9] Neuropathy peripheral includes dysaesthesia, hypoaesthesia, hypoaesthesia oral, neuralgia, paraesthesia, paraesthesia oral, peripheral sensory neuropathy and sciatica.

[10] Haemorrhage includes conjunctival haemorrhage, epistaxis, haematoma, haematuria, haemoperitoneum, haemorrhoidal haemorrhage, lower gastrointestinal haemorrhage, melaena, mouth haemorrhage and subdural haematoma.

[11] Hypertension includes essential hypertension and hypertension.

[12] Dyspnoea includes acute respiratory failure, dyspnoea and dyspnoea exertional.

[13] Cough includes allergic cough, cough, productive cough and upper-airway cough syndrome.

[14] Abdominal pain includes Abdominal discomfort, Abdominal pain and Abdominal pain upper.

[15] Musculoskeletal pain includes arthralgia, back pain, bone pain, musculoskeletal chest pain, musculoskeletal pain, myalgia, neck pain and pain in extremity.

[16] Injection site reaction includes injection site bruising, injection site cellulitis, injection site discomfort, injection site erythema, injection site haematoma, injection site induration, injection site inflammation, injection site oedema, injection site pruritus, injection site rash, injection site reaction and injection site swelling.

[17] Pain includes ear pain, flank pain, groin pain, non-cardiac chest pain, oropharyngeal pain, pain, pain in jaw, toothache and tumour pain.

[18] Oedema includes face oedema, fluid overload, oedema peripheral and peripheral swelling.

[19] Fatigue includes asthenia, fatigue and malaise.

[20] Transaminase elevation includes alanine aminotransferase increased and aspartate aminotransferase increased.

[21] New adverse reaction terms identified using long term follow-up from MajesTEC-1.

Description of selected adverse reactions

Cytokine release syndrome

In MajesTEC-1 (N=165), CRS was reported in 72% of patients following treatment with TECVAYLI. One-third (33%) of patients experienced more than one CRS event. Most patients experienced CRS following Step-up Dose 1 (44%), Step-up Dose 2 (35%), or the initial maintenance dose (24%). Less than 3% of patients developed first occurrence of CRS following subsequent doses of TECVAYLI. CRS events were Grade 1 (50%) and Grade 2 (21%) or Grade 3 (0.6%). The median time to onset of CRS was 2 (Range: 1 to 6) days after the most recent dose, with a median duration of 2 (Range: 1 to 9) days.

The most frequent signs and symptoms associated with CRS were fever (72%), hypoxia (13%), chills (12%), hypotension (12%), sinus tachycardia (7%), headache (7%), and elevated liver enzymes (aspartate aminotransferase and alanine aminotransferase elevation) (3.6% each).

In MajesTEC-1, tocilizumab, corticosteroids and tocilizumab in combination with corticosteroids were used to treat CRS in 32%, 11% and 3% of CRS events, respectively.

Neurologic toxicities, including ICANS

In MajesTEC-1 (N=165), neurologic toxicity events were reported in 15% of patients receiving TECVAYLI. Neurologic toxicity events were Grade 1 (8.5%), Grade 2 (5.5%), or Grade 4 (<1%). The most frequently reported neurologic toxicity event was headache (8%).

ICANS, including Grade 3 and higher, were reported in clinical trials and with post-marketing experience. The most frequent clinical manifestation of ICANS were confusional state, decreased level of consciousness, disorientation, dysgraphia, aphasia, apraxia, and somnolence. The onset of neurologic toxicity can be concurrent with CRS, following resolution of CRS, or in the absence of CRS. The observed time to onset of ICANS ranged from 0 to 21 days after the most recent dose.

Immunogenicity

Patients treated with subcutaneous teclistamab monotherapy (N=238) in MajesTEC-1 were evaluated for antibodies to teclistamab using an electrochemiluminescence-based immunoassay. One subject (0.4%) developed neutralising antibodies to teclistamab of low-titre.

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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form:
https://sideeffects.health.gov.il

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.

Clinical efficacy and safety

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 maintenance 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 maintenance 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 7).

Table 7: 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.

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 (0.05 to 2.0 times the recommended dose). Ninety percent of steady state exposure was achieved after 12 weekly maintenance doses. The mean accumulation ratio between the first and 13th weekly maintenance 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 AUC_{tau}.

The C_{max}, C_{trough}, and AUC_{tau} of teclistamab are presented in Table 8.

Table 8: Pharmacokinetic parameters of teclistamab for the 13th recommended weekly maintenance dose (1.5 mg/kg) in patients with relapsed or refractory multiple myeloma in MajesTEC-1

Pharmacokinetic Parameter	Teclistamab Geometric Mean (CV%)
C_{max} (µg/mL)	23.8 (55%)
C_{trough} (µg/mL)	21.1 (63%)
AUC_{tau} (µg·h/mL)	3 838 (57%)

C_{max} = Maximum serum teclistamab concentration; C_{trough} = Serum teclistamab concentration prior to next dose; CV = geometric coefficient of variation; AUC_{tau} = Area under the concentration-time curve over the weekly dosing interval.

Absorption

The mean bioavailability of teclistamab was 72% when administered subcutaneously. The median (range) T_{max} of teclistamab after the first and 13th weekly maintenance doses 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 maintenance dose of 40.8% (56%). The geometric mean (CV%) clearance is 0.472 L/day (64%) at the 13th weekly maintenance dose. Patients who discontinue teclistamab after the 13th weekly maintenance dose 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 (based on MajesTEC-1) 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/1.73 m^2 ≤ estimated glomerular filtration rate (eGFR) <90 mL/min/1.73 m^2) or moderate renal impairment (30 mL/min/1.73 m^2 ≤ eGFR <60 mL/min/1.73 m^2) 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. No data are available in patients with moderate and 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

Sucrose
Sodium acetate trihydrate
Polysorbate 20
Glacial acetic acid
EDTA disodium salt dihydrate
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
The expiry date of the product is indicated on the packaging materials.

Prepared syringe
The prepared syringes should be administered immediately. If immediate administration is not possible, in-use storage times of the prepared syringe should be no longer than 20 hours at 2 °C - 8 °C or ambient temperature (15 °C – 30 °C). Discard after 20 hours if not used.

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 maintenance 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 9 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 9: 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	2.2	0.22	1
	40-44	2.5	0.25	1
	45-49	2.8	0.28	1
	50-59	3.3	0.33	1
	60-69	3.9	0.39	1
	70-79	4.5	0.45	1
	80-89	5.1	0.51	1
	90-99	5.7	0.57	1
	100-109	6.3	0.63	1
	110-119	6.9	0.69	1
	120-129	7.5	0.75	1
	130-139	8.1	0.81	1
	140-149	8.7	0.87	1
	150-160	9.3	0.93	1

- Use Table 10 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 10: 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	11	1.1	1
	40-44	13	1.3	1
	45-49	14	1.4	1
	50-59	16	1.6	1
	60-69	19	1.9	1
	70-79	22	2.2	1
	80-89	25	2.5	1
	90-99	28	2.8	1
	100-109	31	3.1	2
	110-119	34	3.4	2
	120-129	37	3.7	2
	130-139	40	4.0	2
	140-149	43	4.3	2
	150-160	47	4.7	2

- Use Table 11 to determine the total dose, injection volume and number of vials required based on patient's actual body weight for the maintenance dose using TECVAYLI 90 mg/mL vial.

Table 11: Injection volumes of TECVAYLI (90 mg/mL) for maintenance dose (1.5 mg/kg)

	Body weight (kg)	Total dose (mg)	Volume of injection (mL)	Number of vials (1 vial=1.7 mL)
Maintenance dose (1.5 mg/kg)	35-39	56	0.62	1
	40-44	63	0.70	1
	45-49	70	0.78	1
	50-59	82	0.91	1
	60-69	99	1.1	1
	70-79	108	1.2	1
	80-89	126	1.4	1
	90-99	144	1.6	1
	100-109	153	1.7	1
	110-119	171	1.9	2
	120-129	189	2.1	2
	130-139	198	2.2	2
	140-149	216	2.4	2
	150-160	234	2.6	2

- 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, 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. MANUFACTURER and REGISTRATION HOLDER

Manufacturer: Janseen Biologics B.V., Einsteinweg 101, 2333 CB Leiden, The Netherlands

Registration Holder: J-C Health Care Ltd., Kibbutz Shefayim, 6099000, Israel

8. Registration numbers

Tecvayli 10mg/ml 173-74-37566-00
Tecvayli 90mg/ml 173-75-37567-00

Revised in 09_2025