EUROPEAN MEDICINES AGENCY

Certificate: 01/23/002972
Request: 94048

Certificate of a Medicinal Product

This Certificate conforms to the format recommended by the World Health Organization (WHO).
It establishes the status of the medicinal product and of the applicant for the certificate within the jurisdiction of the regional certifying authority at the time of issue. It is for a single product only at a given point in time since the manufacturing arrangements and approved information for different dosage forms and different strengths can vary

No. of Certificate: ***01/23/002972***

Regional certifying authority:

European Union:

Belgium, Bulgaria, Czechia, Denmark, Germany, Estonia, Ireland, Greece, Spain, France, Croatia, Italy, Cyprus, Latvia, Lithuania, Luxembourg, Hungary, Malta, Netherlands, Austria, Poland, Portugal, Romania, Slovenia, Slovakia, Finland, Sweden and United Kingdom (Northern Ireland)

For the UK, as from 1.1.2021, EU Law applies only to the territory of Northern Ireland (NI) to the extent foreseen in the Protocol on Ireland/NI

Importing (requesting) country:

LEBANON

1.1 Name: (International Nonproprietary Name (INN)/generic/chemical name); brand name of the medicinal product as it is declared in the marketing authorisation and used within the territory of the certifying authority and, if requested, the brand name for the foreign country as declared by the requester, (if different); and pharmaceutical form of the product

TECVAYLI; Solution for injection

1.2 Active substance(s) and amount(s) per unit dose or unit volume:

Teclistamab; 10 mg/ml or 90 mg/ml; 1 vial

For complete composition including excipients, see attached. [1]

1.3 Is this product subject to a Community Marketing Authorisation?

yes, under conditional approval

1.3.1 Are there restrictions of the sale, distribution or administration of the product specified in the marketing authorisation?

not applicable

1.4 Is this product actually on the market within the jurisdiction of the certifying regional authority?

yes

2. Information of Marketing Authorisation:

2.A. Product that is authorised for marketing by the certifying authority: [2]

2.A.1 Number in the Community Register of Medicinal Products and date of issue:

EU/1/22/1675/001-002; 23.08.2022

Confidential

2.A.2 Community Marketing Authorisation Holder (name and address):

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

2.A.3 Status of the Community Marketing Authorisation Holder:

No manufacturing activities as per section 3.1

For categories see section 3.1

2.A.4 Is the European Public Assessment Report (EPAR) appended? (This refers to the document that summarises the technical basis on which the product has been authorised.)

no

2.A.5 Is the attached officially approved product information included in the Community Marketing Authorisation (such as the Summary of Product Characteristics – SPC- or similar)?

yes

2.A.6 Applicant for the Certificate, if different from the Community Marketing Authorisation Holder (name and address)

Cilag AG, Hochstrasse 201, 8200 Schaffhausen, Switzerland

2.A.7 Web-link to the product marketing authorisation information (if available):

https://www.ema.europa.eu/en/medicines/human/EPAR/tecvayli

3.1 List of name and address of the manufacturing site(s) and activities: [4]

a) manufacturing of all steps of the finished medicinal product

b) manufacturing the bulk finished product

c) manufacturing of solvent and diluents

d) quality control of the finished medicinal product

e) batch release of the finished medicinal product in the EU

f) primary packaging of the dosage form

g) secondary packaging of the product

h) other(s) (specify and list in new arrows)

Name of manufacturing site	***Address***	***Activity***
Patheon Manufacturing Services LLC	***5900 Martin Luther King Jr. Hwy Greenville, NC 27834 USA***	***b), f)***
Janssen Biologics B.V.	***Einsteinweg 101 2333 CB Leiden The Netherlands***	***e)***

European Medicines Agency • Domenico Scarlattilaan 6 • 1083 HS Amsterdam • The Netherlands
Telephone +31 (0)88 781 6000
E-mail certificate@ema.europa.eu **Website** www.ema.europa.eu

Name of manufacturing site	***Address***	***Activity***
AndersonBrecon, Inc.	***4545 Assembly Drive Rockford, IL 61109 USA***	***g)***
Janssen Pharmaceutica NV	***Rue du Bois de la Hutte 7 7110 La Louvière Belgium***	***g)***

3.2 Does the certifying authority arrange for periodic inspections of the manufacturing site in which the pharmaceutical form is produced?

yes

If no or not applicable, proceed to question 4.

3.3 Periodicity of routine inspections:

Frequency of inspections is determined on risk-based approach

3.4 Has the manufacturer of this type of pharmaceutical form been inspected? If Yes, when feasible, insert date of inspection(s) (dd/mm/yyyy): [5]

yes

3.5 Do the facilities and operations conform to good manufacturing practices (GMP) as recommended by the World Health Organization (WHO)? [6]

yes

3.6. It is recommended that for products approved, but not manufactured in the country of the certifying authority, the source of information that assures the GMP compliance of the manufacturer(es) is declared:

GMP compliance is checked during the assessment for the marketing authorisation regardless of the location of the site

4. Does the information submitted by the applicant satisfy the certifying authority on all aspects of the manufacture of the product? [7]

yes

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EUROPEAN MEDICINES AGENCY

Certificate: 01/23/002972
Request: 94048

Address of the Certifying Authority

European Medicines Agency
Domenico Scarlattilaan 6, 1083 HS Amsterdam, The Netherlands
Telephone: ***+31 (0)88 781 6000***

E-mail address: ***certificate@ema.europa.eu***

Name and title of authorised person

Signature and date

Name and electronic signature from signatory

DocuSigned by:
Alberto Ganan Jimenez
0C804C075183452...

15 March 2023
Authorised signatory

Stamp

Confidential

Explanatory notes

[1] Details of quantitative composition are preferred but their provision is subject to the agreement of the marketing authorisation holder.

[2] Sections 2A and 2B are mutually exclusive.

[3] In this circumstance, permission for issuing the Certificate is required from the Community Marketing Authorisation Holder. This permission has to be provided to the European Medicines Agency by the applicant (only applicable to section 2.A).

[4] This information can only be provided with the consent of the Community Marketing Authorisation Holder or, in the case of non-registered products, the applicant. It should be noted that information concerning the site of production is part of the Community Marketing Authorisation. If the production site is changed, the Community Marketing Authorisation has to be updated or it is no longer valid.

[5] Currently not feasible.

[6] The requirements for good practices in the manufacture and quality control of medicinal products referred to in the certificate, are those included in the Thirty-second report of the Expert Committee on Specifications for Pharmaceutical Preparations, WHO Technical Report Series, No. 986, 2014, Annex 2 (WHO Good manufacturing practices for medicinal products: main principles). Recommendations specifically applicable to biological products have been formulated by the WHO Expert Committee on Biological Standardization (WHO Good manufacturing Practices for biological products, WHO Technical Report Series, No. 996, 2016, Annex 3).

[7] It is of particular importance when contractors are involved in the manufacture of the product. The applicant should supply the certifying authority with information in order to identify the contracting parties responsible for each stage of manufacture of the finished dosage form and the extent and nature of any controls exercised over each of these parties.

European Medicines Agency • Domenico Scarlattilaan 6 • 1083 HS Amsterdam • The Netherlands
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STATEMENT OF QUANTITATIVE COMPOSITION
DECLARACIÓN DE COMPOSICIÓN CUANTITATIVA
ÉNONCÉ DE LA COMPOSITION QUANTITATIVE

1. Name and pharmaceutical form of the Medicinal Product:
Nombre y forma farmacéutica del medicamento:
Dénomination et forme pharmaceutique du médicament:

TECVAYLI, solution for injection

2. Number(s) in the Community Register of Medicinal Products:
Número(s) de autorización de comercialización comunitaria:
Numéro(s) au registre communautaire de mise sur le marché:

EU/1/22/1675/001-002

3. Qualitative and quantitative composition of the Medicinal Product:
Composición cualitativa y cuantitativa del medicamento:
Composition qualitative et quantitative du médicament:

Active ingredient(s): Principio(s) activo(s): Substance(s) active(s):	Quantities and units: Cantidades y unidades: Quantités et unités:
	Nominal Fill Amount per Vial (3.0 mL) ***Concentration: 10 mg/mL***
Teclistamab	***30 mg***
Other ingredient(s): Otros ingrediente(s): Excipient(s)	Quantities and units: Cantidades y unidades: Quantités et unités:
Sodium acetate trihydrate[a]	***4.5 mg***
Glacial acetic acid[a]	***0.72 mg***
Sucrose	***240 mg***
Polysorbate 20[b,c]	***1.2 mg***
EDTA Disodium Salt Dihydrate	***0.06 mg***
Water for Injection[d]	***q.s. to 3.0 mL***

[a] Combination of listed amounts of sodium acetate trihydrate and glacial acetic acid produces a buffer at target pH of 5.2 and buffer strength of 15 mM
[b] Vegetable based; low peroxide
[c] The concentration of 0.4 mg/mL polysorbate 20 is equivalent to 0.04% (w/v) polysorbate 20
[d] Corresponding name in *Ph. Eur.* monograph is Water for Injections

EDTA = Ethylenediaminetetraacetic acid
q.s. = *Quantum satis* (as much as may suffice)

Active ingredient(s): Principio(s) activo(s): Substance(s) active(s):	Quantities and units: Cantidades y unidades: Quantités et unités:
	Nominal Fill Amount per Vial (1.7 mL) ***Concentration: 90 mg/mL***
Teclistamab	***153 mg***
Other ingredient(s): Otros ingrediente(s): Excipient(s):	Quantities and units: Cantidades y unidades: Quantités et unités:
Sodium acetate trihydrate[a]	***2.6 mg***
Glacial acetic acid[a]	***0.41 mg***
Sucrose	***140 mg***
Polysorbate 20[b,c]	***0.68 mg***
EDTA Disodium Salt Dihydrate	***0.034 mg***
Water for Injection[d]	***q.s. to 1.7 mL***

[a] Combination of listed amounts of sodium acetate trihydrate and glacial acetic acid produces a buffer at target pH of 5.2 and buffer strength of 15 mM
[b] Vegetable based; low peroxide
[c] The concentration of 0.4 mg/mL polysorbate 20 is equivalent to 0.04% (w/v) polysorbate 20
[d] Corresponding name in *Ph. Eur.* monograph is Water for Injections

EDTA = Ethylenediaminetetraacetic acid
q.s. = *Quantum satis* (as much as may suffice)

SUMMARY OF PRODUCT CHARACTERISTICS

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

1. NAME OF THE MEDICINAL PRODUCT

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.

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 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 th 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.

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]**	
Step-up dosing schedule[e]	Day 1	Step-up dose 1	0.06 mg/kg single dose
	Day 3[b]	Step-up dose 2	0.3 mg/kg single dose
	Day 5[c]	First maintenance dose	1.5 mg/kg single dose
Weekly dosing schedule[e]	One week after first maintenance dose and weekly thereafter[d]	Subsequent maintenance doses	1.5 mg/kg once weekly

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

[b] Step-up dose 2 may be given between 2 to 7 days after Step-up dose 1.

[c] First maintenance 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).

[d] Maintain a minimum of five days between weekly maintenance doses.

[e] See Table 2 for recommendations on restarting TECVAYLI after dose delays.

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 7 days	Restart TECVAYLI step-up dosing schedule at Step-up dose 1 (0.06 mg/kg)[a].
Step-up dose 2	8 days to 28 days	Repeat Step-up dose 2 (0.3 mg/kg)[a] and continue TECVAYLI step-up dosing schedule.
	More than 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 dosing schedule at maintenance dose (1.5 mg/kg)[a].
	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 (65 years of age and older)

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

Serious or life-threatening neurologic toxicities, including Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) may occur 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 cells-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.

	that resolves rapidly, or • non-convulsive seizures on electroencephalogram (EEG) that resolve with intervention, or raised intracranial pressure: focal/local oedema on neuroimaging[c].	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 4	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	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.	As above, or consider administration of methylprednisolone 1 000 mg per day intravenously for 3 days; if improves, then manage as above.
		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.	

[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. Progressive multifocal leukoencephalopathy (PML) has also 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).

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 hypogammaglobulinemia 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

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

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 3 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 three 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%)
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%)
	Anaemia[5]	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[6]	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%)
Nervous system disorders	Immune effector cell-associated neurotoxicity syndrome	Common	5 (3.0%)	0
	Encephalopathy[7]	Common	16 (9.7%)	0
	Neuropathy peripheral[8]	Very common	26 (16%)	1 (0.6%)
	Headache	Very common	39 (24%)	1 (0.6%)
Vascular disorders	Hemorrhage[9]	Very common	20 (12%)	5 (3.0%)
	Hypertension[10]	Very common	21 (13%)	9 (5.5%)
Respiratory, thoracic and mediastinal disorders	Hypoxia	Common	16 (9.7%)	6 (3.6%)
	Dyspnoea[11]	Very common	22 (13%)	3 (1.8%)
	Cough[12]	Very common	39 (24%)	0
Gastrointestinal disorders	Diarrhoea	Very common	47 (28%)	6 (3.6%)
	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[13]	Very common	85 (52%)	14 (8.5%)
General disorders and administration site conditions	Pyrexia	Very common	45 (27%)	1 (0.6%)
	Injection site reaction[14]	Very common	62 (38%)	1 (0.6%)
	Pain[15]	Very common	34 (21%)	3 (1.8%)
	Oedema[16]	Very common	23 (14%)	0
	Fatigue[17]	Very common	67 (41%)	5 (3.0%)

Investigations	Blood creatinine increased	Common	9 (5.5%)	0
	Transaminase elevation[18]	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] Anaemia includes anaemia, iron deficiency and iron deficiency anaemia.

[6] 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.

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

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

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

[10] Hypertension includes essential hypertension and hypertension.

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

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

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

[14] 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.

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

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

[17] Fatigue includes asthenia, fatigue and malaise

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

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: 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

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 was reported in 3% of patients receiving TECVAYLI at the recommended dose. The most frequent clinical manifestation of ICANS reported were confusional state (1.2%) and dysgraphia (1.2%). The onset of neurologic toxicity can be concurrent with CRS, following resolution of CRS, or in the absence of CRS. Seven of nine ICANS events (78%) were concurrent with CRS (during or within 7 days of CRS resolution). The median time to onset of ICANS was 4 (Range: 2 to 5) days after the most recent dose, with a median duration of 3 (Range: 1 to 20) days.

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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

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: {group}, ATC code: not yet assigned

Mechanism of action

Teclistamab is a full-size, IgG4-PAA bispecific antibody that targets the CD3 receptor expressed the surface of T cells and B cell maturation antigen (BCMA), which is expressed on the surface

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 (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 allogenic 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.

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 (0.05 to 2.0 times the recommended dose). The mean accumulation ratio following subcutaneous weekly dosing of teclistamab at steady state (based on the 7th weekly maintenance dose), was 2.71- and 3.05-fold for C_{max} and AUC_{tau}, respectively. The mean bioavailability following teclistamab subcutaneous administration was 69%, relative to intravenous dosing.

Pharmacokinetic parameters of teclistamab following the 1st and 7th recommended maintenance dose of 1.5 mg/kg are shown in Table 8.

Table 8: Pharmacokinetic parameters of teclistamab following the at first and seventh recommended maintenance dose (1.5 mg/kg) in patients with relapsed or refractory multiple myeloma in MajesTEC-1

Pharmacokinetic Parameters	**1st maintenance dose of 1.5 mg/kg**	**7th maintenance dose of 1.5 mg/kg (steady-state)**
T_{max} (hours)	72.0 (45.8 – 193) (n=40)	48.9 (0.0 – 166) (n=15)
C_{max} (µg/mL)	8.74 ± 3.65 (n=40)	25.3 ± 11.1 (n=15)
C_{trough} (µg/mL)	7.67 ± 3.52 (n=38)	22.1 ± 10.9 (n=27)
AUC_{tau} (µg·h/mL)	1 169 ± 481 (n=38)	3 905 ± 1 748 (n=13)

T_{max} = Time to reach the C_{max}; C_{max} = Maximum observed serum teclistamab concentration; C_{trough} = Observed serum teclistamab concentration prior to next dose; AUC_{tau} = Area under the concentration-time curve over the weekly dosing interval. Data are presented as mean ± standard deviation, except for T_{max} which is presented as median (minimum, maximum).

Distribution

Based on the population pharmacokinetic model, mean volume of distribution was 4.13 L (48.8% CV (coefficient of variation)) for the central compartment, and 1.34 L for the peripheral compartment.

Excretion

Teclistamab exhibited both time-independent and time-dependent clearance. Based on the population pharmacokinetic model, the mean time-independent clearance of teclistamab is 0.449 L/day (53.6% CV), with the median of time-dependent clearance contributing approximately 43% of the total clearance at baseline and decreasing rapidly thereafter to less than 10% after Week 8.

Based on non-compartmental analysis, the mean half-life (SD) was 3.8 (1.7) days (individual values ranging up to 8.8 days) following the first treatment intravenous dose of teclistamab.

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

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

18 months

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. 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

10. DATE OF REVISION OF THE TEXT

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

ANNEX IV

CONCLUSIONS ON THE GRANTING OF THE CONDITIONAL MARKETING AUTHORISATION PRESENTED BY THE EUROPEAN MEDICINES AGENCY

Conclusions presented by the European Medicines Agency on:

- **Conditional marketing authorisation**

The CHMP having considered the application is of the opinion that the risk-benefit balance is favourable to recommend the granting of the conditional marketing authorisation as further explained in the European Public Assessment Report.