ANNEX I

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

LYNOZYFIC 5 mg concentrate for solution for infusion
LYNOZYFIC 200 mg concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

LYNOZYFIC 5 mg concentrate for solution for infusion

Each vial contains 5 mg of linvoseltamab in 2.5 mL at a concentration of 2 mg/mL.

LYNOZYFIC 200 mg concentrate for solution for infusion

Each vial contains 200 mg of linvoseltamab in 10 mL at a concentration of 20 mg/mL.

Linvoseltamab is a recombinant human immunoglobulin (Ig)G4-based bispecific antibody produced by recombinant DNA technology in Chinese hamster ovary (CHO) cell suspension culture.

Excipient with known effect

The 5 mg vial of linvoseltamab contains 2.5 mg of polysorbate 80 in each 2.5 mL vial which is equivalent to 1 mg/mL.

The 200 mg vial of linvoseltamab contains 10 mg of polysorbate 80 in each 10 mL vial which is equivalent to 1 mg/mL.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

Clear to slightly opalescent, colourless to pale yellow liquid that is essentially free from visible particulates, with a pH of 6.0, and osmolarity of approximately 358 mmol/L (2 mg/mL) and approximately 372 mmol/L (20 mg/mL).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

LYNOZYFIC is indicated as monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least 3 prior therapies, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody, and have demonstrated disease progression on the last therapy.

4.2 Posology and method of administration

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

LYNOZYFIC should be administered by a healthcare professional with immediate access to emergency equipment and appropriate medical support to manage severe reactions such as cytokine release syndrome (CRS), infusion-related reactions (IRR), or immune effector cell-associated neurotoxicity syndrome (ICANS) if they occur (see section 4.4).

Prior to initiating treatment, complete blood count should be performed. Any active infection should be ruled out (see section 4.4). Pregnancy in women of child-bearing potential should also be ruled out (see section 4.6).

Posology

Pretreatment therapy
Pretreatment medicinal products in Table 1 should be administered to reduce the risk of CRS and/or IRR (see sections 4.4 and 4.8). Pretreatment medicinal products should be administered until two full doses are tolerated without CRS and/or IRR.

Table 1: Pretreatment medicinal products

Dose	Pretreatment medicinal products	Administration relative to LYNOZYFIC infusion
Step up dosing (including the 1st 200 mg dose)	40 mg dexamethasone IV	1 to 3 hours prior to infusion
	Antihistamine (e.g., diphenhydramine 25 mg oral or IV)	30 to 60 minutes prior to infusion
	Paracetamol (e.g., 500 to 1000 mg oral)	30 to 60 minutes prior to infusion
2nd 200 mg dose	Dexamethasone	1 to 3 hours prior to infusion
	40 mg dexamethasone IV in patients who experienced CRS and/or IRR with prior infusion	
	10 mg dexamethasone IV in patients who did not experience CRS and/or IRR with prior infusion	
	Antihistamine (e.g., diphenhydramine 25 mg oral or IV)	30 to 60 minutes prior to infusion
	Paracetamol (e.g., 500 to 1000 mg oral)	30 to 60 minutes prior to infusion
Subsequent 200 mg doses	• If the patient experienced CRS and/or IRR with the prior infusion, repeat pretreatment medicinal products as described above for the 2nd 200 mg dose. • Once the 200 mg dose is tolerated without CRS and/or IRR: o If the patient received 40 mg dexamethasone IV with the prior infusion, step down to 10 mg dexamethasone IV and continue other pretreatment medicinal products as described above. o If the patient received 10 mg dexamethasone IV with the prior infusion, discontinue all pretreatment medicinal products.	

Prophylactic therapy
Prophylactic treatment per local institutional guidelines for *Pneumocystis jirovecii* pneumonia (PJP) and herpes simplex and zoster viruses is recommended for all patients. Prophylactic antimicrobials and anti-virals, including prophylaxis against cytomegalovirus (CMV) infection, should be considered based on local institutional guidelines (see section 4.4).

Recommended posology
The recommended step-up treatment doses, full treatment dose, and treatment frequency are presented in Table 2. Each dose should only be administered if the previous dose is tolerated. For doses that are not tolerated, refer to Table 3, Table 4, and Table 5.

All patients should be monitored for signs and symptoms of potential CRS, IRR, and ICANS during administration and for 24 hours after the end of the infusion of the first step-up treatment dose. Patients should be instructed to remain with a caregiver within close proximity of the qualified treatment centre for 24 hours after the first step-up treatment dose (see section 4.4).

Patients who have experienced CRS, IRR, a neurologic adverse reaction, or any grade ≥ 2 adverse event, with the first step-up treatment dose administration should be monitored during administration and for 24 hours after the administration of the second step-up treatment dose and should be instructed to remain with a caregiver within close proximity of the qualified treatment centre for 24 hours (see section 4.4).

Table 2: Recommended posology

Dosing schedule	**Day[a]**	**LYNOZYFIC dose**	
Step-up dosing schedule	Week 1 Day 1	Step-up treatment dose 1	5 mg
	Week 2 Day 1	Step-up treatment dose 2	25 mg
	Week 3 Day 1	First full treatment dose	200 mg
Weekly dosing schedule	Week 4 to Week 13 for 10 treatment doses	Full treatment doses	200 mg
Every 2 weeks dosing schedule	Week 14 and every 2 weeks thereafter	Full treatment doses	200 mg
Patients who have received at least 17 doses of 200 mg and have confirmed response of very good partial response (VGPR) or better per international myeloma working group (IMWG) criteria at or after Week 24[b]			
Every 4 weeks dosing schedule	At week 24 or after and every 4 weeks thereafter	Treatment doses	200 mg
[a] Weekly doses should be at least 5 days apart. [b] Patients who have not achieved VGPR or better at Week 24 should continue receiving LYNOZYFIC every 2 weeks.			

Duration of treatment
Treatment should be continued until disease progression or unacceptable toxicity.

Management of adverse reactions
Table 3 describes the management of CRS. Table 4 describes the management of ICANS. Table 5 describes the management of other adverse events.

Cytokine release syndrome

Identify CRS based on clinical presentation (see section 4.4). Evaluate and treat other causes of fever, hypoxia and hypotension. If CRS is suspected, withhold LYNOZYFIC until CRS resolves. CRS should be managed according to the recommendations in Table 3 and per current practice guidelines.

Supportive therapy for CRS should be administered, which may include intensive care for severe or life-threatening CRS.

Table 3: Recommendations for management of cytokine release syndrome

Grade[a]	Presenting symptoms	Recommendations
Grade 1	Fever ≥ 38 ºC[b]	• Withhold treatment until CRS resolves. • Provide supportive care, which may include intensive care. • Consider anticytokine therapy[c] and/or corticosteroids[d]. • When restarting treatment, refer to Table 6.
Grade 2	Fever ≥ 38 ºC[b] with: Hypotension responsive to fluids and not requiring vasopressors and/or hypoxia requiring low-flow oxygen[e] by nasal cannula or blow-by	• Withhold treatment until CRS resolves. • Provide supportive care, which may include intensive care. • If symptoms do not improve within 4 hours, administer anticytokine therapy[c]. • In patients with organ toxicities, administer corticosteroids[d]. • When restarting treatment, refer to Table 6.
Grade 3	Fever ≥ 38 ºC[b] with: Hypotension requiring a vasopressor (with or without vasopressin) and/or hypoxia requiring high-flow oxygen[e] by nasal cannula, face mask, non-rebreather mask, or Venturi mask.	• Withhold treatment until CRS resolves. • Provide supportive care, which may include intensive care, including anticytokine therapy[c] and corticosteroids[d]. • When restarting treatment, refer to Table 6. • Permanently discontinue treatment if Grade 3 CRS recurs with subsequent infusions.
Grade 4	Fever ≥ 38 °C[b] with: Hypotension requiring multiple vasopressors (excluding vasopressin) and/or hypoxia requiring oxygen by positive pressure (e.g., continuous positive airway pressure (CPAP), bilevel positive airway pressure (BiPAP), intubation, and mechanical ventilation).	• Discontinue treatment permanently. • CRS should be managed per Grade 3 recommendations.
Other	AST/ALT > 5× ULN associated with CRS Grade 3 or less	• Withhold treatment until CRS resolves and AST/ALT are < 3× ULN if baseline was normal or 1.5 to 3× baseline if baseline was abnormal. • Provide supportive care, which may include intensive care, and monitor. • When restarting treatment, refer to Table 6.
[a] Based on Lee criteria for grading CRS (Lee et al., 2019).		

Grade[a]	Presenting symptoms	Recommendations
[b] Attributed to CRS. Fever may not always be present concurrently with hypotension or hypoxia as it may be masked by interventions such as steroids, antipyretics, or anticytokine therapy. [c] 8 mg/kg tocilizumab infused over 1 hour, not to exceed 800 mg, may be considered. [d] E.g., 20 mg dexamethasone per day in divided doses or equivalent. [e] Low-flow oxygen defined as oxygen delivered at < 6 L/minute: high-flow oxygen defined as oxygen delivered at ≥ 6 L/minute.		

Immune effector cell-associated neurotoxicity syndrome (ICANS)

Management recommendations for ICANS are summarized in Table 4. At the first sign of suspected ICANS, withhold LYNOZYFIC and consider consultation with neurologist and other specialists for further evaluation and management. Rule out other causes of neurologic symptoms. Provide supportive therapy, which may include intensive care for severe or life-threatening ICANS.

Table 4: Recommendations for management of ICANS

Grade[a]	Presenting symptoms[b]	Recommendations
All grades	See information per grade.	• Provide supportive therapy, which may include intensive care. Manage per current practice guidelines. • Consider non-sedating, anti-seizure medicinal products for seizure prophylaxis.
Grade 1	ICE[c] score 7-9, or depressed level of consciousness[d]: awakens spontaneously.	• Withhold treatment until neurologic symptoms resolve or return to baseline. • When restarting treatment, refer to Table 6.
Grade 2	ICE[c] score 3-6, or depressed level of consciousness[d]: awakens to voice.	• Withhold treatment until neurologic symptoms resolve or return to baseline. • Administer dexamethasone[e] 10 mg IV every 6 hours. Continue dexamethasone use until resolution to Grade 1 or less, then taper. • When restarting treatment, refer to Table 6.
Grade 3	ICE[c] score 0-2, or depressed level of consciousness[d]: awakens only to tactile stimulus, or seizures, either: • any clinical seizure, focal or generalized, that resolves rapidly, or • non-convulsive seizures on electroencephalogram (EEG) that resolve with intervention, or raised intracranial pressure: focal/local oedema on neuroimaging.	• Withhold treatment until neurologic symptoms resolve or return to baseline. • Consider neurology evaluation. • Administer dexamethasone[e] 10 mg IV every 6 hours. Continue dexamethasone use until resolution to Grade 1 or less, then taper. • When restarting treatment, refer to Table 6. • Permanently discontinue treatment for recurrent Grade 3 ICANS.
Grade 4	ICE[c] score 0, or depressed level of consciousness[d]: either: • patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse, or • stupor or coma,	• Permanently discontinue treatment. • Consider neurology evaluation. • Administer dexamethasone[e] 10 mg IV every 6 hours. Continue dexamethasone use until resolution to Grade 1 or less, then taper.

Grade[a]	Presenting symptoms[b]	Recommendations
	or seizures, either: • life-threatening prolonged seizure (> 5 minutes), or • repetitive clinical or electrical seizures without return to baseline in between, or motor findings: • deep focal motor weakness such as hemiparesis or paraparesis, or raised intracranial pressure/cerebral oedema, with signs/ symptoms such as: • diffuse cerebral oedema on neuroimaging, or • decerebrate or decorticate posturing, or • cranial nerve VI palsy, or • papilledema, or • Cushing's triad.	

[a] Based on American Society for Transplantation and Cellular Therapy (ASTCT) 2019 grading for ICANS.
[b] Management is determined by the most severe event, not attributable to any other cause.
[c] 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.
[d] Not attributable to any other cause.
[e] All references to dexamethasone administration are dexamethasone or equivalent.

Other adverse reactions

Management recommendations for other adverse reactions are summarized in Table 5.

Table 5: Recommendations for management of other adverse reactions

Adverse reaction	Grade	Recommendations
Infusion-related reactions (IRR)	Grade 2	• Stop infusion and treat symptoms. • May resume treatment with the remaining infusion (total infusion time must not exceed 6 hours total) when symptoms are Grade 1 or baseline. • When restarting treatment, refer to Table 6.
	Grade 3	• Stop infusion and treat symptoms. • May resume when symptoms are Grade 1 or baseline. • When restarting treatment, refer to Table 6. • Permanently discontinue treatment if Grade 3 IRR recurs with subsequent infusions.

Adverse reaction	Grade	Recommendations
	Grade 4	• Permanently discontinue treatment and treat symptoms.
Neurologic adverse event (excluding ICANS)	Grade 2	• Withhold treatment until symptoms resolve to Grade 1 or baseline. • When restarting treatment, refer to Table 6.
	Grade 3	• Withhold treatment until Grade 1 or baseline. • When restarting treatment, refer to Table 6.
	Grade 4	• Consider permanent discontinuation of treatment. • If treatment is not permanently discontinued, withhold subsequent treatment doses until Grade 1 or baseline and refer to Table 6 for restarting treatment.
Infections	Grade 3	• Withhold treatment in patients with active infection until the infection improves to Grade 1 or less. • When restarting treatment, refer to Table 6.
	Grade 4	• Consider permanent discontinuation of treatment. If treatment is not permanently discontinued, withhold subsequent treatment doses until Grade 1 or baseline and follow the recommendations in Table 6 for restarting dosing.
Other non-haematologic adverse reactions	Grade 3	• Withhold treatment until Grade 1 or baseline. • When restarting treatment, refer to Table 6.
	Grade 4	• Consider permanent discontinuation of treatment. • If treatment is not permanently discontinued, withhold subsequent treatment doses until Grade 1 or baseline and follow the recommendations in Table 6 for restarting dosing.
Haematologic adverse reactions	Platelet count less than 50 000/mcL with bleeding OR less than 25 000/mcL	• Withhold treatment until 25 000/mcL or higher and no evidence of bleeding. • When restarting treatment, refer to Table 6.
	Absolute neutrophil count less than 1.0 x 10^9/L with Grade 2 or higher infection OR less than 0.5 x 10^9/L	• Withhold treatment until 0.5 x 10^9/L or higher and the infection improves to Grade 1 or less. • When restarting treatment, refer to Table 6.
	Febrile neutropenia	• Withhold treatment until neutrophil count is greater than 1.0 x 10^9/L and fever resolves. • When restarting treatment, refer to Table 6.

Dose modifications based on adverse reactions
Dose delays may be required to manage toxicities related to LYNOZYFIC (see section 4.4). See Tables 3, 4, and 5 for the management of adverse reactions. The recommendations for restarting therapy with LYNOZYFIC after an adverse reaction are listed in Table 6.

When restarting therapy, doses should be administered at least 5 days from the previously administered dose. Step-up treatment doses may be repeated based on clinical judgement. Doses should not exceed those recommended in Table 2. Administer pretreatment medicinal products as per

Table 1. After resuming treatment, if the administered dose is tolerated, continue with the next dose of the recommended dosing regimen per Table 2.

Table 6: Recommendations for restarting therapy with LYNOZYFIC after an adverse reaction

Last dose administered	**Adverse reaction and grade**	**Dose for restarting therapy at the next scheduled dose[a]**	**Additional recommendations for restarting therapy[b]**
5 mg	Grade 1: CRS and ICANS	If ≤ 14 days since last dose, administer 25 mg	• Administer at the same infusion rate from prior dose.
		If > 14 days since last dose, restart step-up dosing from 5 mg	
	Grade 2: CRS, IRR, or ICANS	If ≤ 14 days since last dose, administer 25 mg	• If prior CRS or IRR, consider a decrease in infusion rate up to 50% (no more than 6 hours total) when resuming treatment. • If prior CRS or ICANS, monitor for 24 hours
		If > 14 days since last dose, restart step-up dosing from 5 mg	
	Grade 3: CRS, IRR, or ICANS	Administer 2.5 mg	• If prior CRS or IRR, decrease infusion rate up to 50% (no more than 6 hours total) when resuming treatment. Increase rate on subsequent infusions if tolerated. • If prior CRS or ICANS, hospitalise for 24 hours
	Recurrent Grade 3: CRS, IRR, or ICANS	Permanently discontinue treatment	N/A
	Grade 4: CRS, IRR, or ICANS		
	AST/ALT > 5× ULN associated with CRS Grade 2 or less	Transaminase levels that are trending towards baseline within 7 days from elevation onset, administer 25 mg	• For Grade 2 CRS, consider decreasing the infusion rate up to 50% (no more than 6 hours total) when resuming treatment.
		Transaminase levels that do not trend towards baseline in 7 days from elevation onset, administer 2.5 mg	
	All other adverse reactions in Table 5	If ≤ 14 days since last dose, administer 25 mg	• Administer at the same infusion rate from prior dose
		If > 14 days since last dose, restart step-up dosing from 5 mg	
25 mg	Grade 1: CRS and ICANS	If ≤ 14 days since last dose, administer 200 mg	• Administer at the same infusion rate from prior dose
		If > 14 and ≤ 28 days since last dose, restart step-up dosing from 25 mg	
		If > 28 days since last dose, restart step-up dosing from 5 mg	
	Grade 2: CRS, IRR, or ICANS	If ≤ 14 days since last dose, administer 200 mg	• If prior CRS or IRR, consider a decrease in infusion rate up to 50% (no more than 6 hours total) when resuming treatment.
		If > 14 and ≤ 28 days since last dose, restart step-up dosing from 25 mg	

Last dose administered	Adverse reaction and grade	Dose for restarting therapy at the next scheduled dose[a]	Additional recommendations for restarting therapy[b]
		If > 28 days since last dose, restart step-up dosing from 5 mg	• If prior CRS or ICANS, monitor for 24 hours
	Grade 3: CRS, IRR, or ICANS	Administer 5 mg	• If prior CRS or IRR, decrease infusion rate up to 50% (no more than 6 hours total) when resuming treatment. • If prior CRS or ICANS, hospitalise for 24 hours
	Recurrent Grade 3: CRS, IRR, or ICANS	Permanently discontinue treatment	N/A
	Grade 4: CRS, IRR, or ICANS		
	AST/ALT > 5× ULN associated with CRS Grade 2 or less	Transaminase levels that are trending towards baseline within 7 days from elevation onset, administer 200 mg	• For Grade 2 CRS, consider decreasing the infusion rate up to 50% (no more than 6 hours total) when resuming treatment.
		Transaminase levels that do not trend towards baseline within 7 days from elevation onset, restart step-up dosing from 5 mg	
	All other adverse reactions in Table 5	If ≤ 14 days since last dose, administer 200 mg	• Administer at the same infusion rate from prior dose
		If > 14 and ≤ 28 days since last dose, restart step-up dosing from 25 mg	
		If > 28 days since last dose, restart step-up dosing from 5 mg	
200 mg	Grade 1: CRS and ICANS	If ≤ 49 days since last dose, administer 200 mg	• Administer at the same infusion rate from prior dose
		If > 49 days since last dose, restart step-up dosing from 5 mg	
	Grade 2: CRS, IRR, or ICANS	If ≤ 49 days since last dose, administer 200 mg	• If prior CRS or IRR, consider a decrease in infusion rate up to 50% (no more than 6 hours total) when resuming treatment. • If prior CRS or ICANS, monitor for 24 hours
		If > 49 days since last dose, restart step-up dosing from 5 mg	
	Grade 3: CRS, IRR, or ICANS	If ≤ 49 days since last dose, administer 25 mg	• If prior CRS or IRR, decrease infusion rate up to 50% (no more than 6 hours total) when resuming treatment. • If prior CRS or ICANS, hospitalise for 24 hours
		If > 49 days since last dose, restart step-up dosing from 5 mg	
	Recurrent Grade 3: CRS, IRR, or ICANS	Permanently discontinue treatment	N/A
	Grade 4: CRS, IRR, or ICANS		
	AST/ALT > 5× ULN	Transaminase levels that are trending towards baseline	

Last dose administered	Adverse reaction and grade	Dose for restarting therapy at the next scheduled dose[a]	Additional recommendations for restarting therapy[b]
	associated with CRS Grade 2 or less	within 7 days, administer 200 mg	• For Grade 2 CRS, consider decreasing the infusion rate up to 50% (no more than 6 hours total) when resuming treatment.
		Transaminase levels that do not trend towards baseline in 7 days and it has been ≤ 49 days since last dose, administer 25 mg	
		Transaminase levels that do not trend towards baseline in 7 days and it has been > 49 days since the last dose, restart step-up dosing from 5 mg	
	All other adverse reactions in Table 5	If ≤ 49 days since last dose, administer 200 mg	• Administer at the same infusion rate from prior dose
		If > 49 days since last dose, restart step-up dosing from 5 mg	
[a] When restarting therapy, doses should be administered at least 5 days from the previously administered dose. [b] If infusion rate was decreased and the treatment dose is tolerated, infusion rate can be increased gradually based on clinical judgment on subsequent infusions (minimum duration of 30 minutes).			

Missed doses
If a dose is missed for a reason not included in Tables 3, 4 and 5, the dose should be administered as soon as possible based on Table 7.

Table 7: Recommendations for restarting therapy with LYNOZYFIC after a missed dose

Last dose administered	Time since the last dose administered[a]	Action for next dose.
5 mg	≤ 14 days	Administer 25 mg
	> 14 days	Restart step-up dosing from 5 mg
25 mg	≤ 14 days	Administer 200 mg
	> 14 days and ≤ 28 days	Restart step-up dosing from 25 mg
	> 28 days	Restart step-up dosing from 5 mg
200 mg	≤ 49 days	Administer 200 mg
	> 49 days	Restart step-up dosing from 5 mg
NOTE: Administer pretreatment medicinal products as per Table 1. [a] Consider benefit-risk of restarting LYNOZYFIC in patients who require a dose delay of more than 30 days.		

Special populations

Elderly
No dose adjustment is recommended for elderly patients (see section 5.2).

Renal impairment
No dose adjustment is recommended for patients with mild (CrCL ≥ 60 to < 90 mL/min), moderate (CrCL ≥ 30 to < 60 mL/min), or severe renal impairment (CrCL ≥ 15 to < 30 mL/min) (see section 5.2).

Hepatic impairment
No dose adjustment is recommended for patients with mild hepatic impairment (total bilirubin > ULN to 1.5 × ULN or AST > ULN). LYNOZYFIC has not been studied in patients with moderate (total

bilirubin > 1.5 to 3 × ULN, any AST) or severe (total bilirubin > 3 to 10 × ULN, any AST) hepatic impairment. No dose recommendations can be made for patients with moderate or severe hepatic impairment (see section 5.2).

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

Method of administration

LYNOZYFIC is for intravenous use only.
LYNOZYFIC should be administered as an intravenous infusion through a dedicated infusion line. It is recommended to use a 0.2-micron to 5-micron polyethersulfone (PES) filter (see section 6.6).

- Step-up treatment dose 1, step-up treatment dose 2, and the first full treatment dose of LYNOZYFIC are administered as a 4-hour infusion. If the first full treatment dose of LYNOZYFIC is tolerated, infusion time can be reduced to 1 hour for the next full treatment dose and then subsequently 30 minutes for all following full treatment doses.
- For infusion recommendations when restarting after an adverse reaction, refer to Table 6.
- LYNOZYFIC must not be administered as intravenous push or bolus.

For instructions on dilution 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)

Cases of CRS have been reported in patients receiving linvoseltamab (see section 4.8). CRS is a condition that may be serious or life-threatening.

Clinical signs and symptoms of CRS included, but were not limited to, pyrexia, chills, hypoxia, tachycardia, and hypotension.

Administer pretreatment medicinal products (see Table 1) and initiate therapy according to LYNOZYFIC step-up dosing (see Table 2) to reduce the risk of CRS.

All patients should be monitored for signs and symptoms of CRS during and after infusion. All patients should be counselled to seek immediate medical attention should signs or symptoms of CRS occur.

For the first step-up treatment dose of LYNOZYFIC, all patients should be instructed to remain with a caregiver within close proximity of the qualified treatment centre for 24 hours after the end of infusion.

For the second step-up treatment dose and subsequent doses, patients should be instructed to remain with a caregiver within close proximity of the qualified treatment centre for 24 hours after the end of infusion:

- For the second step-up treatment dose of LYNOZYFIC if the patient experienced CRS with the first step-up treatment dose
- For a subsequent dose if the patient experienced Grade 2 CRS with the prior dose.

Patients that experience a first Grade 3 CRS event at any time should be hospitalised for 24 hours after receiving the next dose.

At the first sign of CRS, patients should be immediately evaluated for hospitalisation, managed per current practice guidelines, and supportive care should be administered; LYNOZYFIC should be withheld until CRS resolves and the next dose should be modified or LYNOZYFIC should be permanently discontinued based on severity (see Table 3).

Infusion related reaction (IRR)
IRR may be clinically indistinguishable from manifestations of CRS. For IRR, interrupt or slow the rate of infusion or permanently discontinue LYNOZYFIC based on severity of reaction (see Table 5).

Immune effector cell-associated neurotoxicity syndrome (ICANS)

Cases of ICANS have been reported in patients receiving linvoseltamab (see section 4.8).

Clinical signs and symptoms of ICANS may include but are not limited to aphasia, cerebral oedema, confusion, depressed level of consciousness, disorientation, encephalopathy, and seizure.

All patients should be monitored for signs and symptoms of ICANS during treatment.

For the first step-up treatment dose of LYNOZYFIC, all patients should be instructed to remain with a caregiver within close proximity of the qualified treatment centre for 24 hours after the end of infusion.

For the second step-up treatment dose and subsequent doses, patients should be instructed to remain with a caregiver within close proximity of the qualified treatment centre for 24 hours after the end of infusion:
- For the second step-up treatment dose of LYNOZYFIC if the patient experienced ICANS with the first step-up treatment dose
- For a subsequent dose if the patient experienced Grade 2 ICANS with the prior dose.

Patients that experience a first Grade 3 ICANS event at any time should be hospitalised for 24 hours after receiving the next dose.

At the first sign of ICANS, the patient should be immediately evaluated; supportive therapy should be provided and further management should be considered per current practice guidelines. LYNOZYFIC should be withheld until ICANS resolves and the next dose should be modified or LYNOZYFIC should be permanently discontinued based on severity (see Table 4). Patients should be counselled to seek immediate medical attention should signs or symptoms of ICANS occur at any time.

Due to the potential for ICANS, patients receiving LYNOZYFIC are at risk of confusion and depressed consciousness. Advise patients to refrain from driving, or operating heavy or potentially dangerous machinery, for 24 hours after completion of each of the step-up treatment doses and in the event of new onset of any neurological symptoms, until symptoms resolve (see section 4.7).

Infections

Cases of serious, life-threatening, or fatal infections have been reported in patients receiving linvoseltamab. Progressive multifocal leukoencephalopathy (PML) has also occurred during therapy with LYNOZYFIC (see section 4.8).

Treatment should not be initiated in patients with active infections. Patients should be monitored for signs and symptoms of infection prior to and during treatment with LYNOZYFIC and treated appropriately. Prophylactic treatment per local institutional guidelines for *Pneumocystis jirovecii* pneumonia (PJP) and herpes simplex and zoster viruses is recommended for all patients. Prophylactic antimicrobials and anti-virals, including prophylaxis against CMV, should be administered according to local institutional guidelines. Vaccination for seasonal influenza, COVID-19, *Haemophilus influenza*, and *Pneumococcus* should be administered for all patients according to local institutional guidelines.

LYNOZYFIC should be withheld or permanent discontinuation of LYNOZYFIC should be considered based on severity of the infection (see Table 5).

Hypogammaglobulinaemia

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

Immunoglobulin (Ig) levels should be monitored prior to and during treatment. Treatment with subcutaneous or IV Ig may be considered if IgG levels fall below 400 mg/dL and patients should be treated according to local institutional guidelines, including infection precautions and antimicrobial prophylaxis.

Neutropenia

Cases of neutropenia and febrile neutropenia have been reported in patients receiving linvoseltamab (see section 4.8). Complete blood cell counts should be monitored at baseline and periodically during treatment and supportive care should be provided per local-guidelines. Patients with neutropenia should be monitored for signs of infection. LYNOZYFIC should be withheld based on severity (see Table 5).

Vaccines

Immune response to vaccines may be reduced when taking LYNOZYFIC.

The safety of immunisation with live viral vaccines during or following LYNOZYFIC treatment has not been studied. Vaccination with live virus vaccines should only be administered at least 4 weeks before starting treatment or after immune recovery occurs following treatment.

Patient card

The prescriber must discuss the risks of LYNOZYFIC therapy with the patient. Patients should be provided with the Patient Card, instructed to carry it at all times, and show it to all of their healthcare professionals. The Patient Card describes the common signs and symptoms of CRS and ICANS, provides instructions on when a patient should seek immediate medical attention, provides monitoring instructions, and has the prescribing physician’s contact details.

Excipients

This medicinal product contains polysorbate 80, which may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

No drug interaction studies have been conducted with LYNOZYFIC.

Transient elevation of cytokines may suppress CYP450 enzyme activities. The highest risk of drug interaction is during the step-up dosing regimen and the first full 200 mg dose in patients who are receiving concomitant CYP450 substrates. Monitor for toxicity or concentrations of medicinal

products that are CYP substrates where minimal changes in concentration may lead to serious adverse reactions (e.g., cyclosporine, phenytoin, sirolimus, and warfarin).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception

Pregnancy status for patients of childbearing potential should be verified prior to starting treatment with LYNOZYFIC.

Patients of childbearing potential should use effective contraception during treatment with LYNOZYFIC and for at least 5 months after the last dose.

Pregnancy

There are no available data on the use of LYNOZYFIC in pregnant women. No animal reproductive or developmental toxicity studies have been conducted with linvoseltamab. Linvoseltamab causes T-cell activation and cytokine release; immune activation may compromise pregnancy maintenance. Human immunoglobulin G (IgG) is known to cross the placenta; therefore, linvoseltamab has the potential to be transferred from the pregnant woman to the developing foetus. LYNOZYFIC is not recommended during pregnancy and in women of childbearing potential not using contraception. Based on its mechanism of action, LYNOZYFIC may cause foetal harm, including B-cell and plasma cell lymphocytopenia, when administered to a pregnant patient.

Breast-feeding

There is no information regarding the presence of linvoseltamab in human milk, the effects on the breastfed infant, or the effects on milk production. It is known that human IgG can be secreted in human milk. Breastfeeding should be discontinued during treatment with LYNOZYFIC and for at least 5 months after the last dose due to the potential risk for serious adverse reactions in the breastfed child.

Fertility

No human data on the effect of linvoseltamab on fertility are available (see section 5.3).

4.7 Effects on ability to drive and use machines

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

Due to the potential for ICANS, patients receiving LYNOZYFIC are at risk of confusion and depressed consciousness (see section 4.4). Patients should be instructed to refrain from driving, or operating heavy or potentially dangerous machinery, for 24 hours after completion of each of the step-up treatment doses and in the event of new onset of any neurological symptoms, until symptoms resolve.

4.8 Undesirable effects

Summary of safety profile

The most frequent adverse reactions were musculoskeletal pain (52%), cytokine release syndrome (46%), neutropenia (43%), cough (42%), diarrhoea (39%), anaemia (38%), fatigue (36%), pneumonia (32%), and upper respiratory tract infection (30%).

Serious adverse reactions occurred in 75% of patients who received LYNOZYFIC. The most frequent serious adverse reactions were cytokine release syndrome (27%), pneumonia (13%), COVID-19 (7%), and acute kidney injury (5%).

Permanent discontinuation of LYNOZYFIC due to adverse reactions occurred in 19% of patients. The most frequent adverse reactions leading to discontinuation were COVID-19 pneumonia (1.7%), *Pneumocystis jirovecii* pneumonia (1.7%), and pseudomonal sepsis (1.7%).

Tabulated list of adverse reactions

The safety population described includes 117 patients with relapsed or refractory multiple myeloma who received LYNOZYFIC at the recommended step-up treatment and full treatment dose (see section 5.1). Unless otherwise stated, the frequencies of adverse reactions in Table 8 are based on all-cause adverse event frequencies identified in 117 patients exposed to linvoseltamab during a median duration of 53 weeks (range 1, 167) in the clinical study.

Adverse reactions observed during the clinical study are listed below by MedDRA system organ class classification and by frequency. Frequency categories are defined as follows: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000); very rare (< 1/10 000) and not known (frequency cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 8: Adverse reactions occurring in patients with multiple myeloma treated with LYNOZYFIC

MedDRA System Organ Class	Adverse reaction	Frequency categories (All grades)	Any grade (%)	Grade 3 or 4 (%)
Infections and infestations	Pneumonia[a]	Very common	32	21
	COVID-19	Very common	17	7
	Upper respiratory tract infection[b]	Very common	30	2.6
	Urinary tract infection[c]	Very common	19	8
	Sepsis[d]	Common	8	3.4
	Cytomegalovirus infection[e]	Common	4.2	2.6
	Progressive multifocal leukoencephalopathy	Uncommon	0.9	0
Blood and lymphatic system disorders	Neutropenia	Very common	43	42
	Thrombocytopenia	Very common	20	15
	Anaemia	Very common	38	31
	Lymphopenia	Very common	12	11
	Febrile neutropenia	Common	7	7
Immune system disorders	Cytokine release syndrome	Very common	46	0.9
	Hypogammaglobulinemia	Very common	16	0.9
Metabolism and nutrition disorders	Decreased appetite	Very common	15	0.9
	Hyperuricaemia	Very common	10	1.7

MedDRA System Organ Class	Adverse reaction	Frequency categories (All grades)	Any grade (%)	Grade 3 or 4 (%)
	Hypophosphataemia	Very common	14	0.9
Psychiatric disorders	Insomnia	Very common	13	0
Nervous system disorders	Encephalopathy (excl. ICANS)[f]	Very common	16	3.4
	Musculoskeletal pain	Very common	52	3.4
	Pain[g]	Very common	22	1.7
	Motor dysfunction[h]	Very common	18	1.7
	Headache[i]	Very common	23	0.9
	ICANS[j]	Common	8	2.6
Vascular disorders	Hypertension	Very common	10	4.3
Respiratory, thoracic and mediastinal disorders	Cough	Very common	42	0
	Dyspnoea	Very common	23	0.9
	Nasal congestion	Very common	18	0
Gastrointestinal disorders	Diarrhoea	Very common	39	1.7
	Constipation	Very common	18	0
	Nausea	Very common	23	0
	Vomiting	Very common	20	0
Skin and subcutaneous tissue disorders	Rash[k]	Very common	19	2.6
General disorders and administration site conditions	Oedema[l]	Very common	21	0.9
	Pyrexia	Very common	17	0
	Fatigue[m]	Very common	36	0
	Chills	Very common	10	0
Investigations	Blood creatinine increased	Very common	12	0
	Weight decreased	Very common	10	0
	Transaminase elevation	Common	9.4	2.6
Injury, poisoning and procedural complications	Infusion related reactions[n]	Common	9	1.7

[a] Pneumonia includes atypical pneumonia, COVID-19 pneumonia, haemophilus infection, influenza, metapneumovirus infection, PJP, pneumonia, pneumonia cytomegaloviral, pneumonia fungal, pneumonia influenzal, and pneumonia viral.

[b] Upper respiratory tract infection includes acute sinusitis, bronchitis, nasopharyngitis, pharyngitis, respiratory tract infection, rhinitis, rhinovirus infection, sinobronchitis, sinusitis, upper respiratory tract infection, and viral upper respiratory tract infection.

[c] Urinary tract infection includes cystitis, escherichia urinary tract infection, klebsiella urinary tract infection, urinary tract infection, urinary tract infection bacterial, and urinary tract infection enterococcal, and urinary tract infection staphylococcal.

MedDRA System Organ Class	Adverse reaction	Frequency categories (All grades)	Any grade (%)	Grade 3 or 4 (%)
[d] Sepsis includes sepsis, septic shock, pseudomonal sepsis, streptococcal sepsis, escherichia sepsis, and haemophilus sepsis. [e] CMV infection includes cytomegalovirus infection reactivation, cytomegalovirus infection, and cytomegalovirus viraemia and excludes pneumonia cytomegaloviral. [f] Encephalopathy includes agitation, amnesia, aphasia, cognitive disorder, confusional state, delirium, depressed level of consciousness, encephalopathy, memory impairment, mental status changes, mood altered, somnolence, toxic encephalopathy, and excludes ICANS. [g] Pain includes ear pain, flank pain, groin pain, oropharyngeal pain, pain, and toothache. [h] Motor dysfunction includes dysarthria, dysphonia, gait disturbance, muscle spasm, muscular weakness, and tremor. [i] Headache includes headache and migraine. [j] ICANS is based on adjudicated ICANS which were reported with the terms ICANS, depressed level of consciousness, encephalopathy, and toxic encephalopathy. [k] Rash includes dermatitis acneiform, dermatitis contact, drug eruption, erythema, rash, rash erythematous, rash maculo-papular, rash pruritic, and stasis dermatitis. [l] Oedema includes face oedema, lip oedema, localised oedema, oedema, and oedema peripheral. [m] Fatigue includes fatigue, lethargy, and malaise. [n] Infusion related reactions related to IVIG administration are not included.				

Description of selected adverse reactions

Cytokine release syndrome
CRS occurred in 46% of patients who received LYNOZYFIC at the recommended dose, with Grade 1 CRS occurring in 35% of patients, Grade 2 in 10%, and Grade 3 in 0.9%. Thirty-eight percent of all patients had CRS following step-up treatment dose 1; 8% of all patients had an initial CRS event following a subsequent dose. Seventeen percent of patients receiving step-up treatment dose 2 developed CRS after step-up treatment dose 2, 10% of patients receiving the first full treatment dose developed CRS after the first full treatment dose of LYNOZYFIC, and 3.6% of patients that received the second full treatment dose developed CRS after the second full treatment dose. The Grade 3 case of CRS was reported after the first step-up treatment dose. Nine patients experienced Grade 2 CRS after receiving either step-up treatment dose 1 or step-up treatment dose 2, and three patients experienced Grade 2 CRS with a dose after step-up treatment dose 2. Recurrent CRS occurred in 20% of patients. CRS resolved in all patients, and the median time to onset of CRS from the end of infusion was 11 (range: -1.1 to 184) hours after the most recent dose with a median duration of 16 (range: 1 to 96) hours.

Clinical signs and symptoms of CRS included, but were not limited to, pyrexia, chills, hypoxia, tachycardia, and hypotension.

In the clinical study, 19% of patients received tocilizumab and 11% received corticosteroids for the management of CRS.

Infusion related reactions
IRR may be clinically indistinguishable from manifestations of CRS. In the patients who were treated with the recommended step-up dosing regimen and pretreatment medicinal products, the rate of IRR was 9%, including 4.3% Grade 2 IRR and 1.7% Grade 3 IRR. If IRR is suspected, patients should be managed according to the recommendations in Table 5.

Immune effector cell-associated neurotoxicity syndrome (ICANS)
ICANS occurred in 8% of patients who received LYNOZYFIC with the recommended dosing regimen, including Grade 3 events in 2.6% of patients. Most patients experienced ICANS following step-up treatment dose 1 (5%). 1.8% of patients experienced initial ICANS following step-up treatment dose 2 and 0.9% of patients developed the first occurrence of ICANS following a subsequent full treatment dose of LYNOZYFIC. Recurrent ICANS occurred in 0.9% of patients. ICANS resolved

in all patients except one who withdrew consent to follow-up. The median time to onset of ICANS was 1 (range: 1 to 4) day after the most recent dose with a median duration of 2 (range: 1 to 11) days. The onset of ICANS can be concurrent with CRS, following resolution of CRS, or in the absence of CRS. All ICANS occurred in patients concurrent with or after resolution of CRS or IRR.

Infections
Serious infections occurred in 43% of patients who received LYNOZYFIC at the recommended dose, with Grade 3 or 4 infections occurring in 36%. Infections that were fatal within 30 days of the last dose occurred in 4% of patients. Serious opportunistic infections occurred in 6% of patients. Two cases of progressive multifocal leukoencephalopathy (PML) occurred in patients receiving LYNOZYFIC; both cases had a fatal outcome.

Neutropenia
Neutropenia (including neutrophil count decreased) occurred in 43% of patients who received LYNOZYFIC at the recommended dose in the clinical study, including 42% Grade 3-4 events. The median time to onset of neutropenia was 73 days (range: 0 to 421 days). Seventy-four percent of patients who had neutropenia received treatment with G-CSF. Febrile neutropenia occurred in 8% of patients.

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

In case of overdose, patients should be closely monitored for signs or symptoms of adverse reactions, and appropriate symptomatic treatment instituted.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, Monoclonal antibodies and antibody drug conjugates, ATC code: not yet assigned

Mechanism of action

Linvoseltamab is a human IgG4-based bispecific antibody that binds to cluster of differentiation 3 (CD3), a T-cell antigen associated with the T-cell receptor complex, 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. Simultaneous engagement of both arms of linvoseltamab results in formation of a synapse between the T-cell and the BCMA-expressing cell, resulting in T-cell activation and generation of polyclonal cytotoxic T-cell response, which result in redirected lysis of the targeted cells, including malignant multiple myeloma B-lineage cells. This effect occurs without regard to T-cell receptor specificity or reliance on major histocompatibility complex (MHC) Class I molecules on the surface of antigen-presenting cells.

Pharmacodynamic effects

Transient elevation of circulating cytokines (IL-2, IL-6, and IFN-γ) was primarily observed during the step-up dose regimen and the first full 200 mg dose. The highest elevation of cytokines was generally observed 4 hours after each infusion and generally returned to baseline prior to the next dose. Limited cytokine release was observed following subsequent doses (see section 4.4).

Immunogenicity
During treatment in LINKER-MM1 (evaluated through 30 months), the overall incidence of treatment-emergent anti-linvoseltamab antibodies was 1.0% (2/192) in patients treated with linvoseltamab. No evidence of anti-drug antibody impact on pharmacokinetics or safety was observed; however, data are still limited.

Clinical efficacy and safety

The efficacy of linvoseltamab was evaluated in patients with relapsed or refractory multiple myeloma in an open-label, multi-centre, multi-cohort, Phase 1/2 study: Study LINKER-MM1. The study included patients who had previously received at least 3 prior therapies, including a proteasome inhibitor (PI), an immunomodulatory agent (IMiD), and an anti-CD38 antibody.

The study excluded patients with known multiple myeloma brain lesions or meningeal involvement, history of a neurodegenerative condition, CNS movement disorder, history of a seizure within 12 months prior to study enrolment, any infection requiring hospitalisation or IV anti-infectives within 2 weeks of first administration of study drug, uncontrolled infection with HIV or HBV, a history of an allogeneic stem cell transplantation at any time, or autologous stem cell transplantation within 12 weeks of the start of study treatment, plasma cell leukaemia, primary systemic light-chain amyloidosis, Waldenstrom macroglobulinaemia, POEMS syndrome, and patients with an Eastern Cooperative Oncology Group performance score (ECOG PS) ≥ 2. Patients treated with prior BCMA-directed bispecific antibodies, bispecific T-cell engaging therapies, and BCMA CAR T cells were excluded. Patients could have received a BCMA antibody-drug conjugate.

All patients in both the Phase 1 and Phase 2 portions of the study received a single step-up treatment dose of 5 mg during week 1 and 25 mg during week 2 of LYNOZYFIC by IV infusion. After step-up dosing, patients received 200 mg of LYNOZYFIC weekly for 14 weeks in the Phase 1 portion of the study and 12 weeks for the Phase 2 portion of the study. Patients then received 200 mg every other week thereafter. After at least 24 weeks, the Phase 2 patients who achieved a VGPR or greater received 200 mg of LYNOZYFIC every 4 weeks. Patients were treated until disease progression or unacceptable toxicity. Patients in the study could receive tocilizumab and corticosteroids for the treatment of CRS.

The efficacy population included 12 patients from the Phase 1 and 105 patients from the Phase 2 portions of the study who received the recommended dose of LYNOZYFIC.

The median age was 70 (range: 37 to 91) years with 26% of patients 75 years or older; 55% were male and 45% were female; 71% were White, 17% were Black or African American, and 9% were Asian.

The International Staging System (ISS) for multiple myeloma at study entry was Stage I in 42%, Stage II in 35%, and Stage III in 18%. High-risk cytogenetics (presence of del(17p), t(4;14) and t(14;16)) were present in 39% of patients. Sixteen percent of patients had extramedullary plasmacytomas and 21% had paramedullary plasmacytomas. Twenty percent of patients had bone marrow plasma cell percentage $\geq 60\%$.

The median number of prior lines of therapy was 5 (range: 2 to 16); 97% of patients received at least 3 prior lines of therapy. Sixty-six percent of patients received prior stem cell transplantation. All patients received prior therapy with a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody. Eighty-two percent of patients were triple-class refractory (refractory to a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody). Nine percent of patients were previously treated with a BCMA antibody-drug conjugate. Eighty-five percent of patients were refractory to last line of therapy.

Efficacy was assessed based on objective response rate (ORR) as determined by blinded independent review committee (IRC), as measured using the international myeloma working group (IMWG) criteria. Secondary endpoints included duration of response (DOR) and rate of minimal residual

disease (MRD) negative status. Data are shown in Table 9. The median (range) follow-up from initial dose for responders was 16 (2.5, 38) months.

In the Phase 2 portion of the study, 97% of responders on treatment after at least 12 months had transitioned to every 4-week dosing.

The median time to complete response (CR) or better was 8 months (range: 2, 14 months).

Table 9: Efficacy results for LINKER-MM1

Efficacy endpoints	**LYNOZYFIC N=117**
Objective response rate (ORR) % (n) (95% CI)	71% (83) (62, 79)
Complete response (CR) or better, % (n) (95% CI)	50% (58) (40, 59)
Stringent complete response (sCR), % (n)	44% (52)
Complete response (CR), % (n)	5% (6)
Very good partial response (VGPR), % (n)	14% (16)
Partial response (PR), % (n)	8% (9)
Duration of response (DOR)[a]	N=83
Median, months (95% CI)	29 (19, NE)
Time to first response (months)	N=83
Median, months (Range)	0.95 (0.5, 6)
MRD negativity rate in patients achieving CR or sCR, % (n) [N=58][b] (95% CI)	41% (24) (29, 55)

[a] DOR was defined as the time from the initial occurrence of a documented PR or CR until the patient experienced an event (documented disease progression or death due to any cause, whichever occurred first).
[b] MRD negativity was defined as the proportion of patients in CR or sCR who test MRD negative. MRD negativity was assessed using a next-generation sequencing assay (ClonoSEQ) based on a threshold of 10^{-5} or the Euroflow assay using a threshold of 10^{-5}.
CI=confidence interval; MRD=minimal residual disease; NE=not estimable

Paediatric population

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

Conditional approval

This medicinal product has been authorised under a so-called 'conditional approval' scheme. This means that further evidence on this medicinal product is awaited. The European Medicines Agency will review new information on this medicinal product at least every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

Pharmacokinetics of linvoseltamab was characterized in patients with relapsed or refractory multiple myeloma over a dose range of 1 mg to 800 mg following intravenous infusion. The C_{max}, C_{trough}, and

AUCτ of linvoseltamab at the end of weekly, every other week dosing regimens and at steady state on every 4 week dosing regimen are presented at the 200 mg dose level in Table 10.

Table 10: Geometric mean (CV%) of model-based exposure parameters of recommended dose for linvoseltamab

Dosing period	C_{max} (mg/L)	C_{trough} (mg/L)	AUCτ[a](mg*day/L)
End of 200 mg weekly dose (Week 14)	124 (50.4)	61.8 (123)	592 (74.6)
End of 200 mg every other week dose (Week 24)	97.9 (52.7)	30.2 (213)	727 (95.3)
End of 200 mg every 4 weeks dose (Week 48)	64.8 (45.1)	6.3 (362)	574 (84.6)
[a] AUCτ for the specified dosing interval.			

Distribution

Based on the population pharmacokinetic model, the estimated geometric mean (CV%) of volume of distribution at steady-state (Vd_{ss}) of linvoseltamab is 7.05 L (33.6%).

Biotransformation

Linvoseltamab is expected to be metabolized into small peptides by catabolic pathways.

Elimination

The elimination of linvoseltamab is mediated by two parallel processes, a linear, non-saturable catabolic process, and a nonlinear, saturable target-mediated pathway.

Based on the population pharmacokinetic model, the time to reach lower limit of quantification (LLOQ) (0.078 mg/L) following the last dose of 200 mg weekly, every other week, and every 4 weeks is presented in Table 11.

Table 11: Elimination of recommended dose for linvoseltamab

Dosing period	Time to reach LLOQ (0.078 mg/L) [a] (Weeks)
200 mg weekly	20.1 [5.86, 40.3]
200 mg every other week	18.9 [5.43, 40.3]
200 mg every 4 weeks	15.6 [5.15, 36.4]
[a] Values are median [5th and 95th percentile]	

Special populations

Results of population pharmacokinetic analyses indicate no clinically relevant differences in exposure (such as C_{trough}, AUCτ) to linvoseltamab based on age (37 to 91 years; N=282), sex, and race [White (N=205), Asian (N=18), or Black (N=44)].

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

Results of population pharmacokinetic analyses indicate no clinically relevant differences in exposure to linvoseltamab between patients with normal renal function (N=78; CrCL ≥ 90 mL/min) and with mild (N=116; CrCL ≥ 60 to < 90 mL/min), moderate (N=76; CrCL ≥ 30 to < 60 mL/min), and severe (N=11; CrCL ≥ 15 to < 30 mL/min) renal impairment.

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

Results of population pharmacokinetic analyses indicate no clinically relevant differences in exposure to linvoseltamab between patients with normal (N=255) and with mild hepatic function (N=27; total bilirubin > ULN to 1.5× ULN or AST > ULN). The effects of moderate (total bilirubin > 1.5 to 3× ULN, any AST) and severe (total bilirubin > 3 to 10× ULN, any AST) hepatic impairment on the PK of linvoseltamab are unknown.

5.3 Preclinical safety data

No carcinogenicity or genotoxicity studies have been conducted with linvoseltamab.

No specific studies have been conducted to evaluate potential effects of linvoseltamab on fertility.

No developmental toxicity studies in animals have been conducted with linvoseltamab. Human IgG is known to cross the placenta; therefore, linvoseltamab has the potential to be transmitted from the mother to the developing foetus. Based on its mechanism of action, linvoseltamab may cause foetal B-cell and plasma cell lymphocytopenia that may be harmful to the foetus and transient CRS that may be harmful to pregnancy maintenance.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Histidine
Histidine hydrochloride monohydrate
Sucrose
Polysorbate 80
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

Infusion solution

Once prepared, administer diluted solution immediately. Chemical and physical in-use stability has been demonstrated for the diluted infusion solution as follows:

- Up to 8 hours at room temperature (20 to 25 °C) from preparation to the start of the infusion.
- Up to 48 hours under refrigeration at 2 to 8 °C from preparation to the start of the infusion.

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

Protect the infusion solution from light during storage.

6.4 Special precautions for storage

Store in a refrigerator at 2 °C to 8 °C.

Do not freeze.

Keep the vial in the outer carton in order to protect from light.

For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

5 mg concentrate for solution for infusion

2.5 mL of concentrate in a 5 mL Type 1 clear glass vial with a grey chlorobutyl stopper with coating and a 20 mm aluminium seal cap with a white flip-off button.

Pack of one vial.

200 mg concentrate for solution for infusion

10 mL of concentrate in a 20 mL Type 1 clear glass vial with a grey chlorobutyl stopper with coating and a 20 mm aluminium seal cap with a blue flip-off button.

Pack of one vial.

6.6 Special precautions for disposal and other handling

Instructions for dilution

Use aseptic technique to prepare LYNOZYFIC. Each vial is intended for single-dose only. Discard any unused portion left in the vial.

Do not shake the vial.

Visually inspect for particulate matter and discoloration prior to administration. LYNOZYFIC is a clear to slightly opalescent, colourless to pale yellow liquid that is essentially free from visible particulates. Discard the vial if the solution is cloudy, discoloured, or contains particulate matter.

Withdraw the desired dose from the vial of LYNOZYFIC based on Table 12 and transfer into an intravenous infusion bag of sodium chloride 9 mg/mL (0.9%) solution for injection. LYNOZYFIC is compatible with polyvinyl chloride (PVC) non-di-ethylhexylphthalate (non-DEHP), polyolefin (PO), or ethyl vinyl acetate (EVA) infusion bags. Mix diluted solution by gentle inversion. Do not shake the solution.

Table 12: LYNOZYFIC volumes for addition to infusion bag

LYNOZYFIC dose (mg)	Amount of LYNOZYFIC per vial (mg)	Concentration of vial (mg/mL)	Number of vials required	Total volume of LYNOZYFIC to prepare dose (mL)	Sodium Chloride 9 mg/mL (0.9%) Injection, USP Infusion Bag (PVC or PO) Volume (mL)
5	5	2	1	2.5	50 or 100
25	5	2	5	12.5	50 or 100
200	200	20	1	10	50 or 100
Modified dose due to adverse event[a]					
2.5	5	2	1	1.25	50
[a] For instructions on when to use the modified dose refer to Tables 3, 4, and 5.					

For storage conditions of the infusion solution, see section 6.3.

After LYNOZYFIC has been diluted as instructed, administer as follows:

- Connect the prepared IV infusion bag containing the final LYNOZYFIC solution to IV tubing constructed of PVC, polyethylene (PE)-lined PVC, or polyurethane (PU). It is recommended to use a 0.2-micron to 5-micron polyethersulfone (PES) filter.
- Prime with LYNOZYFIC to the end of the IV tubing.
- Do not mix LYNOZYFIC with other drugs or concurrently administer other drugs through the same intravenous line.
- Upon completion of LYNOZYFIC infusion, flush the infusion line with adequate volume of sterile sodium chloride 9 mg/mL (0.9%) solution for injection to ensure that the entire contents of the infusion bag are administered.
- Total infusion time should include flushing of the infusion line.

Disposal

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

7. MARKETING AUTHORISATION HOLDER

Regeneron Ireland DAC.
One Warrington Place,
Dublin 2
D02 HH27
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/25/1917/001
EU/1/25/1917/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first 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 II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Regeneron Pharmaceuticals Inc.
81 Columbia Turnpike
Rensselaer, NY 12144
United States

Name and address of the manufacturer responsible for batch release

Regeneron Ireland Designated Activity Company
Raheen Business Park Ballycummin
Limerick
Ireland

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in Article 9 of Regulation (EC) No 507/2006 and, accordingly, the marketing authorisation holder (MAH) shall submit PSURs every 6 months.

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

The MAH shall ensure that in each Member State where LYNOZYFIC is marketed, all patients/carers who are expected to use LYNOZYFIC have access to/are provided with the Patient Card which will inform and explain to patients the risks of cytokine release syndrome (CRS) and immune-effector cell-associated neurotoxicity syndrome (ICANS). The Patient Card also includes a warning message for healthcare professionals treating the patient that the patient is receiving LYNOZYFIC, which may cause CRS or ICANS.

The Patient Card will contain the following key messages:
- A description of the key signs and symptoms of CRS and ICANS
- A description of when to seek urgent attention from the healthcare provider or seek emergency help, should signs and symptoms of CRS or ICANS present themselves
- A reminder that for the first step-up treatment dose of LYNOZYFIC, all patients should be instructed to remain with a caregiver within close proximity of the qualified treatment centre for 24 hours after the end of infusion.
- A reminder for the second step-up treatment dose of LYNOZYFIC, or any subsequent doses, that the treating physician will inform the patient if it is considered necessary for them to remain with a caregiver within close proximity of the qualified treatment centre for 24 hours after the end of infusion.
- The prescribing physician's contact details

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

This being a conditional marketing authorisation and pursuant to Article 14a(4) of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
In order to further characterize the duration of response and long-term safety in subjects with multiple myeloma who have received at least 3 prior therapies, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 antibody, the MAH shall submit the final study report of R5458-ONC-1826, a phase 1/2, open-label, first-in-human study of linvoseltamab monotherapy in participants with RRMM.	January 2027
In order to confirm the efficacy and safety of linvoseltamab indicated as monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least 3 prior therapies, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody, and have demonstrated disease progression on the last therapy; the MAH shall submit the results of study R5458-ONC-2245, an open-label phase 3 randomized active controlled study designed to evaluate the efficacy and safety of linvoseltamab monotherapy versus elotuzumab, pomalidomide and dexamethasone (EPd) in participants with RRMM who have received 1 to 4 prior lines of therapy including a proteasome inhibitor and lenalidomide.	June 2027

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

LYNOZYFIC 5 mg concentrate for solution for infusion
linvoseltamab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 5 mg of linvoseltamab in 2.5 mL at a concentration of 2 mg/mL.

3. LIST OF EXCIPIENTS

Excipients: histidine, histidine hydrochloride monohydrate, sucrose, polysorbate 80, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion
5 mg/2.5 mL
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single-dose only
Read the package leaflet before use.
For intravenous infusion after dilution
Do not shake the vial.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the vial in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Regeneron Ireland DAC
One Warrington Place
Dublin 2, D02 HH27, Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/25/1917/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

LYNOZYFIC 5 mg concentrate for solution for infusion
linvoseltamab
IV after dilution

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

5 mg/2.5 mL

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

LYNOZYFIC 200 mg concentrate for solution for infusion
linvoseltamab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 200 mg of linvoseltamab in 10 mL at a concentration of 20 mg/mL.

3. LIST OF EXCIPIENTS

Excipients: histidine, histidine hydrochloride monohydrate, sucrose, polysorbate 80, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion
200 mg/10 mL
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single-dose only
Read the package leaflet before use.
For intravenous infusion after dilution
Do not shake the vial.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.

Keep the vial in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Regeneron Ireland DAC
One Warrington Place
Dublin 2, D02 HH27, Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/25/1917/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

LYNOZYFIC 200 mg concentrate for solution for infusion
linvoseltamab
IV after dilution

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

200 mg/10 mL

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

LYNOZYFIC 5 mg concentrate for solution for infusion
LYNOZYFIC 200 mg concentrate for solution for infusion
linvoseltamab

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist, or nurse.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What LYNOZYFIC is and what it is used for

LYNOZYFIC is a cancer medicine that contains the active substance linvoseltamab.

Linvoseltamab is used in adults to treat a type of cancer of the bone marrow called multiple myeloma. Linvoseltamab is used on its own in patients who have received at least three previous treatments for their cancer, including an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 antibody, and whose cancer has worsened since receiving the last treatment.

The active substance in LYNOZYFIC, linvoseltamab, is a bispecific monoclonal antibody. It is a type of protein that is designed to recognise and attach to two targets in the body: the B cell maturation antigen (BCMA) on the surface of multiple myeloma cancer cells and CD3 on the surface of T cells (cells in the immune system). By attaching to these target proteins, linvoseltamab brings the cancer cells and T cells together. This activates the T cells, which then kill the multiple myeloma cancer cells.

2. What you need to know before you are given LYNOZYFIC

You must not be given LYNOZYFIC if:

- you are allergic to linvoseltamab, or any of the other ingredients of this medicine (listed in section 6).

If you are not sure if you are allergic, talk to your doctor or nurse before you are given LYNOZYFIC.

Warnings and precautions

Talk to your doctor or nurse before you are given LYNOZYFIC if:
- you have had a seizure in the past 12 months because LYNOZYFIC may cause neurologic side effects.

Tests and checks

Before you are given LYNOZYFIC:
- Your doctor will check your blood for signs of infection. If you have any infection, it will be treated before you start LYNOZYFIC.
- Your doctor will also check if you are pregnant or breast-feeding (see 'Pregnancy and breastfeeding' section in section 2).

During treatment with LYNOZYFIC,
your doctor will monitor you for side effects. Your doctor will regularly check your blood counts, because the number of blood cells and other blood components may go down.

Look out for serious side effects

- Treatment with LYNOZYFIC can cause cytokine release syndrome (CRS). CRS is an immune reaction that may be serious or life-threatening. Seek immediate medical treatment if you develop symptoms of CRS, including: fever, chills, difficulty breathing, fast heartbeat, or feeling dizzy or light-headed.

- Treatment with LYNOZYFIC can cause a serious immune reaction called immune effector cell-associated neurotoxicity syndrome (ICANS). Contact your doctor immediately if you develop symptoms of ICANS, including: trouble speaking, writing, or understanding things, feeling confused or being less alert or aware, feeling disoriented, or seizures.

  Due to the possibility of developing ICANS with LYNOZYFIC, you cannot drive or operate heavy machinery for 24 hours after receiving treatment with the first and second doses of LYNOZYFIC or if you have any symptoms such as feeling tired, dizzy, or confused while receiving treatment with LYNOZYFIC.

- Treatment with LYNOZYFIC can cause serious, life-threatening or fatal infections, including a rare but serious brain infection called progressive multifocal leukoencephalopathy (PML). Contact your doctor immediately if you develop symptoms of infection, including: fever, chills, shivering, fatigue, cough, shortness of breath, fast breathing, fast pulse, clumsiness, weakness, difficulty with walking, changes in vision, memory loss, or difficulty speaking or thinking.

- Treatment with LYNOZYFIC can cause hypogammaglobulinaemia, a condition in which the body does not produce enough immunoglobulins (also known as antibodies), which are important to fight infections.

- Treatment with LYNOZYFIC can cause neutropenia (low levels of neutrophils, a type of white blood cell), which can increase your risk of infection, and febrile neutropenia (low levels of neutrophils with fever).

Tell your doctor or nurse right away if you have any of the side effects listed above during treatment with LYNOZYFIC – see 'Serious side effects' in section 4 for more information. You will also be provided with a patient card which includes information on the side effects of CRS and ICANS that can occur with LYNOZYFIC and how to recognise them. You should carry your patient card at all times and show it to any healthcare professional who is treating you.

Children and adolescents

Do not give LYNOZYFIC to children or adolescents below 18 years of age. This is because LYNOZYFIC has not been studied in this age group.

Other medicines and LYNOZYFIC

Tell your doctor or nurse if you are taking, have recently taken, or might take any other medicines. This includes medicines you can get without a prescription and herbal medicines.

Talk to your doctor or nurse before you are given LYNOZYFIC if you have had a recent vaccination or are going to have a vaccination.

You may receive live vaccines more than four weeks before your first dose of LYNOZYFIC and in the months after stopping treatment with LYNOZYFIC. Your doctor will check if you could receive a live vaccine after stopping treatment.

Pregnancy and breast-feeding
It is not known if LYNOZYFIC affects an unborn baby or if it passes into breast milk. Tell your doctor or nurse before you are given LYNOZYFIC if you are pregnant, think you might be pregnant, or are planning to have a baby. Your doctor may also perform a pregnancy test before giving you LYNOZYFIC.

Contraception
If you could become pregnant, you must use effective contraception during treatment and for at least 5 months after stopping treatment with LYNOZYFIC.

Pregnancy
LYNOZYFIC is not recommended during pregnancy and in women who could become pregnant and are not using contraception. This medicine may harm the unborn baby if it is used during pregnancy. If you become pregnant while being treated with this medicine, tell your doctor or nurse straight away.

Breast-feeding
You should not breast-feed during treatment and for at least 5 months after your last treatment with LYNOZYFIC. This is because it is not known whether any LYNOZYFIC passes into breast milk and could affect the baby.

Driving and using tools or machines
LYNOZYFIC has a major influence on the ability to drive and use machines. Do not drive, use tools, operate heavy machinery, or do things that could pose a danger to yourself:
- for 24 hours after having your first and second doses of LYNOZYFIC, or
- if you get new symptoms such as dizziness or confusion at any time during treatment with LYNOZYFIC (see “Possible side effects” in section 2), or
- if told not to by your doctor.

LYNOZYFIC contains polysorbate 80
The 5 mg vial of linvoseltamab contains 2.5 mg of polysorbate 80 in each 2.5 mL vial which is equivalent to 1 mg/mL.

The 200 mg vial of linvoseltamab contains 10 mg of polysorbate 80 in each 10 mL vial which is equivalent to 1 mg/mL.

Polysorbates may cause allergic reactions. Tell your doctor if you have any known allergies.

3. How LYNOZYFIC is given

LYNOZYFIC will be given to you under the supervision of a doctor experienced in treating multiple myeloma. Follow the treatment schedule explained to you by your doctor. Check with your doctor if you are not sure.

When LYNOZYFIC is given
This medicine is first given at lower doses, called step-up treatment doses, before you are given full treatment doses.
- On Week 1 Day 1, you will be given the first step-up treatment dose of 5 mg
- On Week 2 Day 1, you will be given the second step-up treatment dose of 25 mg
- On Week 3 Day 1, you will be given the first full treatment dose of 200 mg

You will then receive full treatment doses of 200 mg:
- once a week for 10 doses (Week 4 to Week 13)
- and then every other week (Week 14 to Week 24)

If you continue to benefit from LYNOZYFIC after at least 17 treatment doses, your doctor will decide if you continue to receive full treatment doses:
- every 2 weeks or
- every 4 weeks (if your treatment response is very good)

Your doctor may continue your treatment for as long as you continue to respond to LYNOZYFIC or for as long as side effects are not too severe. Your doctor may modify your dose or when you receive LYNOZYFIC if you have certain side effects.

How LYNOZYFIC is given and monitoring
LYNOZYFIC is given into a vein, as a drip (intravenous infusion). Your doctor will adjust the time required for infusion depending on how you respond to treatment.
- Step-up treatment dose 1, step-up treatment dose 2, and the first full treatment dose will be given over 4 hours.
- You should be monitored for potential side effects during administration and for 24 hours after the first infusion.
    - This is to watch for any signs or symptoms of CRS, 'infusion-related reactions' (IRR), or ICANS (see "Look out for serious side effects" section in section 2).
- If you have had CRS, ICANS or any other moderate or severe side effects after the first dose, you should be monitored for 24 hours after the second dose.
- You should plan to stay close to the location where you had your treatment with a caregiver during the 24-hour monitoring period.
- If you do not have any side effects after the step-up treatment doses and the first full treatment dose, your doctor may give the next infusion over 1 hour. If tolerated, your doctor may then give your other infusions over 30 minutes.

Other medicines given before treatment with LYNOZYFIC
You will be given other medicines before each of your first four doses of LYNOZYFIC. These help to lower the chance of side effects, such as cytokine release syndrome or infusion-related reactions. These may include medicines to reduce the risk of:
- an allergic reaction (antihistamines)
- inflammation (corticosteroids)
- fever (such as paracetamol)

You may also be given these medicines for later doses of LYNOZYFIC based on any side effects you have.

You will likely be given additional medicines to lower the chance of getting an infection and/or based on any side effects you have or your medical history.

If you are given more LYNOZYFIC than you should
This medicine will be given by your doctor or nurse, and it is unlikely that you will receive too much. In the event that you are given too much (an overdose), your doctor will check you for side effects.

If you forget your appointment to have LYNOZYFIC
It is very important to go to all your appointments. If you miss an appointment, make another one as soon as possible.

If you have any further questions on the use of this medicine, ask your doctor or nurse.

If you stop receiving LYNOZYFIC
Do not stop treatment with LYNOZYFIC unless you have discussed this with your doctor. This is because stopping your treatment may make your condition worse.

If you have any further questions on the use of this medicine, ask your doctor or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects
Get medical help straight away if you get any of the following serious side effects, which may be severe and can in rare cases be fatal when not treated right and on time.

Very common (may affect more than 1 in 10 people)
- cytokine release syndrome (CRS) - which may include fever, feeling dizzy or light-headed, chills, difficulty breathing, or fast heartbeat,
- lung infection (pneumonia), with symptoms such as cough, fever, difficulty breathing, or chest pain
- COVID-19 infection, with symptoms such as fever, chills, cough, difficulty breathing, sore throat, fatigue, or new loss of taste or smell
- urinary tract infection, with symptoms such as fever, chills, pain or burning feeling when passing urine, increased urge to pass urine, or back pain
- low levels of antibodies called 'immunoglobulins' in the blood (hypogammaglobulinaemia), which may make infections more likely
- low levels of a type of white blood cells (neutropenia) which may make infections more likely – shown in blood tests

Common (may affect up to 1 in 10 people)
- Infusion-related reactions (IRR), which may include fever, feeling dizzy or light-headed, chills, difficulty breathing, or fast heartbeat
- signs of a serious immune reaction called 'immune effector cell-associated neurotoxicity syndrome' (ICANS) - some of the signs are:
  - trouble speaking, writing, or understanding things
  - feeling confused or being less alert or aware
  - feeling disoriented
  - seizures
- low number of a type of white blood cell with a fever (febrile neutropenia)
- severe infection throughout the body (sepsis)
- CMV infection (can cause serious blood and tissue infections)

Uncommon (may affect up to 1 in 100 people)
- progressive multifocal leukoencephalopathy (PML) The symptoms of PML may include clumsiness, weakness, difficulty with walking, changes in vision, memory loss, or difficulty speaking or thinking.

Tell your doctor right away if you notice any of the serious side effects listed above.

Other side effects
Other side effects are listed below. Tell your doctor or nurse if you get any of these side effects.

Very common (may affect more than 1 in 10 people)
- infected nose, sinuses or throat (upper respiratory tract infection)
- low levels of blood platelets (thrombocytopenia) that may make you more likely to bruise or bleed
- low levels of red blood cells (anaemia)
- low number of white blood cells (lymphopenia)
- decreased appetite
- increased levels of uric acid in the blood
- low levels of phosphate (hypophosphataemia)
- trouble sleeping (insomnia)
- change in brain function (encephalopathy)
- pain or muscle aches
- pain
- muscle weakness or changes in muscle movement
- headache
- high blood pressure (hypertension)
- cough
- being short of breath (dyspnoea)
- nasal congestion
- diarrhoea
- constipation
- feeling sick (nausea)
- vomiting
- rash
- swollen hands, ankles, or feet (oedema)
- fever
- feeling very tired (fatigue)
- chills
- increased levels of creatinine in the blood
- weight decreased

Common (may affect up to 1 in 10 people)
- increased level of liver enzymes transaminase in the blood

Reporting of side effects

If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store LYNOZYFIC

LYNOZYFIC will be stored at the hospital or clinic by your doctor.

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and vial after "EXP". The expiry date refers to the last day of that month.

Unopened vial
- Store in a refrigerator (2 °C to 8 °C).
- Do not freeze.
- Keep the vial in the outer carton to protect from light.

Infusion solution
Once prepared, administer diluted solution immediately. Chemical and physical in-use stability has been demonstrated for the diluted infusion solution as follows:
- Up to 8 hours at room temperature (20 to 25 °C) from preparation to the start of the infusion.
- Up to 48 hours under refrigeration at 2 to 8 °C from preparation to the start of the infusion.

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

Protect the infusion solution from light during storage.

Your doctor will dispose of any unneeded medicine appropriately. These measures will help protect the environment.

6. Contents of the pack and other information

The active substance is linvoseltamab.
- Each vial contains 5 mg of linvoseltamab in 2.5 mL (2 mg/mL).
- Each vial contains 200 mg of linvoseltamab in 10 mL (20 mg/mL).

The other ingredients are histidine, histidine hydrochloride monohydrate, sucrose, polysorbate 80, and water for injections (see "LYNOZYFIC contains polysorbate 80" in section 2).

What LYNOZYFIC looks like and contents of the pack

LYNOZYFIC concentrate for solution for infusion is supplied as a clear to slightly opalescent, colourless to pale yellow liquid essentially free of particulates, provided in a glass vial.

LYNOZYFIC is supplied in two strengths (5 mg and 200 mg). Each pack of LYNOZYFIC contains one vial.

Marketing Authorisation Holder

Regeneron Ireland Designated Activity Company (DAC)
One Warrington Place
Dublin 2, D02 HH27
Ireland
Tel: +353 (0) 61 533 400

Manufacturer

Regeneron Ireland DAC
Raheen Business Park Ballycummin
Limerick
Ireland

This leaflet was last revised in

This medicine has been given 'conditional approval'. This means that there is more evidence to come about this medicine. The European Medicines Agency will review new information on this medicine at least every year and this leaflet will be updated as necessary.

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu

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The following information is intended for healthcare professionals only:
Procedures for proper handling and disposal of anticancer medicinal products should be considered.

Instructions for dilution
Use aseptic technique to prepare LYNOZYFIC. Each vial is intended for single-dose only. Discard any unused portion left in the vial.

Do not shake the vial.

Visually inspect for particulate matter and discoloration prior to administration. LYNOZYFIC is a clear to slightly opalescent, colourless to pale yellow liquid that is essentially free from visible particulates. Discard the vial if the solution is cloudy, discoloured, or contains particulate matter.

Withdraw the desired dose from the vial of LYNOZYFIC based on Table 1 and transfer into an intravenous infusion bag of sodium chloride 9 mg/mL (0.9%) solution for injection. LYNOZYFIC is compatible with polyvinyl chloride (PVC) non-di-ethylhexylphthalate (non-DEHP), polyolefin (PO), or ethyl vinyl acetate (EVA) infusion bags. Mix diluted solution by gentle inversion. Do not shake the solution.

Table 1: LYNOZYFIC volumes for addition to infusion bag

LYNOZYFIC dose (mg)	**Amount of LYNOZYFIC per vial (mg)**	**Concentration of vial (mg/mL)**	**Number of vials required**	**Total volume of LYNOZYFIC to prepare dose (mL)**	**Sodium Chloride 9 mg/mL (0.9%) Injection, USP Infusion Bag (PVC or PO) Volume (mL)**
5	5	2	1	2.5	50 or 100
25	5	2	5	12.5	50 or 100
200	200	20	1	10	50 or 100
Modified dose due to adverse event[a]					
2.5	5	2	1	1.25	50
[a] For instructions on when to use the modified dose refer to Table 3, Table 4, and Table 5 of the SmPC.					

After LYNOZYFIC has been diluted as instructed, administer as follows:

- Connect the prepared IV infusion bag containing the final LYNOZYFIC solution to IV tubing constructed of PVC, polyethylene (PE)-lined PVC, or polyurethane (PU). It is recommended to use a 0.2-micron to 5-micron polyethersulfone (PES) filter.
- Prime with LYNOZYFIC to the end of the IV tubing.
- Do not mix LYNOZYFIC with other drugs or concurrently administer other drugs through the same intravenous line.
- Upon completion of LYNOZYFIC infusion, flush the infusion line with adequate volume of sterile sodium chloride 9 mg/mL (0.9%) solution for injection to ensure that the entire contents of the infusion bag are administered.
- Total infusion time should include flushing of the infusion line.

Once prepared, administer diluted solution immediately. Chemical and physical in-use stability has been demonstrated for the diluted infusion solution as follows:

- Up to 8 hours at room temperature (20 to 25 °C) from preparation to the start of the infusion.

- Up to 48 hours under refrigeration at 2 to 8 °C from preparation to the start of the infusion.

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

Protect the infusion solution from light during storage.

Disposal

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

ANNEX IV

CONCLUSIONS ON THE GRANTING OF THE CONDITIONAL MARKETING AUTHORISATION

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.