

▼ 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

Lunsumio 5 mg solution for injection
Lunsumio 45 mg solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Lunsumio 5 mg solution for injection

Each vial contains 5 mg of mosunetuzumab in 0.5 mL at a concentration of 10 mg/mL.

Lunsumio 45 mg solution for injection

Each vial contains 45 mg of mosunetuzumab in 1 mL at a concentration of 45 mg/mL.

Mosunetuzumab is a full-length, humanised anti-CD20/CD3 immunoglobulin (Ig)G1 isotype that is produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology.

Excipient with known effect

Each 5 mg vial contains 0.3 mg of polysorbate 20.
Each 45 mg vial contains 0.6 mg of polysorbate 20.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection

Clear, colourless to slightly brownish-yellow, preservative free liquid and pH 5.8. Osmolality of the 5 mg mosunetuzumab is 260-360 mOsm/kg and osmolality of the 45 mg mosunetuzumab is 275-375 mOsm/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Lunsumio as monotherapy is indicated for the treatment of adult patients with relapsed or refractory follicular lymphoma (FL) who have received at least two prior systemic therapies.

4.2 Posology and method of administration

Lunsumio must only be administered under the supervision of a healthcare professional qualified in the use of anti-cancer therapies, in a setting with appropriate medical support to manage severe reactions such as cytokine release syndrome (CRS) and Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) (see below and section 4.4).

It is important to check the product labels to ensure that the correct formulation (intravenous or subcutaneous fixed dose) is being administered to the patient, as prescribed. Lunsumio subcutaneous formulation is not intended for intravenous administration and should be administered via a subcutaneous injection only.

Posology

Prophylaxis and premedication

Lunsumio subcutaneous injection should be administered to well-hydrated patients.

Table 1 provides details on recommended premedication for CRS.

Table 1 Premedication to be administered to patients prior to Lunsumio subcutaneous injection

Patients requiring premedication	Premedication
Cycles 1 all patients	Intravenous or oral corticosteroids: dexamethasone 20 mg (preferred) or methylprednisolone 80 mg
Cycles 2+: patients who experienced any grade CRS with the previous dose	Anti-histamine ^a : 50-100 mg diphenhydramine hydrochloride or equivalent oral or intravenous anti-histamine
	Anti-pyretic ^a : 500-1000 mg paracetamol

^aAnti-histamines and anti-pyretics are optional in cycle 1 and beyond

The recommended dose of Lunsumio subcutaneous injection for each 21 day-cycle is detailed in Table 2.

Table 2 Dose of Lunsumio subcutaneous injection for patients with relapsed or refractory follicular lymphoma

Day of treatment		Dose of Lunsumio
Cycle 1	Day 1	5 mg
	Day 8	45 mg
	Day 15	45 mg
Cycle 2 and beyond	Day 1	45 mg

Duration of treatment

Lunsumio subcutaneous injection should be administered for 8 cycles, unless a patient experiences unacceptable toxicity or disease progression.

For patients who achieve a complete response, no further treatment beyond 8 cycles is required. For patients who achieve a partial response or have stable disease in response to treatment with Lunsumio subcutaneous injection after 8 cycles, an additional 9 cycles of treatment (17 cycles total) should be administered, unless a patient experiences unacceptable toxicity or disease progression.

Delayed or missed dose

Table 3 Recommendations for restarting therapy with Lunsumio subcutaneous injection after dose delay

Last dose administered	Time since the last dose administered	Action for next dose(s)
5 mg Cycle 1 Day 1	1 week to 2 weeks	Administer 45 mg (Cycle 1 Day 8)*, then resume the planned treatment schedule
	> 2 weeks	Repeat 5 mg (Cycle 1 Day 1)*, then administer 45 mg (Cycle 1 Day 8)* and resume the planned treatment schedule

45 mg Cycle 1 Day 8	1 week to less than 6 weeks	Administer 45 mg (Cycle 1 Day 15)*, then resume the planned treatment schedule
	≥ 6 weeks	Repeat 5 mg*, then administer 45 mg (Cycle 1 Day 15)* 7 days later and resume the planned treatment schedule
45 mg Cycle 1 Day 15	1 week to less than 6 weeks	Administer 45 mg (Cycle 2 Day 1), then resume the planned treatment schedule
	≥ 6 weeks	Repeat 5 mg (Cycle 2 Day 1)*, then administer 45 mg (Cycle 2 Day 8)* followed by 45 mg on Day 1 of subsequent cycles
45 mg Cycle 2 and beyond	3 weeks to less than 6 weeks	Administer 45 mg, then resume the planned treatment schedule
	≥ 6 weeks	Repeat 5 mg* on Day 1 during the next cycle, then administer 45 mg* on Day 8, followed by 45 mg on Day 1 of subsequent cycles

*Administer premedication as per Cycle 1

Note that all references to Cycle and Day are to the nominal Cycle and Day.

Dose modification

Patients who experience grade 3 or 4 reactions (e.g. serious infection, tumour flare, tumour lysis syndrome) should have treatment temporarily withheld until symptoms are resolved (see section 4.4).

Cytokine Release Syndrome

CRS should be identified based on clinical presentation (see section 4.4). Patients should be evaluated and treated for, other causes of fever, hypoxia, and hypotension, such as infections/sepsis. If CRS is suspected, patients should be managed according to the recommendations in Table 4.

Table 4 CRS grading¹ and management

CRS grade	CRS management ²	Next scheduled injection of <u>Lunsumio</u>
Grade 1 Fever $\geq 38^{\circ}\text{C}$	The symptoms should be treated If CRS lasts > 48 hours after symptomatic management: Dexamethasone³ and/or tocilizumab^{4,5} should be considered	Ensure symptoms are resolved for at least 72 hours prior to next dose Consider administration of premedication with antihistamines, anti-pyretic medication, and monitor closely for CRS
Grade 2 Fever $\geq 38^{\circ}\text{C}$ and/or hypotension not requiring vasopressors and/or hypoxia requiring low-flow oxygen ⁶ by nasal cannula or blow-by	The symptoms should be treated If no improvement occurs after symptomatic management: Dexamethasone³ and/or tocilizumab^{4,5} should be considered	The symptoms should be resolved for at least 72 hours prior to next injection Premedication should be maximised as appropriate ⁷ and patients monitored more frequently
Grade 3 Fever $\geq 38^{\circ}\text{C}$ and/or hypotension requiring a vasopressor (with or without vasopressin) and/or hypoxia requiring high flow oxygen ⁸ by nasal cannula, face mask, non-rebreather mask, or Venturi mask	The symptoms should be treated Dexamethasone ³ and tocilizumab ^{4,5} should be administered If CRS is refractory to dexamethasone and tocilizumab: Alternative immunosuppressants⁹ and methylprednisolone 1 000 mg/day intravenously should be administered until clinical improvement	The symptoms should be resolved for at least 72 hours prior to next injection Patients should be monitored more frequently and hospitalised for the next dose Premedication should be maximised as appropriate ⁷ If CRS occurred after 5 mg or 45 mg, the next dose should be 5 mg. The treatment schedule should be resumed after recovery. If CRS Grade 3 occurs with next doses permanently discontinue treatment.

Grade 4 Fever $\geq 38^{\circ}\text{C}$ and/or hypotension requiring multiple vasopressors (excluding vasopressin) and/or hypoxia requiring oxygen by positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation)	• Treatment with Lunsumio subcutaneous injection should be permanently discontinued • The symptoms should be treated • Dexamethasone³ and tocilizumab^{4,5} should be administered If CRS is refractory to dexamethasone and tocilizumab: • Alternative immunosuppressants⁹ and methylprednisolone 1 000 mg/day intravenously should be administered until clinical improvement
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¹ ASTCT = American Society for Transplantation and Cellular Therapy. Premedication may mask fever, therefore if clinical presentation is consistent with CRS, please follow these management guidelines.

² If CRS is refractory to management, consider other causes including haemophagocytic lymphohistiocytosis

³ Dexamethasone should be administered at 10 mg orally every 6 hours (or equivalent) until clinical improvement

⁴ In study GO29781, tocilizumab was administered intravenously at a dose of 8 mg/kg (not to exceed 800 mg per infusion), as needed for CRS management

⁵ If no clinical improvement in the signs and symptoms of CRS occurs after the first dose, a second dose of intravenous tocilizumab 8 mg/kg may be administered at least 8 hours apart (maximum 2 doses per CRS event). Within each time period of 6 weeks of Lunsumio subcutaneous injection treatment, the total amount of tocilizumab doses should not exceed 3 doses

⁶ Low-flow oxygen is defined as oxygen delivered at < 6 L/minute

⁷ Refer to Table 1 for additional information

⁸ High-flow oxygen is defined as oxygen delivered at ≥ 6 L/minute

⁹ Riegler L et al. (2019)

Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) grading and management

ICANS should be identified based on clinical presentation (see Section 4.4). Rule out other causes of neurologic symptoms. If ICANS is suspected, it should be managed according to the recommendations in Table 5.

Table 5 Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)

Grade ^a	Actions
Grade 1 ICE ^b 7-9 or depressed level of consciousness but awakens spontaneously	Withhold Lunsumio subcutaneous injection and monitor neurologic toxicity symptoms until ICANS resolves.^{c,d} Provide supportive therapy and consider neurologic consultation and evaluation.

	Consider a single dose of dexamethasone 10 mg, if not taking other corticosteroids. Consider non-sedating, anti-seizure medicinal products (e.g., levetiracetam) for seizure prophylaxis.
Grade 2 ICE^b 3-6 or depressed level of consciousness but awakens to voice	Withhold Lunsumio subcutaneous injection and monitor neurologic toxicity symptoms until ICANS resolves.^{c,d} Provide supportive therapy and consider neurologic consultation and evaluation. Treat with dexamethasone 10 mg intravenously every 6 hours, if not taking other corticosteroids, until improvement to Grade 1, then taper. Consider non-sedating, anti-seizure medicinal products (e.g., levetiracetam) for seizure prophylaxis.
Grade 3 ICE^b 0-2 or depressed level of consciousness but awakens to tactile stimulus or any clinical seizure that resolves rapidly or focal/local oedema on neuroimaging	Withhold Lunsumio subcutaneous injection and monitor neurologic toxicity symptoms until ICANS resolves.^{d,e} Provide supportive therapy, which may include intensive care, and consider neurologic consultation and evaluation. Treat with dexamethasone 10 mg intravenously every 6 hours, if not taking other corticosteroids, until improvement to Grade 1, then taper. Consider non-sedating anti-seizure medication for seizure prophylaxis until resolution of ICANS. Use anti-seizure medication for seizure management as needed. For recurrent grade 3 ICANS, consider permanently discontinuing Lunsumio subcutaneous injection.
Grade 4 ICE^b is 0 or patient is unarousable or requires vigorous or repetitive tactile stimuli, or life-threatening prolonged seizure (> 5 min) or repetitive seizures without return to baseline or deep focal motor weakness or diffuse cerebral oedema on neuroimaging	Permanently discontinue Lunsumio subcutaneous injection. Provide supportive therapy, which may include intensive care, and consider neurologic consultation and evaluation. Treat with dexamethasone 10 mg intravenously every 6 hours, if not taking other corticosteroids, until improvement to Grade 1, then taper. Alternatively, consider administration of methylprednisolone 1 000 mg per day intravenously

	for 3 days, if symptoms improve, then manage as above. Consider non-sedating anti-seizure medication for seizure prophylaxis until resolution of ICANS. Use anti-seizure medication for seizure management as needed.
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^a American Society for Transplantation and Cellular Therapy (ASTCT) consensus grading criteria.

^b If patient is arousable and able to perform Immune Effector Cell-Associated Encephalopathy (ICE) Assessment, assess: Orientation (oriented to year, month, city, hospital = 4 points); Naming (name 3 objects, e.g., point to clock, pen, button = 3 points); Following Commands (e.g., “show me 2 fingers” or “close your eyes and stick out your tongue” = 1 point); Writing (ability to write a standard sentence = 1 point; and Attention (count backwards from 100 by ten = 1 point). If patient is unarousable and unable to perform ICE Assessment (Grade 4 ICANS) = 0 points.

^c Consider the type of neurologic toxicity before deciding to withhold Lunsumio subcutaneous injection.

^d See *Delayed or missed dose* for guidance on restarting Lunsumio subcutaneous injection after dose delay.

^e Evaluate benefit/risk before restarting Lunsumio subcutaneous injection.

Special populations

Elderly

No dose adjustment of Lunsumio subcutaneous injection is required in patients ≥ 65 years of age (see section 5.2).

Renal impairment

Lunsumio subcutaneous injection has not been studied in patients with severe renal impairment. Dose adjustments are not considered necessary in patients with mild to moderate renal impairment based on pharmacokinetics (see section 5.2).

Hepatic impairment

Lunsumio subcutaneous injection has not been studied in patients with hepatic impairment. Dose adjustments are not considered necessary based on pharmacokinetics (see section 5.2).

Paediatric population

The safety and efficacy of Lunsumio subcutaneous injection in children below 18 years of age have not yet been established.

Method of administration

The 5 mg and 45 mg doses should be administered as subcutaneous injection only. The injection should be administered subcutaneously into the tissue of the abdomen or thigh, changing the site of injection with each dose and never into areas where the skin has tattoos, moles or scars or areas where the skin is red, bruised, tender, hard, or not intact.

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 traceability of biological medicinal products, the trade name and the batch number of the administered product should be clearly recorded.

Cytokine Release Syndrome (CRS)

CRS, including life-threatening reactions, have occurred in patients receiving Lunsumio subcutaneous injection (see section 4.8). Signs and symptoms included pyrexia, hypotension, and hypoxia, CRS events occurred predominantly in cycle 1 and were mainly associated with Day 1 and Day 8 dose administrations. The most frequently reported CRS signs and symptoms in $\geq 10\%$ of patients treated with Lunsumio subcutaneous injection who experienced CRS events of any grade by ASTCT 2019 (36 patients) were pyrexia, hypotension, hypoxia, chills, tachycardia and headache.

Patients should be premedicated with corticosteroids, antipyretics and antihistamines at least through cycle 1. Patients must receive adequate hydration prior to the administration of Lunsumio subcutaneous injection. Patients should be monitored for signs or symptoms of CRS. Patients should be counselled to seek immediate medical attention should signs or symptoms of CRS occur at any time. Physicians should institute treatment with supportive care, tocilizumab and/or corticosteroids as indicated. (see section 4.2).

Serious infections

Serious infections such as pneumonia, bacteraemia, sepsis, septic shock, and opportunistic infections have occurred in patients receiving Lunsumio subcutaneous injection, some of which were life-threatening or fatal events (see section 4.8). Febrile neutropenia was observed in patients after receiving Lunsumio subcutaneous injection. Cases of progressive multifocal leukoencephalopathy (PML) have been reported in patients receiving CD20-directed monoclonal antibodies, including CD3-CD20 bispecific antibodies.

Lunsumio subcutaneous injection should not be administered in the presence of active infections. Caution should be exercised when considering the use of Lunsumio subcutaneous injection in patients with a history of recurring or chronic infections (e.g., chronic, active Epstein-Barr Virus), with underlying conditions that may predispose to infections or who have had significant prior immunosuppressive treatment. Patients should be administered prophylactic antibacterial, antiviral and/or antifungal medicinal products, as appropriate. Patients should be monitored for signs and symptoms of infection, before and after Lunsumio subcutaneous injection administration, and treated appropriately. In the event of febrile neutropenia, patients should be evaluated for infection and managed with antibiotics, fluids and other supportive care, according to local guidelines. Patients should be monitored for new or worsening neurological toxicities. If neurological symptoms suggestive of PML occur during Lunsumio therapy, treatment with Lunsumio should be discontinued and appropriate diagnostic and treatment measures, including consultation with a neurologist, be initiated.

Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)

ICANS have occurred in patients receiving Lunsumio subcutaneous injection, including serious and life threatening reactions. The onset of ICANS can be concurrent with CRS, following resolution of CRS, or in the absence of CRS. Manifestations of ICANS reported in clinical trials included confusional state, lethargy, encephalopathy, depressed level of consciousness, and memory impairment. The majority of cases occurred during Cycle 1.

Patients should be monitored for signs and symptoms of ICANS following Lunsumio subcutaneous injection administration. Patients must be counselled to seek immediate medical attention should signs or symptoms occur at any time (see Patient card below).

Patients should be advised to exercise caution while (or avoid if symptomatic) driving, cycling or using heavy or potentially dangerous machines (see section 4.7).

At the first signs or symptoms of ICANS, manage according to the ICANS guidance provided in Table 5. Treatment with Lunsumio subcutaneous injection should be withheld or discontinued permanently as recommended.

Haemophagocytic lymphohistiocytosis

Haemophagocytic lymphohistiocytosis (HLH), including fatal cases, have been reported in patients receiving Lunsumio. HLH is a life-threatening syndrome characterized by fever, hepatomegaly and cytopenias. HLH should be considered when the presentation of CRS is atypical or prolonged. Patients should be monitored for clinical signs and symptoms of HLH (see Section 4.2). For suspected HLH, Lunsumio must be interrupted and treatment for HLH initiated.

Tumour flare

Tumour flare has been reported in patients treated with Lunsumio subcutaneous injection (see section 4.8). Manifestations included new or worsening pleural effusions, localised pain and swelling at the sites of lymphoma lesions and tumour inflammation. Consistent with the mechanism of action of Lunsumio subcutaneous injection, tumour flare is likely due to the influx of T-cells into tumour sites following Lunsumio subcutaneous injection administration.

There are no specific risk factors for tumour flare that have been identified, however, there is a heightened risk of compromise and morbidity due to mass effect secondary to tumour flare in patients with bulky tumours located in close proximity to airways and/or a vital organ. Patients treated with Lunsumio subcutaneous injection should be monitored and evaluated for tumour flare at critical anatomical sites.

Tumour lysis syndrome (TLS)

TLS can occur in patients receiving Lunsumio subcutaneous injection (see section 4.8). Patients must have adequate hydration prior to the administration of Lunsumio subcutaneous injection. Patients should be administered prophylactic anti-hyperuricemic therapy (e.g. allopurinol, rasburicase), as appropriate. Patients should be monitored for signs or symptoms of TLS, especially patients with high tumour burden or rapidly proliferative tumours, and patients with reduced renal function. Patients should be monitored for blood chemistries and abnormalities should be managed promptly.

Immunisation

Live and/or live-attenuated vaccines should not be given concurrently with Lunsumio subcutaneous injection. Studies have not been conducted in patients who recently received live vaccines.

Patient card

The prescriber must discuss the risks of Lunsumio therapy with the patient. The patient should be provided with the patient card and instructed to carry it at all times. The patient card describes the common signs and symptoms of CRS and ICANS, including instructions on when a patient should seek medical attention.

Excipient with known effect

This medicinal product contains polysorbate 20. Each vial of Lunsumio 5 mg solution for injection contains 0.3 mg of polysorbate 20, and each vial of Lunsumio 45 mg solution for injection contains 0.6 mg of polysorbate 20, which is equivalent to 0.6 mg/mL. Polysorbates may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

A transient clinically relevant effect on CYP450 substrates with a narrow therapeutic index (e.g. warfarin, voriconazole, cyclosporine, etc) cannot be excluded, since initiation of Lunsumio subcutaneous injection treatment causes a transient increase in cytokine levels which may cause inhibition of CYP450 enzymes. On initiation of Lunsumio subcutaneous injection therapy in patients being treated with CYP450 substrates with a narrow therapeutic index, therapeutic monitoring should be considered. The dose of the concomitant medicinal product should be adjusted as needed.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception

Women of childbearing potential should use effective contraception while receiving Lunsumio subcutaneous injection and for at least 3 months after the last injection of Lunsumio subcutaneous injection.

Pregnancy

There are no data from the use of Lunsumio subcutaneous injection in pregnant women. Animal studies are insufficient with respect to reproductive toxicity (see section 5.3). Lunsumio subcutaneous injection is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding

It is unknown whether mosunetuzumab/metabolites are excreted in human milk. A risk to newborns/infants cannot be excluded. Breast-feeding should be discontinued during treatment with Lunsumio subcutaneous injection.

Fertility

No human data on fertility are available. No impairments were observed in male or female reproductive organs in the 26-week toxicity studies with cynomolgus monkeys at exposures (AUC) similar to exposure (AUC) in patients receiving the recommended dose.

4.7 Effects on ability to drive and use machines

Lunsumio subcutaneous injection has a major influence on the ability to drive and use machines. Due to the potential for ICANS, patients receiving Lunsumio subcutaneous injection are at risk of depressed level of consciousness (see section 4.4). Due to the potential for ICANS, patients should be advised to exercise caution while (or avoid if symptomatic) driving, cycling or using heavy or potentially dangerous machines.

4.8 Undesirable effects

Summary of safety profile

The adverse reactions described in this section were identified from the pivotal clinical trial GO29781 in patients treated at the recommended intravenous dose (n=218) and the recommended subcutaneous dose (n=139). Patients had follicular lymphoma (51.8%), diffuse large B-cell lymphoma (26.9%), transformed follicular lymphoma (9.8%) mantle cell lymphoma (7.3%), Richter's transformation (3.9%), and other histologies (0.3%). The median number of cycles of Lunsumio subcutaneous received was 8 (range 1 -17), 47.5% of patients received 8 cycles, and 16.6% received more than 8 cycles up to 17 cycles.

Patients who received the recommended intravenous dose (n=218) and subcutaneous (n=139) dose are pooled (n=357) for this safety population. In this pooled safety population, the most common adverse reactions ($\geq 20\%$) observed were cytokine release syndrome, neutropenia, rash and upper respiratory tract infection and injection site reactions in those treated with subcutaneous mosunetuzumab. The most common serious adverse reactions ($\geq 2\%$) observed included cytokine release syndrome (CRS) (17% by ASTCT grading system), pyrexia (3%), sepsis (3%), upper respiratory tract infection (3%) and pneumonia (5%). Permanent discontinuation of Lunsumio due to an adverse reaction occurred in 5.8% (21/357) of patients. In patients who received the recommended subcutaneous dose (n=139), the adverse reactions that led to discontinuation in more than one patient were COVID-19 1.4% (2/139) and COVID-19 pneumonia 3.6% (5/139).

Tabulated list of adverse reactions

The adverse reactions are listed below by MedDRA system organ class (SOC) and categories of frequency. Frequency categories are defined as very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1\,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$) and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 6 Adverse reactions occurring in patients treated with Lunsumio

System organ class / preferred term or adverse reaction	All grades ²²	Grade 3 – 4
Infections and infestations		
Upper respiratory tract infection ¹	Very common	Common
Viral infection ²	Common	Uncommon
Urinary tract infection ³	Common	Common
Pneumonia ⁴	Common	Common
Lower respiratory tract infection ⁵	Common	Uncommon
Sepsis ⁶	Common	Common
Fungal infection ⁷	Common	Uncommon
Bacterial infection ⁸	Uncommon	Uncommon
Neoplasms benign, malignant and unspecified (including cysts and polyps)		
Tumour flare ⁹	Common	Uncommon
Blood and lymphatic system disorders		
Neutropenia ¹⁰	Very common	Very common
Anaemia	Very common	Common
Thrombocytopenia ¹¹	Very common	Common
Febrile neutropenia	Common	Common
Immune system disorders		

System organ class / preferred term or adverse reaction	All grades²²	Grade 3 – 4
Cytokine release syndrome ¹²	Very common	Common
Haemophagocytic lymphohistiocytosis ^{13,20}	Uncommon	Uncommon
Metabolism and nutrition disorders		
Hypophosphataemia ¹⁴	Very common	Very common
Hypokalaemia ¹⁵	Very common	Common
Hypomagnesaemia ¹⁶	Common	Very rare
Tumour lysis syndrome	Uncommon	Uncommon
Nervous system disorders		
Headache ¹⁷	Very common	Uncommon
Dizziness ¹⁸	Common	Very rare
Immune effector cell-associated neurotoxicity syndrome ^{19,20}	Common	Very rare
Gastrointestinal disorders		
Diarrhoea	Very common	Uncommon
Nausea	Very common	Uncommon
Skin and subcutaneous tissue disorders		
Rash ²¹	Very common	Common
Pruritus	Very common	Very rare
Dry skin	Very common	Very rare
Skin exfoliation	Common	Very rare
General disorders and administration site conditions		
Pyrexia	Very common	Common
Chills	Very common	Uncommon
Injection site reactions	Very common	Very rare
Investigations		
Alanine aminotransferase, increased	Common	Common
Aspartate aminotransferase, increased	Common	Common

¹ Upper respiratory tract infection includes upper respiratory tract infection, nasopharyngitis, sinusitis, respiratory tract infection, viral upper respiratory tract infection, rhinovirus infection, viral sinusitis, respiratory tract infection viral, and COVID-19

² Viral infection includes cytomegalovirus infection, cytomegalovirus infection reactivation, Epstein-Barr virus

infection reactivation, ophthalmic herpes simplex and herpes zoster reactivation

³ Urinary tract infection (UTI) includes UTI, pyelonephritis acute, and Escherichia UTI

⁴ Pneumonia includes pneumonia and COVID-19 pneumonia

⁵ Lower respiratory tract infection includes lower respiratory tract infection and bronchitis

⁶ Sepsis includes sepsis and septic shock,

⁷ Fungal infection includes Candida sepsis and *Pneumocystis jirovecii* pneumonia

⁸ Bacterial infection includes sinusitis bacterial and bacteraemia

⁹ Tumour flare includes tumour flare, pleural effusion, tumour inflammation and flank pain

¹⁰ Neutropenia includes neutropenia and neutrophil count decreased

¹¹ Thrombocytopenia includes thrombocytopenia and platelet count decreased

¹² By American Society for Transplantation and Cellular Therapy

¹³ Haemophagocytic lymphohistocytosis (HLH) includes HLH

¹⁴ Hypophosphatemia includes hypophosphatemia and blood phosphorus decreased

¹⁵ Hypokalemia includes hypokalemia and blood potassium decreased

¹⁶ Hypomagnesemia includes hypomagnesemia and blood magnesium decrease

¹⁷ Headache includes headache, migraine and head discomfort

¹⁸ Dizziness includes dizziness and vertigo

¹⁹ Consistent with the medical concept of ICANS according to American Society for Transplantation and Cellular Therapy and includes confusional state, ICANS, lethargy, encephalopathy, depressed level of consciousness, and memory impairment

²⁰ The frequency calculation is based on additional clinical studies

²¹ Rash includes rash, rash erythematous, exfoliative rash, rash macular, rash maculo-papular, rash pruritic, rash pustular, erythema, palmar erythema, dermatitis, dermatitis acneiform, dermatitis contact, palmar-planta erythrodysesthesia and rash morbilliform

²² Fatal outcome occurred for terms HLH, COVID-19, COVID-19 pneumonia, and septic shock in Lunsumio subcutaneous injection and for terms pneumonia and sepsis in Lunsumio intravenous infusion

Description of selected adverse reactions

Cytokine release syndrome (CRS)

CRS (ASTCT grading system) of any grade occurred in 26% (36/139) of patients, with grade 2 occurring in 7.2%, grade 3 occurring in 1.4% treated with Lunsumio subcutaneous injection.

CRS of any grade occurred in 15.8% of patients after the Cycle 1, Day 1 dose; 11.7% after the Cycle 1, Day 8 dose; 2.2% after the Cycle 1, Day 15 dose, 0.8% occurred in patients after the Cycle 2 and 0% in Cycles 3 and beyond. The median time to CRS onset from the start of administration in Cycle 1 Day 1 was 17.62 hours (range: 7.2-33.4 hours), Cycle 1 Day 8 was 51.5 hours (range: 30.3-112.5 hours), Cycle 1 Day 15 was 46.7 hours (range: 23.2-61.5 hours), and Cycle 2 Day 1 was 34.85 hours (range: 34.8-34.8 hours). CRS resolved in all patients, and the median duration of CRS events was 2 days (range 1-15 days).

Of the 36 patients that experienced CRS, the most common signs and symptoms of CRS included pyrexia (97.2%), hypotension (22%), hypoxia (19.4%), chills (13.9%), headache (11.1%) and tachycardia (11.1%).

Tocilizumab and/or corticosteroids were used to manage a CRS event in 12% of patients: 5.7% received tocilizumab alone, 4.3% received corticosteroids alone, and 1.4% received both tocilizumab and corticosteroids. Patients with grade 3 CRS received tocilizumab, corticosteroids, vasopressors and/or oxygen supplementation.

Hospitalisations due to CRS occurred in 11.5% of patients and the median duration of hospitalisation for serious CRS events was 4.0 days (range 1-34 days).

Neutropenia

In patients treated with Lunsumio intravenous infusion or subcutaneous injection, neutropenia of any grade occurred in 26.1% (93/357) of patients, including 22.7% Grade 3-4 events. The median time to onset of first neutropenia/neutrophil count decreased events was 50 days (range: 1-280 days), with

median duration of 8 days (range: 1-487 days). Of the 93 patients who had neutropenia/neutrophil count decreased events 68% (63/93) received treatment G-CSF to treat the events.

Serious infections

In patients treated with Lunsumio intravenous infusion or subcutaneous injection, serious infections of any grade occurred in 17% (60/357) of patients. Five (1.4%) of patients experienced serious infections concurrently with grade 3-4 neutropenia. The median time to onset of first serious infection was 92 days (range: 1-408 days), with median duration of 15.5 days (range: 2-174 days). Grade 5 events occurred in 2.5% (9/357) of patients, which included COVID-19 pneumonia, COVID-19, pneumonia, septic shock and sepsis.

Opportunistic Infections

In patients treated with Lunsumio intravenous infusion or subcutaneous injection, opportunistic infections of any grade occurred in 3.1% (11/357) of patients. Pneumocystis jirovecii pneumonia was reported in 5 patients (1.4%), with 2 patients (0.6%) experiencing Grade 3 events. Cytomegalovirus infection/reactivation were reported in 4 patients (1.1%), with 2 patients (0.6%) experiencing Grade 3 cytomegalovirus infection reactivation.

Immune Effector Cell-Associated Neurotoxicity Syndrome

Across a broader clinical trial population, Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) occurred in 2.1% (20/949) of patients, 19 patients had Grade 1-2 events and 1 patient had Grade 3 event. The majority of events occurred during the first cycle of treatment. The majority of cases resolved. The median time to onset from initial dose was 17 days (range: 1 to 48 days). The median duration was 3 days (range: 1-20 days). Immune Effector Cell-Associated Encephalopathy (ICE) scoring was not systematically performed across the referenced trial population.

Tumour flare

In patients treated with Lunsumio intravenous infusion or subcutaneous injection, tumour flare (including pleural effusion and tumour inflammation) occurred in 3.1% (11/357) of patients, which included 1.4% grade 2 and 1.4% grade 3 events. The median time to onset was 13 days (range 2-84 days), and median duration was 36 days (range 15-105 days).

Tumour Lysis Syndrome (TLS)

In patients treated with Lunsumio intravenous infusion or subcutaneous injection, TLS occurred in 0.6% (2/357) of patients, concurrent with CRS. One patient with follicular lymphoma was in the leukemic phase who experienced Grade 4 TLS. TLS onset was on days 2 and 24, and resolved within 3 and 6 days, respectively.

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 (see details below).

Ireland

HPRA Pharmacovigilance

Website: www.hpra.ie

Malta

ADR Reporting Website: <https://medicinesauthority.gov.mt/adrportal>

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; Other monoclonal antibodies and antibody drug conjugates, ATC code: L01FX25

Mechanism of action

Mosunetuzumab is an anti-CD20/CD3 T-cell engaging bispecific antibody targeting CD20-expressing B-cells. It is a conditional agonist; targeted B-cell killing is observed only upon simultaneous binding to CD20 on B-cells and CD3 on T-cells. Engagement of both arms of mosunetuzumab results in the formation of an immunologic synapse between a target B-cell and a cytotoxic T cell leading to T-cell activation. Subsequent directed release of perforin and granzymes from T-cell activation through the immunologic synapsis induce B-cell lysis leading to cell death.

Lunsumio subcutaneous injection caused B-cell depletion (defined as CD19 B-cell counts < 5 cells/uL) after the initial cycle of administration (by Cycle 2 Day 1) by both intravenous and subcutaneous administration routes in a majority of patients (95.2% and 94.1% respectively) and depletion was maintained throughout the duration of treatment.

Clinical efficacy and safety

Relapsed or refractory B-cell Non-Hodgkin's lymphoma

An open-label, multicenter, multi-cohort study (GO29781) was conducted to evaluate Lunsumio SC in patients with relapsed or refractory B-cell non-Hodgkin's lymphoma. In the follicular lymphoma (FL) subcutaneous cohort (n=94), patients with relapsed or refractory FL (grade 1-3A) were required to have received at least two prior systemic therapies, including an anti-CD20 monoclonal antibody and an alkylating agent.

The study excluded patients with active autoimmune disease, active infections (i.e. chronic active EBV, acute or chronic hepatitis C, hepatitis B, HIV), progressive multifocal leukoencephalopathy, a history of CNS lymphoma, a history of macrophage activation syndrome/haemophagocytic lymphohistiocytosis, prior allogeneic stem cell transplant, or prior organ transplantation.

Patients received Lunsumio subcutaneously in a 21-day Cycle as follows:

- Cycle 1 Day 1: 5 mg
- Cycle 1 Day 8: 45 mg
- Cycle 1 Day 15: 45 mg
- Cycle 2 and beyond Day 1: 45 mg

The median number of cycles was 8, 63% received 8 cycles, and 14.9% received more than 8 cycles up to 17 cycles.

The median age was 65 years (range 35 to 84 years) with 50% being > age 65, and 12.8% being ≥ age 75. Fifty-six percent were male, 85% were white, 11% were Asian, 2% were Black, 100% had an ECOG performance status of 0 or 1 and 25% of patients had bulky disease (at least one lesion > 6 cm). The median number of prior therapies was 3 (range: 2-9), with 47% receiving 2 prior therapies, 19 % receiving 3 prior therapies and 34% receiving more than 3 prior therapies.

All patients received prior anti-CD20 and alkylator therapies, 20% received autologous stem cell transplant, 12% received PI3K inhibitors, 16% received prior rituximab plus lenalidomide therapy, and 4% received CAR-T therapies. Sixty-seven percent of patients were refractory to prior anti-CD20 monoclonal antibody therapy and 46% were refractory to both anti-CD20 monoclonal antibody and alkylator therapy. Sixty-three percent of patients were refractory to the last prior therapy and 44% had progression of disease within 24 months of first systemic therapy.

The primary objective in this cohort was to demonstrate pharmacokinetic non-inferiority (PKNI) of Lunsumio subcutaneous injection compared to Lunsumio intravenous infusion based on the exposure endpoints of AUC_{0-84 days}, and C_{trough}(Cycle 3). The efficacy results are summarised in Table 7.

Table 7 Summary of efficacy in patients with relapsed/refractory FL

Efficacy parameter	Lunsumio subcutaneous injection N=94
Median observation time 20.7 months (range 1 – 34 months)	
Complete response (CR), n (%) , (95% CI)	55 (58.5) (47.9, 68.6)
Objective response rate (ORR), n (%) (95% CI)	70 (74.5) (64.4, 82.9)
Partial response (PR) n (%) (95% CI)	15 (16.0) (9.2, 25.0)
Duration of response (DOR)¹	N=70
Patients with event, n (%)	26 (37.1)
Median, months (95% CI)	22.4 (16.8, 22.8)
K-M event-free proportion, 12 months (95% CI)	69.9 (58.5, 81.4)
18 months (95% CI)	59.6 (45.8, 73.3)
Duration of complete response (DOCR)²	N=55
Patients with event, n (%)	19 (34.5)
Median, months (95% CI)	20.8 (18.8, NR)
K-M event-free proportion, 12 months (95% CI)	72.4 (59.9, 84.8)
18 months (95% CI)	65.6 (51.0, 80.2)

CI=confidence interval; K-M=Kaplan-Meier; NR=not reached.

Clinical Cut-off: 01 February 2024

¹ DOR is defined as the time from the initial occurrence of a documented PR or CR until the patient experiences an event (documented disease progression or death due to any cause, whichever occurs first).

² DOCR is defined as the time from the initial occurrence of a documented CR until the patient experiences an event (documented disease progression or death due to any cause, whichever occurs first).

The median follow-up for DOR was 16.0 months. Additional exploratory efficacy outcomes included the median time to first response (2.8 months, range: 1-16) and the median time to first complete response (2.9 months, range: 1-14).

Immunogenicity

The immunogenicity of mosunetuzumab was evaluated using an enzyme-linked immunosorbent assay (ELISA). No patients tested positive for anti-mosunetuzumab antibodies in 216 ADA-evaluable patients who received Lunsumio single-agent subcutaneous treatments in Groups D and F of Study GO27981. Based on the available information, the clinical relevance of anti-mosunetuzumab antibodies could not be assessed.

Paediatric population

The European Medicines Agency has deferred the obligation to submit results of studies with Lunsumio in one or more subsets of the paediatric population in treatment of mature B-cell neoplasms (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

The Lunsumio subcutaneous monotherapy dosing regimen of 5/45/45 mg was found to be pharmacokinetically non-inferior to the Lunsumio intravenous infusion 1/2/60/30 mg monotherapy dosing regimen in relapsed or refractory follicular lymphoma patients with ≥ 2 prior therapies. The subcutaneous intravenous geometric mean ratio (90% CI) was 1.39 (1.20 - 1.61) for $C_{\text{troughCYC3_OBS}}$ and 1.06 (0.92 - 1.21) for AUC_{0-84} .

Similar to Lunsumio intravenous infusion, Lunsumio subcutaneous injection pharmacokinetic exposure increased in an approximately dose-proportional manner over the dose ranges studied. As compared to the intravenous route, the subcutaneous route maintained a high relative bioavailability, and had a slower absorption resulting in a lower C_{max} , and delayed T_{max} .

After the first cycle (i.e. 21 days) of the dosing with mosunetuzumab, the serum concentration reaches the C_{max} before the start of Cycle 2 Day 1 of the mosunetuzumab subcutaneous dosing regimen with an average maximum concentration of 3.81 $\mu\text{g/mL}$ and %CV of 53.9%. Pharmacokinetic exposures are summarized in Table 8.

Table 8 Exposure parameters of mosunetuzumab subcutaneous injection

	Model-predicted AUC (day·$\mu\text{g/mL}$)¹	Model-predicted C_{max} ($\mu\text{g/mL}$)¹	Model-predicted C_{trough} ($\mu\text{g/mL}$)¹
Cycle 1 (0 - 21 days)	36.7 (57.0)	3.81 (53.9)	3.45 (54.1)
Cycle 2 (21 - 42 days)	82.3 (50.9)	5.16 (50.3)	2.52 (55.7)
Steady-state ²	72.8 (34.5)	4.40 (36.7)	2.41 (34.2)

¹ Values are geometric mean with geometric CV%

² Steady-state values are approximated at Cycle 4 (63 – 84 days)

Absorption

Lunsumio is administered subcutaneously. T_{max} was reached around 4 to 7 days. Relative bioavailability (F) of the subcutaneous injection regimen relative to the intravenous infusion regimen at steady state was 0.898 (95% CI: 0.828 – 0.975).

Distribution

The population estimate of central volume of distribution for mosunetuzumab was 5.49 L with intravenous infusion and subcutaneous injection of Lunsumio. Because mosunetuzumab is an antibody, protein binding studies were not conducted.

Biotransformation

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

Elimination

Based on a population pharmacokinetic analysis, when administered intravenously, the estimated mean CL_{ss} and baseline clearance (CL_{base}) were 1.08 L/day and 0.584 L/day, respectively. The terminal half-life for mosunetuzumab subcutaneous was 16.8 days at steady state based on population pharmacokinetic PK model estimates.

Elderly

Age did not have an effect on the pharmacokinetics of mosunetuzumab based on a population pharmacokinetic analysis with patients aged 18 - 88 years (n=228). No effect age related effect on subcutaneous absorption of mosunetuzumab was observed for patients in this age groups.

Bodyweight

Like other therapeutic proteins, bodyweight was positively associated with mosunetuzumab estimated clearance and volume of distribution. However, based on exposure-response analysis and clinical exposure margins, considering the exposures in patients at either “low” (<50 kg) or “high” (≥ 112 kg) weight, no dose adjustment is required due to patient bodyweight.

Gender

Based upon population pharmacokinetic analysis, steady-state clearance of mosunetuzumab is marginally lower in females (~13%) compared to males. No dose adjustment is required due to gender, based on exposure-response analysis.

Race

Race (Asian vs. non-Asian) was not identified as a covariate influencing mosunetuzumab pharmacokinetics.

Renal impairment

No dedicated studies have been conducted to determine the effect of renal impairment on the pharmacokinetics of mosunetuzumab. The renal elimination of intact mosunetuzumab, an IgG monoclonal antibody, is expected to be low and of minor importance.

The population pharmacokinetic PK analysis of mosunetuzumab subcutaneous administration showed that creatinine clearance (CrCl) does not affect pharmacokinetics of mosunetuzumab. Pharmacokinetics of mosunetuzumab in patients with mild (CrCl 60 to 89 mL/min, n=92) or moderate (CrCl 30 to 59 mL/min, n=41) renal impairment were similar to those in patients with normal renal function (CrCl ≥ 90 mL/min, n=88). Pharmacokinetic data in patients with severe renal impairment (CrCl 15 to 29 mL/min) is limited (n=1), therefore no dose recommendations can be made. Lunsumio

subcutaneous injection was not studied in patients with end-stage renal disease and/or who are on dialysis.

Hepatic impairment

No specific studies have been conducted to determine the effect of hepatic impairment on the pharmacokinetics of mosunetuzumab. IgGs are mainly eliminated via intracellular catabolism and hepatic impairment is not expected to influence clearance of mosunetuzumab.

The population PK analysis of mosunetuzumab showed that hepatic impairment does not affect pharmacokinetics of mosunetuzumab. Pharmacokinetics of mosunetuzumab in patients with mild hepatic impairment (total bilirubin > ULN to $1 \times$ ULN or AST > ULN, n=35) were similar to those in patients with normal hepatic function (n=191). The number of patients with moderate (total bilirubin > 1.5–3 x ULN, any AST, n=1) or severe (total bilirubin > 3–10 x ULN, any AST, n=2) hepatic impairment is limited.

Paediatric population

No studies have been conducted to investigate the pharmacokinetics of mosunetuzumab in the paediatric population (< 18 years old).

5.3 Preclinical safety data

Systemic toxicity

Key nonclinical findings with mosunetuzumab identified in single- and repeat-dose toxicity studies up to 26-weeks in duration included transient post-dose CRS primarily limited to the first dose, vascular/perivascular inflammatory cell infiltrates that were primarily in the CNS and infrequently in other organs that were likely secondary to cytokine release and immune cell activation, and increased susceptibility to infection following chronic dosing due to sustained B-cell depletion.

All of the findings were considered pharmacologically-mediated effects and reversible. Across studies there was a single incidence of convulsion in one animal at C_{max} and AUC exposures (time-averaged over 7 days) of 3.3- and 1.8- fold higher, respectively, than those in patients receiving Lunsumio at the recommended dose and schedule in Study GO29781.

Impairment of fertility

An assessment of the male and female reproductive organs was included in a 26-week chronic toxicity study in sexually mature cynomolgus monkeys administered by intravenous infusion. Mosunetuzumab had no effect on either male or female reproductive organs at exposures (AUC) similar to exposure (AUC) in patients receiving the recommended dose.

Reproductive toxicity

No developmental toxicity studies in animals have been conducted with mosunetuzumab. Based on low placental transfer of antibodies during the first trimester, the mechanism of action and available data of mosunetuzumab, and the data on the anti-CD20 antibody class, the risk for teratogenicity is low. Studies with mosunetuzumab in non-pregnant animals have demonstrated that prolonged B-cell depletion can lead to increased risk of opportunistic infection, which may cause foetal loss. Transient CRS associated with Lunsumio administration may also be harmful to pregnancy.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

L-histidine

L-methionine
Acetic acid (pH adjustment)
Sucrose
Polysorbate 20 (E 432)
Water for injections

6.2 Incompatibilities

No incompatibilities between Lunsumio Subcutaneous formulation and polypropylene or polycarbonate syringe material or stainless- steel transfer and injection needles and polyethylene Luer cone stoppers have been observed.

6.3 Shelf life

Unopened vial

3 years

Prepared Syringe

Once transferred from the vial to the syringe, Lunsumio solution for injection should be injected immediately because the medicine does not contain any antimicrobial-preservative. If not used immediately, in-use storage times and conditions are the responsibility of the user and would normally not be longer than 24 hours at 2-8°C, unless preparation has taken place in controlled and validated aseptic conditions.

If Lunsumio solution for injection is transferred from the vial to the syringe in a controlled and validated aseptic conditions, the medicine in the capped syringe can be stored in the refrigerator at 2°C to 8°C for up to 28 days protected from light and/or at 9°C to 30°C for up to 24 hours at ambient light.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).

Do not freeze.

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

For storage conditions, see section 6.3.

6.5 Nature and contents of container

5 mg solution for injection

Type I glass-vial with a fluororesin-laminated rubber stopper and an aluminium seal with a plastic brown flip-off cap containing 5 mg of solution for injection.

Pack of one vial.

45 mg solution for injection

Type I glass-vial with a fluororesin-laminated rubber stopper and an aluminium seal with a plastic lavender flip-off cap containing 45 mg of solution for injection.

Pack of one vial.

6.6 Special precautions for disposal and other handling

General precaution

To prevent medication errors, check the vial labels to ensure that the drug being prepared and administered is Lunsumio for subcutaneous injection and not Lunsumio for intravenous infusion.

Lunsumio contains no preservative and is intended for single-dose only. Proper aseptic technique throughout the handling of this medicinal product should be followed. Do not shake.

Lunsumio subcutaneous injection should be inspected visually to ensure there is no particulate matter or discolouration prior to administration. The vial should be discarded if particulate matter is present.

Each Lunsumio vial is ready-to-use for one subcutaneous injection and should not be diluted. The Lunsumio subcutaneous injection solution should be withdrawn using an appropriately sized transfer needle (18G to 21G recommended). The transfer needle should be removed and an appropriately sized injection needle (25G to 30G recommended) should be attached. The smallest syringe that can accurately deliver the injection volume should be used.

The peel-off label from the leaflet should be applied to the syringe.

Disposal

The release of pharmaceuticals into the environment should be minimised. Medicinal products should not be disposed of via wastewater and disposal through household waste should be avoided.

The following points should be strictly adhered to regarding the use and disposal of syringes and other medicinal sharps:

- Needles and syringes should never be reused.
- Place all used needles and syringes into a sharps container (puncture-proof disposable container).

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

7. MARKETING AUTHORISATION HOLDER

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

8. MARKETING AUTHORISATION NUMBERS

EU/1/22/1649/003
EU/1/22/1649/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 3 June 2022
Date of latest renewal: 21 May 2026

10. DATE OF REVISION OF THE TEXT

18 September 2026

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