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

Lunsumio 1 mg concentrate for solution for infusion
Lunsumio 30 mg concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Lunsumio 1 mg concentrate for solution for infusion

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

Lunsumio 30 mg concentrate for solution for infusion

Each vial contains 30 mg of mosunetuzumab in 30 mL at a concentration of 1 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 1 mg vial contains 0.6 mg of polysorbate 20.
Each 30 mg vial contains 18 mg of polysorbate 20.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

Clear, colourless liquid, pH 5.8 and osmolality of 240-356 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 intravenous formulation is not intended for subcutaneous administration and should be administered via intravenous infusion only.

Posology
Prophylaxis and premedication

Lunsumio should be administered to well-hydrated patients.

Table 1 provides details on recommended premedication for CRS and infusion related reactions.

Table 1 Premedication to be administered to patients prior to Lunsumio infusion

Patients requiring premedication	**Premedication**	**Administration**
Cycles 1 and 2: all patients Cycles 3 and beyond: patients who experienced any grade CRS with previous dose	Intravenous corticosteroids: dexamethasone 20 mg (preferred) or methylprednisolone 80 mg	Complete at least 1 hour prior to Lunsumio infusion
	Anti-histamine: 50-100 mg diphenhydramine hydrochloride or equivalent oral or intravenous anti-histamine	At least 30 minutes prior to Lunsumio infusion
	Anti-pyretic: 500-1000 mg paracetamol	

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

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

Day of treatment		**Dose of Lunsumio**	**Rate of infusion**
Cycle 1	Day 1	1 mg	Infusions of Lunsumio in Cycle 1 should be administered over a minimum of 4 hours.
	Day 8	2 mg	
	Day 15	60 mg	
Cycle 2	Day 1	60 mg	If the infusions were well-tolerated in Cycle 1, subsequent infusions of Lunsumio may be administered over 2 hours.
Cycles 3 and beyond	Day 1	30 mg	

Duration of treatment

Lunsumio 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 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 intravenous infusion after dose delay

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

Last dose administered	Time since the last dose administered	Action for next dose(s)
2 mg Cycle 1 Day 8	1 to 2 weeks	Administer 60 mg (Cycle 1 Day 15), then resume the planned treatment schedule.
	Greater than 2 weeks to less than 6 weeks	Repeat 2 mg (Cycle 1 Day 8), then administer 60 mg (Cycle 1 Day 15) and resume the planned treatment schedule.
	Greater than or equal to 6 weeks	Repeat 1 mg (Cycle 1 Day 1) and 2 mg (Cycle 1 Day 8), then administer 60 mg (Cycle 1 Day 15) and resume the planned treatment schedule.
60 mg Cycle 1 Day 15	1 week to less than 6 weeks	Administer 60 mg (Cycle 2 Day 1), then resume the planned treatment schedule.
	Greater than or equal to 6 weeks	Repeat 1 mg (Cycle 2 Day 1) and 2 mg (Cycle 2 Day 8), then administer 60 mg (Cycle 2 Day 15), followed by 30 mg (Cycle 3 Day 1) and then resume the planned treatment schedule.
60 mg Cycle 2 Day 1	3 weeks to less than 6 weeks	Administer 30 mg (Cycle 3 Day 1), then resume the planned treatment schedule.
	Greater than or equal to 6 weeks	Repeat 1 mg (Cycle 3 Day 1) and 2 mg (Cycle 3 Day 8), then administer 30 mg (Cycle 3 Day 15)*, followed by 30 mg (Cycle 4 Day 1) and then resume the planned treatment schedule.
30 mg Cycle 3 onwards	3 weeks to less than 6 weeks	Administer 30 mg, then resume the planned treatment schedule.
	Greater than or equal to 6 weeks	Repeat 1 mg on Day 1 and 2 mg on Day 8 during the next cycle, then administer 30 mg on Day 15*, followed by 30 mg on Day 1 of subsequent cycles.

*For the Day 1, Day 8, and Day 15 doses in the next cycle, administer premedication as per Table 1 for all patients
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. Infusion related reactions (IRR) may be clinically indistinguishable from manifestations of CRS. If CRS or IRR is suspected, patients should be managed according to the recommendations in Table 4.

Table 4 CRS grading[1] and management

CRS grade	CRS management[2]	Next scheduled infusion of Lunsumio
Grade 1 Fever ≥ 38ºC	If CRS occurs during infusion: • The infusion should be interrupted and symptoms treated • The infusion should be re-started at the same rate once the symptoms resolve	The symptoms should be resolved for at least 72 hours prior to next infusion The patient should be monitored more frequently

	• If symptoms recur with re-administration, the current infusion should be discontinued If CRS occurs post-infusion: • The symptoms should be treated If CRS lasts > 48 hours after symptomatic management: • Dexamethasone[3] and/or tocilizumab[4,5] should be considered	
Grade 2 Fever ≥ 38ºC and/or hypotension not requiring vasopressors and/or hypoxia requiring low-flow oxygen[6] by nasal cannula or blow-by	If CRS occurs during infusion: • The infusion should be interrupted and symptoms treated • The infusion should be re-started at 50% the rate once the symptoms resolve • If symptoms recur with re-administration, the current infusion should be discontinued If CRS occurs post-infusion: • The symptoms should be treated If no improvement occurs after symptomatic management: • Dexamethasone[3] and/or tocilizumab[4,5] should be considered	The symptoms should be resolved for at least 72 hours prior to next infusion Premedication should be maximised as appropriate[7] Consideration should be given to administration of the next infusion 50% rate, with more frequent monitoring of the patient
Grade 3 Fever ≥ 38ºC 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	If CRS occurs during infusion: • The current infusion should be discontinued • The symptoms should be treated • Dexamethasone[3] and tocilizumab[4, 5] should be administered If CRS occurs post-infusion: • The symptoms should be treated • Dexamethasone[3] and tocilizumab[4, 5] should be administered If CRS is refractory to dexamethasone and tocilizumab: • Alternative immunosuppressants[9] 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 infusion Patients should be hospitalised for the next infusion Premedication should be maximised as appropriate[7] The next infusion should be administered at a 50% rate
Grade 4 Fever ≥ 38ºC and/or hypotension requiring multiple vasopressors (excluding vasopressin)	If CRS occurs during or post-infusion: • Treatment with Lunsumio should be permanently discontinued • The symptoms should be treated • Dexamethasone[3] and tocilizumab[4, 5] should be administered If CRS is refractory to dexamethasone and tocilizumab:	

and/or hypoxia requiring oxygen by positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation)	• Alternative immunosuppressants[9] and methylprednisolone 1 000 mg/day intravenously should be administered until clinical improvement

[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 intravenously 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 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 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 10mg, 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 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 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.
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. 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.

[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.
[d] See *Delayed or missed dose* for guidance on restarting Lunsumio after dose delay.

[e] Evaluate benefit/risk before restarting Lunsumio.

Special populations

Elderly

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

Renal impairment

Lunsumio 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 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 in children below 18 years of age have not yet been established.

Method of administration

Lunsumio is for intravenous use only.

Lunsumio must be diluted using aseptic technique under the supervision of a healthcare professional. It should be administered as an intravenous infusion through a dedicated infusion line. Do not use an in-line filter to administer Lunsumio. Drip chamber filters can be used to administer Lunsumio.

The first cycle of Lunsumio should be administered over a minimum of 4 hours as intravenous infusion. If the infusions are well-tolerated in cycle 1, the subsequent cycles may be administered over a 2-hours infusion.

Lunsumio 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 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 (see section 4.8). Signs and symptoms included pyrexia, chills, hypotension, tachycardia, hypoxia, and headache. Infusion related reactions may be clinically indistinguishable from manifestations of CRS. CRS events occurred predominantly in cycle 1 and were mainly associated with Day 1 and Day 15 dose administrations.

Patients should be premedicated with corticosteroids, antipyretics and antihistamines at least through cycle 2. Patients must receive adequate hydration prior to the administration of Lunsumio. 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, and sepsis or septic shock have occurred in patients receiving Lunsumio, some of which were life-threatening or fatal events (see section 4.8). Febrile neutropenia was observed in patients after receiving Lunsumio infusion.

Lunsumio should not be administered in the presence of active infections. Caution should be exercised when considering the use of Lunsumio 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 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.

Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)

ICANS have occurred in patients receiving Lunsumio, 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 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 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 (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, tumour flare is likely due to the influx of T-cells into tumour sites following Lunsumio 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 should be monitored and evaluated for tumour flare at critical anatomical sites.

Tumour lysis syndrome (TLS)

TLS has been reported in patients receiving Lunsumio (see section 4.8). Patients must have adequate hydration prior to the administration of Lunsumio. 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. 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 1 mg concentrate for solution for infusion contains 0.6 mg of polysorbate 20, and each vial of Lunsumio 30 mg concentrate for solution for infusion contains 18 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 treatment causes a transient increase in cytokine levels which may cause inhibition of CYP450 enzymes. On initiation of Lunsumio 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 and for at least 3 months after the last infusion of Lunsumio.

Pregnancy

There are no data from the use of Lunsumio in pregnant women. Animal studies are insufficient with respect to reproductive toxicity (see section 5.3). Lunsumio 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 therapy.

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 has a major influence on the ability to drive and use machines. Due to the potential for ICANS, patients receiving Lunsumio 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 intravenously received was 8 (range 1 -17), 37% of patients received 8 cycles, and 15% 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 (≥ 20%) observed were cytokine release syndrome, neutropenia, rash and upper respiratory tract infection. The most common serious adverse reactions (≥ 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 intravenous dose (n=218), CRS was the only adverse reaction that led to discontinuation in more than one patient (2 patients [0.9%]).

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 (≥ 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 (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[19]**	**Grade 3 – 4**
Infections and infestations		
Upper respiratory tract infection[1]	Very Common	Common
Urinary tract infection[2]	Common	Common

System organ class / preferred term or adverse reaction	All grades[19]	Grade 3 – 4
Pneumonia[3]	Common	Common
Lower respiratory tract infection[4]	Common	Uncommon
Sepsis[5]	Common	Common
Neoplasms benign, malignant and unspecified (including cysts and polyps)		
Tumour flare[6]	Common	Uncommon
Blood and lymphatic system disorders		
Neutropenia[7]	Very common	Very common
Anaemia	Very common	Common
Thrombocytopenia[8]	Very common	Common
Febrile neutropenia	Common	Common
Immune system disorders		
Cytokine release syndrome[10]	Very common	Common
Haemophagocytic lymphohistiocytosis[9,17]	Uncommon	Uncommon
Metabolism and nutrition disorders		
Hypophosphataemia[11]	Very common	Very common
Hypokalaemia[12]	Very common	Common
Hypomagnesaemia[13]	Common	Very rare
Tumour lysis syndrome	Uncommon	Uncommon
Nervous system disorders		
Headache[14]	Very common	Uncommon
Dizziness[15]	Common	Uncommon
Immune effector cell-associated neurotoxicity syndrome[16,17]	Common	Very rare
Gastrointestinal disorders		
Diarrhoea	Very common	Uncommon
Nausea	Very common	Uncommon
Skin and subcutaneous tissue disorders		
Rash[18]	Very common	Common
Pruritus	Very common	Very rare

System organ class / preferred term or adverse reaction	All grades[19]	Grade 3 – 4
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
Investigations		
Alanine aminotransferase, increased	Common	Common
Aspartate aminotransferase, increased	Common	Common

[1] Upper respiratory tract infection includes upper respiratory tract infection, viral upper respiratory tract infection, nasopharyngitis, sinusitis, rhinovirus infection, sinusitis bacterial, viral sinusitis, respiratory tract infection, COVID-19 and respiratory tract infection viral
[2] Urinary tract infection (UTI) includes UTI, Escherichia UTI, pyelonephritis acute
[3] Pneumonia includes pneumonia and COVID-19 pneumonia
[4] Lower respiratory tract infection includes lower respiratory tract infection and bronchitis
[5] Sepsis includes sepsis, septic shock, bacteraemia, Candida sepsis
[6] Tumour flare includes tumour flare, pleural effusion, tumour inflammation and flank pain
[7] Neutropenia includes neutropenia and neutrophil count decreased
[8] Thrombocytopenia includes thrombocytopenia and platelet count decreased
[9] Haemophagocytic lymphohistocytosis (HLH) includes HLH
[10] By American Society for Transplantation and Cellular Therapy
[11] Hypophosphatemia includes hypophosphatemia and blood phosphorus decreased
[12] Hypokalemia includes hypokalemia and blood potassium decreased
[13] Hypomagnesemia includes hypomagnesemia and blood magnesium decrease
[14] Headache includes headache, migraine and head discomfort
[15] Dizziness includes dizziness and vertigo
[16] 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
[17] The frequency calculation is based on additional clinical studies
[18] 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 erythrodysaesthesia and rash morbiliform
[19] Grade 5 AEs only occurred for ADR terms HLH, pneumonia, sepsis and URTI (i.e., COVID-19) in mosunetuzumab subcutaneous injection (1 each) and for ADR terms Pneumonia and Sepsis in mosunetuzumab intravenous infusion (1 each)

Description of selected adverse reactions

Cytokine release syndrome (CRS)

In patients treated with Lunsumio intravenous infusion, CRS (ASTCT grading system) of any grade occurred in 39% (86/218) of patients, with grade 2 occurring in 14%, grade 3 occurring in 2.3%, and grade 4 occurring in 0.5% of patients treated with Lunsumio. The one patient with the grade 4 event was a patient with FL in the leukemic phase who also experienced concurrent TLS.

CRS of any grade occurred in 15% of patients after the Cycle 1, Day 1 dose; 5% after the Cycle 1, Day 8 dose; 33% after the Cycle 1, Day 15 dose, 5% occurred in patients after the Cycle 2 and 1% in Cycles 3 and beyond. The median time to CRS onset from the start of administration in Cycle 1 Day 1 was 5 hours (range: 1-73 hours), Cycle 1 Day 8 was 28 hours (range: 5-81 hours), Cycle 1 Day 15 was 25 hours (range: 0.1-391 hours), and Cycle 2 Day 1 was 46 hours (range: 12-82 hours). CRS resolved in all patients, and the median duration of CRS events was 3 days (range 1-29 days).

Of the 86 patients that experienced CRS, the most common signs and symptoms of CRS included pyrexia (98%), chills (36%), hypotension (35%), tachycardia (24%), hypoxia (22%) and headache (16%).

Tocilizumab and/or corticosteroids were used to manage a CRS event in 16% of patients: 6% received tocilizumab alone, 6% received corticosteroids alone, and 4% received both tocilizumab and corticosteroids. Among the 10% of patients who received tocilizumab (with or without a corticosteroid), 86% received only one dose of tocilizumab, with no more than two doses of tocilizumab administered for a single CRS event. In patients experiencing Grade 2 CRS, 48% of patients were treated with symptomatic management without corticosteroids or tocilizumab, 18% received tocilizumab alone, 21% received corticosteroids alone, and 12% received both corticosteroids and tocilizumab. Patients with grade 3 or grade 4 CRS received tocilizumab, corticosteroids, vasopressors and/or oxygen supplementation. Three percent of patients experienced hypotension and/or hypoxia without fever following Lunsumio administration; 2% of patients received tocilizumab and/or corticosteroids in the absence of fever.

Hospitalisations due to CRS occurred in 21% of patients and the median duration of hospitalisation was 5 days (range 0-30 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.

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 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; 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 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, multicentre, multi-cohort study (GO29781) was conducted to evaluate Lunsumio in patients with relapsed or refractory B-cell non-Hodgkin's lymphoma for whom there was no available therapy expected to improve survival. In the follicular lymphoma (FL) cohort (n=90), 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. Patients with FL Grade 3b and patients with transformed FL at study entry were not eligible; those with a history of transformed FL but FL Grade 1-3A at study entry were included in the FL cohort.

The study excluded patients with Eastern Cooperative Oncology Group (ECOG) performance status ≥ 2, significant cardiovascular disease (such as New York Heart Association Class III or IV cardiac disease, myocardial infarction within the last 6 months, unstable arrhythmias, or unstable angina), significant active pulmonary disease, impaired renal functions (Creatinine clearance [CrCl] < 60 mL/min with elevated serum creatinine level), active autoimmune disease requiring immunosuppressive therapy, active infections (i.e., chronic active EBV, acute or chronic hepatitis C, hepatitis B, HIV), progressive multifocal leukoencephalopathy, current or a history of CNS lymphoma or CNS disease, a history of macrophage activation syndrome / haemophagocytic lymphohistiocytosis, prior allogeneic stem cell transplant, or prior organ transplantation.

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

- Cycle 1 Day 1: 1 mg
- Cycle 1 Day 8: 2 mg
- Cycle 1 Day 15: 60 mg
- Cycle 2 Day 1: 60 mg
- Cycle 3 and beyond Day 1: 30 mg

The median number of cycles was 8, 59% received 8 cycles, and 18% received more than 8 cycles up to 17 cycles.

The median age was 60 years (range 29 to 90 years) with 31% being > age 65, and 7.8% being ≥ age 75. Sixty-one percent were male, 82% were white, 9% were Asian, 4% were Black, 100% had an ECOG performance status of 0 or 1 and 34% of patients had bulky disease (at least one lesion > 6 cm). The median number of prior therapies was 3 (range: 2-10), with 38% receiving 2 prior therapies, 31% receiving 3 prior therapies and 31% receiving more than 3 prior therapies.

All patients received prior anti-CD20 and alkylator therapies, 21% received autologous stem cell transplant, 19% received PI3K inhibitors, 9% received prior rituximab plus lenalidomide therapy, and 3% received CAR-T therapies. Seventy-nine percent of patients were refractory to prior anti-CD20 monoclonal antibody therapy and 53% were refractory to both anti-CD20 monoclonal antibody and alkylator therapy. Sixty-nine percent of patients were refractory to the last prior therapy and 52% had progression of disease within 24 months of first systemic therapy.

The primary efficacy endpoint was complete response (CR) as assessed by an independent review facility (IRF) according to standard criteria for NHL (Cheson 2007). The efficacy results are summarised in Table 7.

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

Efficacy parameter	**Lunsumio N=90**
Median observation time 18.3 months (range 2 – 27 months)	
Complete Response (CR), n (%), (95% CI)	54 (60.0) (49.1, 70.2)
Objective Response Rate (ORR), n (%) (95% CI)	72 (80.0) (70.3, 87.7)
Partial Response (PR) n (%) (95% CI)	18 (20.0) (12.3, 29.8)
Duration of Response (DOR)[1]	
Patients with event, n (%)	29 (40.3)
Median, months (95% CI)	22.8 (9.7, NR)
K-M event-free proportion	
12 months (95% CI)	61.8 (50.0, 73.7)
18 months (95% CI)	56.9 (44.1, 69.6)
Duration of Complete Response (DOCR)[2]	
Patients with event, n (%)	16 (29.6)
Median, months (95% CI)	NR (14.6, NR)
K-M event-free proportion,	
12 months (95% CI)	71.4 (57.9, 84.9)
18 months (95% CI)	63.7 (48.0, 79.4)

CI=confidence interval; K-M=Kaplan-Meier; NR=not reached.
Clinical Cut-off: 27 August 2021
Hypothesis testing was conducted on the primary endpoint of IRF assessed CR rate.
[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 14.9 months. Additional exploratory efficacy outcomes included the median time to first response (1.4 months, range: 1.1 - 8.9) and the median time to first complete response (3.0 months, range: 1.1- 18.9).

Immunogenicity

The immunogenicity of mosunetuzumab was evaluated using an enzyme-linked immunosorbent assay (ELISA). No patients tested positive for anti-mosunetuzumab antibodies in 418 ADA-evaluable patients who received Lunsumio single-agent intravenous treatments in 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

Mosunetuzumab pharmacokinetic (PK) exposure increased in an approximately dose-proportional manner over the dose range studied, from 0.05 to 60 mg. The population pharmacokinetic following intravenous administrations of Lunsumio was described by a 2-compartment PK model with time-dependent clearance, which was parameterised as descending to a steady-state plateau (CL_{ss}) from a baseline value (CL_{base}) at the start of treatment according to transitional half-life of 16.3 days. Moderate to high pharmacokinetic variability for mosunetuzumab was observed and characterised by inter-individual variability (IIV) ranging from 18% to 86% coefficient of variation (CV) for mosunetuzumab PK parameters: IIV was estimated for CL_{base} (63% CV), central volume of distribution (31% CV), peripheral volume of distribution (25% CV), CL_{ss} (18% CV), and transitional half-life (86% CV).

After the first two Cycles (i.e., 42 days) of the dosing with Lunsumio, the serum concentration reaches the C_{max} at the end of dose of Cycle 2 Day 1 of the Lunsumio intravenous infusion with an average maximal concentration of 17.9 µg/mL and %CV of 49.6%. The average total two cycles (42 days) mosunetuzumab exposure AUC was 126 day·mg/mL with %CV of 44.4%.

Absorption

Lunsumio is administered intravenously.

Distribution

The population estimate of central volume of distribution for mosunetuzumab was 5.49 L with intravenous infusion 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, 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 estimate was 16.1 days at steady state based on population pharmacokinetic model estimates. The results obtained in study GO29781 indicate that mosunetuzumab serum concentration reaches the C_{max} at the end of the intravenous infusion and declines in a bi-exponential fashion.

Special populations

Elderly

Age did not have an effect on the pharmacokinetics of mosunetuzumab based on a population pharmacokinetic analysis with patients aged 19-96 years (n=439). No clinically important difference was observed in the pharmacokinetics of mosunetuzumab for patients in this age group.

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 PK analysis of mosunetuzumab 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=178) or moderate (CrCl 30 to 59 mL/min, n=53) renal impairment were similar to those in patients with normal renal function (CrCl ≥ 90 mL/min, n=200). 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 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 1.5 x ULN or AST > ULN, n=53) were similar to those in patients with normal hepatic function (n=384). The number of patients with moderate hepatic impairment is limited (total bilirubin > 1.5–3 x ULN, any AST, n=2) and no patients with severe hepatic impairment have been studied.

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

- Do not mix Lunsumio with, or administer through the same infusion line, as other medicinal products.
- Do not use solvents other than sodium chloride 9 mg/mL (0.9%) solution for injection or sodium chloride 4.5 mg/mL (0.45%) solution for injection to dilute Lunsumio since its use has not been tested.
- No incompatibilities have been observed between Lunsumio and intravenous infusion bags with product contacting materials of polyvinyl chloride (PVC), or polyolefins (PO) such as polyethylene (PE) and polypropylene (PP). In addition, no incompatibilities have been observed with infusion sets or infusion aids with product contacting materials of PVC, PE, polyurethane (PUR), polybutadiene (PBD), silicone, acrylonitrile butadiene styrene (ABS), polycarbonate (PC), polyetherurethane (PEU), fluorinated ethylene propylene (FEP), or polytetrafluorethylene (PTFE), or with drip chamber filter membrane composed of polyamide (PA).

- Do not use an in-line filter.

6.3 Shelf life

Unopened vial

3 years

Diluted solution

Chemical and physical in-use stability has been demonstrated for 24 hours at 2 °C - 8 °C and 24 hours at 9 °C - 30 °C.

From a microbiological point of view, the product should be used immediately. 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 °C to 8 °C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store in a refrigerator (2 °C - 8 °C).
Do not freeze.
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

1 mg concentrate for solution for infusion

Type I glass-vial with a fluororesin-laminated rubber stopper and an aluminium seal with a plastic dark grey flip-off cap containing 1 mg of concentrate for solution for infusion.

Pack of one vial.

30 mg concentrate for solution for infusion

Type I glass-vial with a fluororesin-laminated rubber stopper and an aluminium seal with a plastic light blue flip-off cap containing 30 mg of concentrate for solution for infusion.

Pack of one vial.

6.6 Special precautions for disposal and other handling

General precautions

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

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.

Instructions for dilution

Lunsumio must be diluted into a PVC or polyolefin (PO) such as polyethylene (PE) and polypropylene infusion bag containing sodium chloride 9 mg/mL (0.9%) solution for injection or sodium chloride 4.5 mg/mL (0.45%) solution for injection by a healthcare professional using aseptic technique prior to administration.

Use sterile needle and syringe to prepare Lunsumio. Discard any unused portion.

A dedicated infusion line should be used during intravenous administration.

Do not use an in-line filter to administer Lunsumio.

Drip chamber filters can be used to administer Lunsumio.

Preparation for infusion

1. Withdraw and discard a volume of sodium chloride 9 mg/mL (0.9%) solution for injection or sodium chloride 4.5 mg/mL (0.45%) solution for injection equal to the volume of the Lunsumio required for the patient's dose from the infusion bag according to the Table 8. below.
2. Withdraw the required volume of Lunsumio from the vial using a sterile syringe and dilute into the infusion bag. Discard any unused portion left in the vial.

Table 8: Dilution of Lunsumio

Day of treatment		**Dose of Lunsumio**	**Volume of Lunsumio in sodium chloride 9 mg/mL (0.9%) or 4.5 mg/mL (0.45%) solution for injection**	**Size of infusion bag**
Cycle 1	Day 1	1 mg	1 mL	50 mL or 100 mL
	Day 8	2 mg	2 mL	50 mL or 100 mL
	Day 15	60 mg	60 mL	100 mL or 250 mL
Cycle 2	Day 1	60 mg	60 mL	100 mL or 250 mL
Cycle 3 and beyond	Day 1	30 mg	30 mL	100 mL or 250 mL

3. Gently mix the infusion bag by slowly inverting the bag. Do not shake.
4. Inspect the infusion bag for particulates and discard if present.
5. Apply the peel-off label from the leaflet to the infusion bag.

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

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/1/22/1649/001
EU/1/22/1649/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 3 June 2022
Date of latest renewal: 14 April 2025

10. DATE OF REVISION OF THE TEXT

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

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

[a]Anti-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 grading[1] and management

CRS grade	**CRS management[2]**	**Next scheduled injection of <u>Lunsumio</u>**
Grade 1 Fever ≥ 38ºC	The symptoms should be treated If CRS lasts > 48 hours after symptomatic management: • Dexamethasone[3] 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 ≥ 38ºC 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: • Dexamethasone[3] 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 ≥ 38ºC 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 immunosuppressants[9] 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 ≥ 38ºC 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 • Dexamethasone[3] and tocilizumab[4, 5] should be administered If CRS is refractory to dexamethasone and tocilizumab: • Alternative immunosuppressants[9] and methylprednisolone 1 000 mg/day intravenously should be administered until clinical improvement

[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.

[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 ≥10% of patients treated with Lunsumio subcutaneous injection in the 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, COVID-19, and sepsis 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.

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.

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.

Excipients 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 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 (≥ 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 (≥ 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 (≥ 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 (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[19]**	**Grade 3 – 4**
Infections and infestations		
Upper respiratory tract infection[1]	Very Common	Common
Urinary tract infection[2]	Common	Common
Pneumonia[3]	Common	Common
Lower respiratory tract infection[4]	Common	Uncommon
Sepsis[5]	Common	Common
Neoplasms benign, malignant and unspecified (including cysts and polyps)		
Tumour flare[6]	Common	Uncommon
Blood and lymphatic system disorders		
Neutropenia[7]	Very common	Very common
Anaemia	Very common	Common
Thrombocytopenia[8]	Very common	Common
Febrile neutropenia	Common	Common
Immune system disorders		
Cytokine release syndrome[9]	Very common	Common
Haemophagocytic lymphohistiocytosis[10,17]	Uncommon	Uncommon
Metabolism and nutrition disorders		
Hypophosphataemia[11]	Very common	Very common
Hypokalaemia[12]	Very common	Common
Hypomagnesaemia[13]	Common	Very rare
Tumour lysis syndrome	Uncommon	Uncommon

System organ class / preferred term or adverse reaction	All grades[19]	Grade 3 – 4
Nervous system disorders		
Headache[14]	Very common	Uncommon
Dizziness[15]	Common	Very rare
Immune effector cell-associated neurotoxicity syndrome[16,17]	Common	Very rare
Gastrointestinal disorders		
Diarrhoea	Very common	Uncommon
Nausea	Very common	Uncommon
Skin and subcutaneous tissue disorders		
Rash[18]	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, viral upper respiratory tract infection, nasopharyngitis, sinusitis, rhinovirus infection, sinusitis bacterial, viral sinusitis, respiratory tract infection, COVID-19 and respiratory tract infection viral
[2] Urinary tract infection (UTI) includes UTI, Escherichia UTI, pyelonephritis acute
[3] Pneumonia includes pneumonia and COVID-19 pneumonia
[4] Lower respiratory tract infection includes lower respiratory tract infection and bronchitis
[5] Sepsis includes sepsis, septic shock, bacteraemia, Candida sepsis
[6] Tumour flare includes tumour flare, pleural effusion, tumour inflammation and flank pain
[7] Neutropenia includes neutropenia and neutrophil count decreased
[8] Thrombocytopenia includes thrombocytopenia and platelet count decreased
[9] By American Society for Transplantation and Cellular Therapy
[10] Haemophagocytic lymphohistocytosis (HLH) includes HLH
[11] Hypophosphatemia includes hypophosphatemia and blood phosphorus decreased
[12] Hypokalemia includes hypokalemia and blood potassium decreased
[13] Hypomagnesemia includes hypomagnesemia and blood magnesium decrease
[14] Headache includes headache, migraine and head discomfort
[15] Dizziness includes dizziness and vertigo

[16] 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
[17] The frequency calculation is based on additional clinical studies
[18] 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 erythrodysaesthesia and rash morbiliform
[19] Grade 5 AEs only occurred for ADR terms HLH, pneumonia, sepsis and URTI (i.e., COVID-19) in mosuntezumab subcutaneous injection (1 each) and for ADR terms pneumonia and sepsis in mosunetuzumab intravenous infusion (1 each)

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.

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 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; 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 $AUC_{0\text{-}84\ days}$, 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) Partial response (PR) n (%) (95% CI)	70 (74.5) (64.4, 82.9) 15 (16.0) (9.2, 25.0)
Duration of response (DOR)[1] Patients with event, n (%) Median, months (95% CI) K-M event-free proportion,	N=70 26 (37.1) 22.4 (16.8, 22.8)

Efficacy parameter	Lunsumio subcutaneous injection N=94
12 months (95% CI) 18 months (95% CI)	69.9 (58.5, 81.4) 59.6 (45.8, 73.3)
Duration of complete response (DOCR)[2] Patients with event, n (%) Median, months (95% CI) K-M event-free proportion, 12 months (95% CI) 18 months (95% CI)	N=55 19 (34.5) 20.8 (18.8, NR) 72.4 (59.9, 84.8) 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 pharmokinetically 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 $C_{troughCYC3\_OBS}$ 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 µg/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·µg/mL)[1]	**Model-predicted C_{max} (µg/mL)[1]**	**Model-predicted C_{trough} (µg/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× x 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 nee (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: 14 April 2025

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://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

Genentech, Inc.
1 DNA Way
South San Francisco, CA 94080
USA

F. Hoffmann-La Roche AG
Grenzacherstrasse 124
4058 Basel
Switzerland

Name and address of the manufacturer responsible for batch release

Roche Pharma AG
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

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 Lunsumio is marketed, all patients/carers who are expected to use Lunsumio 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 Lunsumio.

The patient card shall contain the following key messages:
- A description of the key signs and symptoms of CRS
- A description of the key signs and symptoms of 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
- 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 14-a(4) of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due Date
In order to provide further evidence of efficacy and safety of mosunetuzumab in follicular lymphoma, the MAH will provide results from Study GO42909, a randomised, open-label, multicentre trial evaluating mosunetuzumab in combination with lenalidomide in comparison to rituximab in combination with lenalidomide in patients with follicular lymphoma after at least one line of systemic therapy.	Q3 2026

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Lunsumio 1 mg concentrate for solution for infusion
mosunetuzumab

2. STATEMENT OF ACTIVE SUBSTANCE

Each vial contains 1 mg mosunetuzumab at a concentration of 1 mg/ml.

3. LIST OF EXCIPIENTS

Excipients: L-histidine, L-methionine, acetic acid, sucrose, polysorbate 20, water for injections.
See leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

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

5. METHOD AND ROUTE OF ADMINISTRATION

For single use only
Read the package leaflet before use
For intravenous use after dilution

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 WARNINGS, IF NECESSARY

Do not shake the vial
Do not use in-line filter

On the inside flap of the outer carton

Do not use in-line filter
Apply peel-off label from the enclosed leaflet to the infusion bag

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

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

12. MARKETING AUTHORISATION NUMBER

EU/1/22/1649/001

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 unique identifier included

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

2 mL VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTES OF ADMINISTRATION

Lunsumio 1 mg sterile concentrate
mosunetuzumab
IV use after dilution

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 mg/1 mL

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Lunsumio 30 mg concentrate for solution for infusion
mosunetuzumab

2. STATEMENT OF ACTIVE SUBSTANCE

Each vial contains 30 mg mosunetuzumab at a concentration of 1 mg/ml.

3. LIST OF EXCIPIENTS

Excipients: L-histidine, L-methionine, acetic acid, sucrose, polysorbate 20, water for injections.
See leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion
30 mg/30 mL
1 vial

5. METHOD AND ROUTE OF ADMINISTRATION

For single use only
Read the package leaflet before use
For intravenous use after dilution

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 WARNINGS, IF NECESSARY

Do not shake the vial
Do not use in-line filter

On the inside flap of the outer carton

Do not use in-line filter
Apply peel-off label from the enclosed leaflet to the infusion bag

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

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

12. MARKETING AUTHORISATION NUMBER

EU/1/22/1649/002

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 unique identifier included

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

50 mL VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Lunsumio 30 mg concentrate for solution for infusion
mosunetuzumab
For intravenous use after dilution

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

30 mg/30 mL

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Lunsumio 5 mg solution for injection
mosunetuzumab

2. STATEMENT OF ACTIVE SUBSTANCE

Each vial contains 5 mg mosunetuzumab at a concentration of 5 mg/0.5ml.

3. LIST OF EXCIPIENTS

Excipients: L-histidine, L-methionine, acetic acid, sucrose, polysorbate 20, water for injections.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
5 mg/0.5 mL
1 vial

5. METHOD AND ROUTE OF ADMINISTRATION

For single use only
Read the package leaflet before use
For subcutaneous use

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 WARNINGS, IF NECESSARY

Do not shake the vial

On the inside flap of the outer carton
5 mg
subcutaneous
Apply peel-off label from the enclosed leaflet to the syringe

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

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

12. MARKETING AUTHORISATION NUMBER

EU/1/22/1649/003

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 unique identifier included

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

2 mL VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Lunsumio 5 mg solution for injection
mosunetuzumab
For subcutaneous use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

5 mg/0.5 mL

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Lunsumio 45 mg solution for injection
mosunetuzumab

2. STATEMENT OF ACTIVE SUBSTANCE

Each vial contains 45 mg mosunetuzumab at a concentration of 45 mg/ml.

3. LIST OF EXCIPIENTS

Excipients: L-histidine, L-methionine, acetic acid, sucrose, polysorbate 20, water for injections.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
45 mg/mL
1 vial

5. METHOD AND ROUTE OF ADMINISTRATION

For single use only
Read the package leaflet before use
For subcutaneous use

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 WARNINGS, IF NECESSARY

Do not shake the vial

On the inside flap of the outer carton
45 mg
subcutaneous
Apply peel-off label from the enclosed leaflet to the syringe

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

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

12. MARKETING AUTHORISATION NUMBER

EU/1/22/1649/004

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 unique identifier included

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

2 mL VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Lunsumio 45 mg solution for injection
mosunetuzumab
For subcutaneous use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

45 mg/mL

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Lunsumio 1 mg concentrate for solution for infusion
Lunsumio 30 mg concentrate for solution for infusion
mosunetuzumab

▼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 start taking 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, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Lunsumio is and what it is used for

Lunsumio contains the active substance mosunetuzumab, which is a type of antibody. This is a cancer medicine. It is used to treat adults who have a blood cancer called follicular lymphoma (FL).

In FL, a type of white blood cells called ‘B cells’ become cancerous. The abnormal B cells do not work properly and grow too quickly, crowding out the normal B cells in the bone marrow and lymph nodes that help protect you from infection.

Lunsumio is given to patients who have tried at least two previous treatments for FL, when either the cancer has not responded to them, or it has come back again.

How Lunsumio works

The active substance in Lunsumio, mosunetuzumab, is a monoclonal antibody, a type of protein that attaches to specific targets in the body. In this case, mosunetuzumab attaches to a target substance found on B cells, including the cancerous B cells, and another target found on ‘T cells’, a different type of white blood cell. T cells are another part of the body’s defences that can destroy invading cells. By attaching the two cells together like a bridge, Lunsumio encourages the T cells to destroy the cancerous B cells. This helps control the FL and prevent its spread.

2. What you need to know before you use Lunsumio

You must not be given Lunsumio

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

If you are not sure, talk to your doctor or nurse before you are given Lunsumio.

Warnings and precautions

Talk to your doctor or nurse before you are given Lunsumio if any of the following apply to you (or you are not sure):
- you have ever had heart, lung or kidney problems
- you have an infection, or have had an infection in the past which lasted a long time or keeps coming back
- you are due to have a vaccine or you know you may need to have one in the near future.

If any of the above apply to you (or you are not sure), talk to your doctor or nurse before having this medicine.

Tell your doctor straight away if you get symptoms of any of the side effects listed below during or after treatment with Lunsumio. You may need additional medical treatment. The symptoms of each side effect are listed in section 4.

- **Cytokine release syndrome (CRS) –** a condition associated with medicines that stimulate T cells.
  - Before each infusion, you may be given medicines, which help reduce possible side effects of cytokine release syndrome
- **Immune effector cell-associated neurotoxicity syndrome (ICANS) –** a condition associated with effects on the nervous system. Symptoms include feeling confused, problems with memory, language or judgement, disorientation and confusion often accompanied by hallucination (seeing, hearing or feeling things that are not there), and not being able to concentrate.
- **Haemophagocytic lymphohistiocytosis –** a condition where the immune system makes too many infection-fighting cells called histiocytes and lymphocytes. Signs and symptoms may overlap with CRS, your doctor will check for this condition if your CRS does not respond to treatment or lasts longer than expected.
- **Tumour lysis syndrome –** some people may get unusual levels of some salts in the blood **–** caused by the fast breakdown of cancer cells during treatment.
  - Your doctor or nurse will do blood tests to check for this condition. Before each dose infusion, you should be well-hydrated and may be given medicines that can help reduce high levels of uric acid. These may help reduce possible side effects of tumour lysis syndrome.
- **Tumour flare –** as your cancer is destroyed, it may react and appear to get worse **–** this is called 'tumour flare reaction'.
- **Infections –** you may get signs of infection, which can vary depending on where in the body the infection is.

Children and adolescents

This medicine should not be used in children or adolescents under the age of 18. This is because there is no information about use in this age group.

Other medicines and Lunsumio

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

Pregnancy and breast-feeding

It is important to tell your doctor before and during treatment if you are pregnant, think you may be pregnant, or are planning to get pregnant. This is because Lunsumio may affect your unborn baby.

- Do not use Lunsumio during pregnancy, unless after discussion with your doctor, it is agreed that the benefits of treatment outweigh any risk to the unborn baby.

Contraception

Women who could become pregnant must use effective contraception during treatment – and for 3 months after the last dose of Lunsumio.

- Talk to your doctor or nurse about suitable methods of contraception.

Breast-feeding

You must not breast-feed during and for at least 3 months after your last treatment. This is because it is not known whether any Lunsumio passes into breast milk and could therefore affect the baby.

Driving and using machines

Lunsumio has a major influence on your ability to drive, cycle or use any tools or machines. Due to the possible symptoms of ICANS, you should be careful while driving, cycling or using heavy or potentially dangerous machines. If you currently have such symptoms, avoid these activities and contact your doctor, nurse, or pharmacist. See section 4 for more information about side effects.

Lunsumio contains polysorbate

This medicine contains the following amount of polysorbate 20, which is equivalent to 0.6 mg/mL:
- Lunsumio 1 mg: each vial contains 0.6 mg of polysorbate 20
- Lunsumio 30 mg: each vial contains 18 mg of polysorbate 20

Polysorbate 20 may cause allergic reactions. Tell your doctor if you have any known allergies.

3. How Lunsumio is given

Lunsumio is given under the supervision of a doctor experienced in giving such treatments. Follow the treatment schedule explained to you by your doctor. Check with your doctor if you are not sure.

How Lunsumio is given

It is given into a vein, as a drip (infusion).
- It is given over 4 hours during the first cycle. Each cycle is 21 days and in the first cycle, you will be given the 4 hour infusion on day 1, day 8 and day 15.
- If side effects are not too severe, the dose may be given over 2 hours during the following cycles

Medicines given before Lunsumio treatment

You may be given other medicines 30 to 60 minutes before you are given Lunsumio. This is to help prevent infusion reactions and fever. These other medicines may include:
- Corticosteroids – such as dexamethasone or methylprednisolone
- Paracetamol
- An antihistamine - such as diphenhydramine

How much Lunsumio is given

Lunsumio is normally given in cycles of 21 days. The recommended treatment duration is at least 8 treatment cycles. However, depending on side effects and how the disease responds to treatment, you may be given up to 17 cycles.

In cycle 1, you will be given 3 doses of Lunsumio in the 21 days:
- Day 1**:** 1 mg
- Day 8**:** 2 mg
- Day 15**:** 60 mg

In cycle 2, you will be given just one dose:
- Day 1**:** 60 mg

In cycles 3 to 17, you will be given just one dose:
- Day 1**:** 30mg

If you miss a dose of Lunsumio

If you miss an appointment, make another one straight away. For the treatment to be fully effective, it is very important not to miss a dose.

If you stop receiving Lunsumio

Do not stop treatment with Lunsumio unless you have discussed this with your doctor. This is because stopping 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

Tell your doctor straight away if you notice any of the symptoms of the following serious side effects. You may only get one or some of these symptoms.

Cytokine release syndrome
Symptoms can include:
- fever (38°C or higher)
- chills or shaking chills
- cold or pale clammy skin
- difficulty breathing
- feeling dizzy or lightheaded
- fast or uneven heartbeat
- confusion
- feeling very tired or weak
- fainting
- blurred vision
- headache.

Haemophagocytic lymphohistiocytosis

Symptoms can include:

- fever
- enlarged liver and/or spleen
- skin rash
- lymph node enlargement
- easy bruising
- kidney abnormalities
- breathing problems
- heart problems.

Tumour lysis syndrome

Symptoms can include:

- fever
- chills
- feeling or being sick (nausea and vomiting)
- confusion
- being short of breath
- fits (seizures)
- uneven heartbeat
- dark or cloudy urine
- unusual tiredness
- muscle or joint pain.

Shown in blood tests

- increase in potassium, phosphate or uric acid – which can cause kidney problems (part of tumour lysis syndrome)

Tumour flare

Symptoms can include:

- tender swollen lymph nodes
- chest pain
- cough or difficulty breathing easily
- pain at the site of the tumour.

Infections

Symptoms can include:

- fever
- cough
- chest pain
- tiredness
- shortness of breath
- painful rash
- sore throat
- burning pain when passing urine
- feeling weak or generally unwell.

Immune effector cell-associated neurotoxicity syndrome (ICANS)

The symptoms can occur days or weeks after you receive the infusion and may initially be subtle.
Symptoms can include:

- confusion/disorientation
- tiredness
- altered mental state
- lowered mental state
- impaired memory

If you have any of these symptoms after treatment with Lunsumio, tell your doctor straight away. You may need medical treatment.

Other side effects
Very common: may affect more than 1 in 10 people
- Rash
- Itchy skin
- Dry skin
- Diarrhoea
- Headache
- Fever
- Chills
- Cytokine release syndrome

Shown in blood tests
- Low levels of some white blood cells (neutropenia)
- Low number of red blood cells, which can cause tiredness and shortness of breath
- Low platelet count, which may make you more likely to bruise or bleed (thrombocytopenia)
- Low level of phosphate, potassium or magnesium
- High level of alanine aminotransferase in the blood

Common: may affect up to 1 in 10 people
- Lung infection
- Infection of upper airways (infection of nose, throat, sinuses)
- Urinary tract infection
- Fever due to low levels of neutrophils (a type of white blood cell)
- Tumour flare
- A serious immune reaction affecting the nervous system (immune effector cell-associated neurotoxicity syndrome)

Shown in blood tests
- Increased levels of liver enzymes, which may be a sign of liver problems

Uncommon: may affect up to 1 in 100 people
- A rapid breakdown of tumour cells resulting in chemical changes in the blood and damage to organs, including the kidneys, heart, and liver (tumour lysis syndrome)
- A condition where the immune system makes too many infection-fighting cells called histiocytes and lymphocytes (haemophagocytic lymphohistiocytosis).

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist 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 Lunsumio

Lunsumio will be stored by the healthcare professionals at the hospital or clinic. The storage details that they must take account of are as follows
- 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 the vial after EXP. The expiry date refers to the last day of that month.
- Store in a refrigerator (2°C – 8°C).

- Do not freeze.
- The diluted solution should not be kept more than 24 hours at 2°C – 8°C and 24 hours at 9°C – 30°C.
- Keep the container in the outer carton in order to protect from light.

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

6. Contents of the pack and other information

What Lunsumio contains

The active substance is mosunetuzumab.
- Lunsumio 1 mg: Each vial contains 1 milligram (mg) mosunetuzumab in 1 mL at a concentration of 1 mg/mL.
- Lunsumio 30 mg: Each vial contains 30 milligrams (mg) mosunetuzumab in 30 mL at a concentration of 1 mg/mL.
- The other ingredients are: L-histidine, L-methionine, acetic acid, sucrose, polysorbate 20 (E432), water for injections (see section 2 “Lunsumio contains polysorbate”).

What Lunsumio looks like and contents of the pack

Lunsumio is a concentrate for solution for infusion (sterile concentrate). It is a clear, colourless liquid provided in a glass vial.

Each pack of Lunsumio contains one vial.

Marketing Authorisation Holder

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

Manufacturer

Roche Pharma AG
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Luxembourg/Luxemburg
N.V. Roche S.A.
België/Belgique/Belgien
Tél/Tel: +32 (0) 2 525 82 11

Latvija
Roche Latvija SIA
Tel: +371 - 6 7039831

България
Рош България ЕООД
Тел: +359 2 474 5444

Lietuva
UAB “Roche Lietuva”
Tel: +370 5 2546799

Česká republika
Roche s. r. O.
Tel: +420 - 2 20382111

Danmark
Roche Pharmaceuticals A/S
Tlf.: +45 - 36 39 99 99

Deutschland
Roche Pharma AG
Tel: +49 (0) 7624 140

Eesti
Roche Eesti OÜ
Tel: + 372 - 6 177 380

Ελλάδα, Κύπρος
Roche (Hellas) A.E.
Ελλάδα
Τηλ: +30 210 61 66 100

España
Roche Farma S.A.
Tel: +34 - 91 324 81 00

France
Roche
Tél: +33 (0) 1 47 61 40 00

Hrvatska
Roche d.o.o.
Tel: +385 1 4722 333

Ireland, Malta
Roche Products (Ireland) Ltd.
Ireland, L-Irlanda
Tel: +353 (0) 1 469 0700

Ísland
Roche Pharmaceuticals A/S
c/o Icepharma hf
Sími: +354 540 8000

Italia
Roche S.p.A.
Tel: +39 - 039 2471

Magyarország
Roche (Magyarország) Kft.
Tel: +36 1 279 4500

Nederland
Roche Nederland B.V.
Tel: +31 (0) 348 438050

Norge
Roche Norge AS
Tlf: +47 - 22 78 90 00

Österreich
Roche Austria GmbH
Tel: +43 (0) 1 27739

Polska
Roche Polska Sp.z o.o.
Tel: +48 - 22 345 18 88

Portugal
Roche Farmacêutica Química, Lda
Tel: +351 - 21 425 70 00

România
Roche România S.R.L.
Tel: +40 21 206 47 01

Slovenija
Roche farmacevtska družba d.o.o.
Tel: +386 - 1 360 26 00

Slovenská republika
Roche Slovensko, s.r.o.
Tel: +421 - 2 52638201

Suomi/Finland
Roche Oy
Puh/Tel: +358 (0) 10 554 500

Sverige
Roche AB
Tel: +46 (0) 8 726 1200

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.

Other sources of information

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

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

1. Withdraw and discard a volume of sodium chloride 9 mg/mL (0.9%) solution for injection or sodium chloride 4.5 mg/mL (0.45%) solution for injection equal to the volume of the Lunsumio required for the patient's dose from the infusion bag according to the table below.
2. Withdraw the required volume of Lunsumio from the vial using a sterile syringe and dilute into the infusion bag. Discard any unused portion left in the vial.

Table 1: Dilution of Lunsumio

Day of treatment		**Dose of Lunsumio**	**Volume of Lunsumio in sodium chloride 9 mg/mL (0.9%) or 4.5 mg/mL (0.45%) solution for injection**	**Size of infusion bag**
Cycle 1	Day 1	1 mg	1 mL	50 mL or 100 mL
	Day 8	2 mg	2 mL	50 mL or 100 mL
	Day 15	60 mg	60 mL	100 mL or 250 mL
Cycle 2	Day 1	60 mg	60 mL	100 mL or 250 mL
Cycle 3 and beyond	Day 1	30 mg	30 mL	100 mL or 250 mL

3. Gently mix the infusion bag by slowly inverting the bag. Do not shake.
4, Inspect the infusion bag for particulates and discard if present.
5. Apply the peel-off label from the leaflet to the infusion bag.

Diluted solution

The product should be used immediately. 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°C to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

Peel-off label

Peel and apply this label to the infusion bag

Package leaflet: Information for the patient

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

▼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 start taking 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, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Lunsumio is and what it is used for

Lunsumio contains the active substance mosunetuzumab, which is a type of antibody. This is a cancer medicine. It is used to treat adults who have a blood cancer called follicular lymphoma (FL).

In FL, a type of white blood cells called ‘B-cells’ become cancerous. The abnormal B cells do not work properly and grow too quickly, crowding out the normal B cells in the bone marrow and lymph nodes that help protect you from infection.

Lunsumio is given to patients who have tried at least two previous treatments for FL, when either the cancer has not responded to them, or it has come back again.

How Lunsumio works

The active substance in Lunsumio, mosunetuzumab, is a monoclonal antibody, a type of protein that attaches to specific targets in the body. In this case, mosunetuzumab attaches to a target substance found on B cells, including the cancerous B cells, and another target found on ‘T-cells’, a different type of white blood cell. T cells are another part of the body’s defences that can destroy invading cells. By attaching the two cells together like a bridge, Lunsumio encourages the T cells to destroy the cancerous B-cells. This helps control the FL and prevent its spread.

2. What you need to know before you use Lunsumio

You must not be given Lunsumio

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

If you are not sure, talk to your doctor or nurse before you are given Lunsumio.

Warnings and precautions

Talk to your doctor or nurse before you are given Lunsumio if any of the following apply to you (or you are not sure):
- you have ever had heart, lung or kidney problems
- you have an infection, or have had an infection in the past which lasted a long time or keeps coming back
- you are due to have a vaccine or you know you may need to have one in the near future.

If any of the above apply to you (or you are not sure), talk to your doctor or nurse before having this medicine.

Tell your doctor straight away if you get symptoms of any of the side effects listed below during or after treatment with Lunsumio. You may need additional medical treatment. The symptoms of each side effect are listed in section 4.

- **Cytokine release syndrome (CRS) –** a condition associated with medicines that stimulate T cells.
  - Before each injection, you may be given medicines, which help reduce possible side effects of cytokine release syndrome.
- **Immune effector cell-associated neurotoxicity syndrome (ICANS) –** a condition associated with effects on the nervous system. Symptoms include feeling confused, problems with memory, language or judgement, disorientation and confusion often accompanied by hallucination (seeing, hearing or feeling things that are not there), and not being able to concentrate.
- **Haemophagocytic lymphohistiocytosis –** is a condition where the immune system makes too many infection-fighting cells called histiocytes and lymphocytes. Signs and symptoms may overlap with CRS, your doctor will check for this condition if your CRS does not respond to treatment or lasts longer than expected.
- **Tumour lysis syndrome –** some people may get unusual levels of some salts in the blood caused by the fast breakdown of cancer cells during treatment.
  - Your doctor or nurse will do blood tests to check for this condition. Before each injection, you should be well-hydrated and may be given medicines that can help reduce high levels of uric acid. These may help reduce possible side effects of tumour lysis syndrome.
- **Tumour flare –** as your cancer is destroyed, it may react and appear to get worse **–** this is called ‘tumour flare reaction’.
- **Infections –** you may get signs of infection, which can vary depending on where in the body the infection is.

Children and adolescents

This medicine should not be used in children or adolescents under the age of 18. This is because there is no information about use in this age group.

Other medicines and Lunsumio

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

Pregnancy and breast-feeding

It is important to tell your doctor before and during treatment if you are pregnant, think you may be pregnant, or are planning to get pregnant. This is because Lunsumio may affect your unborn baby.

- Do not use Lunsumio during pregnancy, unless after discussion with your doctor, it is agreed that the benefits of treatment outweigh any risk to the unborn baby.

Contraception

Women who could become pregnant must use effective contraception during treatment – and for 3 months after the last dose of Lunsumio.

- Talk to your doctor or nurse about suitable methods of contraception.

Breast-feeding

You must not breast-feed during and for at least 3 months after your last treatment. This is because it is not known whether any Lunsumio passes into breast milk and could therefore affect the baby.

Driving and using machines

Lunsumio has a major influence on your ability to drive, cycle or use any tools or machines. Due to the possible symptoms of ICANS, you should be careful while driving, cycling or using heavy or potentially dangerous machines. If you currently have such symptoms, avoid these activities and contact your doctor, nurse, or pharmacist. See section 4 for more information about side effects.

Lunsumio contains polysorbate

This medicine contains the following amount of polysorbate 20, which is equivalent to 0.6 mg/mL:
- Lunsumio 5 mg: each vial contains 0.3 mg of polysorbate 20
- Lunsumio 45 mg: each vial contains 0.6 mg of polysorbate 20

Polysorbate 20 may cause allergic reactions. Tell your doctor if you have any known allergies.

3. How Lunsumio is given

Lunsumio is given under the supervision of a doctor experienced in giving such treatments. Follow the treatment schedule explained to you by your doctor. Check with your doctor if you are not sure.

How Lunsumio is given

Lunsumio solution for injection (5 mg and 45 mg)
It is given as an injection under the skin

Medicines given before Lunsumio treatment

You may be given other medicines 30 to 60 minutes before you are given Lunsumio. This is to help prevent infusion reactions and fever. These other medicines may include:
- Corticosteroids – such as dexamethasone or methylprednisolone
- Paracetamol
- An antihistamine - such as diphenhydramine

How much Lunsumio is given

In cycle 1, you will be given 3 doses of Lunsumio in the 21 days:
- Day 1**:** 5 mg
- Day 8**:** 45 mg
- Day 15**:** 45 mg

In cycle 2 to 17, you will be given just one dose:
- Day 1**:** 45 mg

If you miss a dose of Lunsumio

If you miss an appointment, make another one straight away. For the treatment to be fully effective, it is very important not to miss a dose.

If you stop receiving Lunsumio

Do not stop treatment with Lunsumio unless you have discussed this with your doctor. This is because stopping 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

Tell your doctor straight away if you notice any of the symptoms of the following serious side effects. You may only get one or some of these symptoms.

Cytokine release syndrome
Symptoms can include:
- fever (38°C or higher)
- chills or shaking chills
- cold or pale clammy skin
- difficulty breathing
- feeling dizzy or lightheaded
- fast or uneven heartbeat
- confusion
- feeling very tired or weak
- fainting
- blurred vision
- headache.

Haemophagocytic lymphohistiocytosis
Symptoms can include:
- fever
- enlarged liver and/or spleen
- skin rash
- lymph node enlargement
- easy bruising
- kidney abnormalities
- breathing problems
- heart problems.

Tumour lysis syndrome
Symptoms can include:
- fever
- chills
- feeling or being sick (nausea and vomiting)
- confusion
- being short of breath

- fits (seizures)
- uneven heartbeat
- dark or cloudy urine
- unusual tiredness
- muscle or joint pain.

Shown in blood tests

- increase in potassium, phosphate or uric acid – which can cause kidney problems (part of tumour lysis syndrome)

Tumour flare

Symptoms can include:

- tender swollen lymph nodes
- chest pain
- cough or difficulty breathing easily
- pain at the site of the tumour.

Infections

Symptoms can include:

- fever
- cough
- chest pain
- tiredness
- shortness of breath
- painful rash
- sore throat
- burning pain when passing urine
- feeling weak or generally unwell.

Immune effector cell-associated neurotoxicity syndrome (ICANS)

The symptoms can occur days or weeks after you receive the dose and may initially be subtle.
Symptoms can include:

- confusion/disorientation
- tiredness
- altered mental state
- lowered mental state
- impaired memory

If you have any of these symptoms after treatment with Lunsumio, tell your doctor straight away. You may need medical treatment.

Other side effects

Very common: may affect more than 1 in 10 people

- Rash
- Itchy skin
- Dry skin
- Diarrhoea
- Headache
- Fever
- Chills
- Cytokine release syndrome
- Injection site reaction (only when given under the skin)

Shown in blood tests

- Low levels of some white blood cells (neutropenia)
- Low number of red blood cells, which can cause tiredness and shortness of breath

- Low platelet count, which may make you more likely to bruise or bleed (thrombocytopenia)
- Low level of phosphate, potassium or magnesium
- High level of alanine aminotransferase in the blood

Common: may affect up to 1 in 10 people
- Lung infection
- Infection of upper airways (infection of nose, throat, sinuses)
- Urinary tract infection
- Fever due to low levels of neutrophils (a type of white blood cell)
- Tumour flare
- A serious immune reaction affecting the nervous system (immune effector cell-associated neurotoxicity syndrome)

Shown in blood tests
- Increased levels of liver enzymes, which may be a sign of liver problems

Uncommon: may affect up to 1 in 100 people
- A rapid breakdown of tumour cells resulting in chemical changes in the blood and damage to organs, including the kidneys, heart, and liver (tumour lysis syndrome)
- A condition where the immune system makes too many infection-fighting cells called histiocytes and lymphocytes (haemophagocytic lymphohistiocytosis).

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist 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 Lunsumio

Lunsumio will be stored by the healthcare professionals at the hospital or clinic. The storage details that they must take account of are as follows
- 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 the vial after EXP. The expiry date refers to the last day of that month.
- Store in a refrigerator (2°C – 8°C).
- Do not freeze.
- The prepared syringe for subcutaneous injection should be administered immediately. If not used immediately, the capped syringe should not be kept more than 28 days at 2°C – 8°C and 24 hours at 9°C – 30°C.
- Keep the container in the outer carton in order to protect from light.

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

6. Contents of the pack and other information

What Lunsumio contains

- The active substance is mosunetuzumab.
- Lunsumio 5 mg: Each vial contains 5 milligrams (mg) mosunetuzumab in 0.5 mL at a concentration of 10 mg/mL.
- Lunsumio 45 mg: Each vial contains 45 milligrams (mg) mosunetuzumab in 1 mL at a concentration of 45 mg/mL

- The other ingredients are: L-histidine, L-methionine, acetic acid, sucrose, polysorbate 20 (E432), water for injections (see section 2 “Lunsumio contains polysorbate”)

What Lunsumio looks like and contents of the pack

Lunsumio is a solution for injection (sterile solution). It is a clear, colourless to slightly brownish-yellow liquid provided in a glass vial.

Each pack of Lunsumio contains one vial.

Marketing Authorisation Holder

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

Manufacturer

Roche Pharma AG
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Luxembourg/Luxemburg
N.V. Roche S.A.
België/Belgique/Belgien
Tél/Tel: +32 (0) 2 525 82 11

България
Рош България ЕООД
Тел: +359 2 474 5444

Česká republika
Roche s. r. O.
Tel: +420 - 2 20382111

Danmark
Roche Pharmaceuticals A/S
Tlf.: +45 - 36 39 99 99

Deutschland
Roche Pharma AG
Tel: +49 (0) 7624 140

Latvija
Roche Latvija SIA
Tel: +371 - 6 7039831

Lietuva
UAB “Roche Lietuva”
Tel: +370 5 2546799

Magyarország
Roche (Magyarország) Kft.
Tel: +36 1 279 4500

Nederland
Roche Nederland B.V.
Tel: +31 (0) 348 438050

Norge
Roche Norge AS
Tlf: +47 - 22 78 90 00

Eesti
Roche Eesti OÜ
Tel: + 372 - 6 177 380

Ελλάδα, Κύπρος
Roche (Hellas) A.E.
Ελλάδα
Τηλ: +30 210 61 66 100

España
Roche Farma S.A.
Tel: +34 - 91 324 81 00

France
Roche
Tél: +33 (0) 1 47 61 40 00

Hrvatska
Roche d.o.o.
Tel: +385 1 4722 333

Ireland, Malta
Roche Products (Ireland) Ltd.
Ireland, L-Irlanda
Tel: +353 (0) 1 469 0700

Ísland
Roche Pharmaceuticals A/S
c/o Icepharma hf
Sími: +354 540 8000

Italia
Roche S.p.A.
Tel: +39 - 039 2471

Österreich
Roche Austria GmbH
Tel: +43 (0) 1 27739

Polska
Roche Polska Sp.z o.o.
Tel: +48 - 22 345 18 88

Portugal
Roche Farmacêutica Química, Lda
Tel: +351 - 21 425 70 00

România
Roche România S.R.L.
Tel: +40 21 206 47 01

Slovenija
Roche farmacevtska družba d.o.o.
Tel: +386 - 1 360 26 00

Slovenská republika
Roche Slovensko, s.r.o.
Tel: +421 - 2 52638201

Suomi/Finland
Roche Oy
Puh/Tel: +358 (0) 10 554 500

Sverige
Roche AB
Tel: +46 (0) 8 726 1200

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.

Other sources of information

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

The following information is intended for healthcare professionals only:

Procedures for proper handling and disposal of anticancer medicinal products should be considered

Instructions for preparation

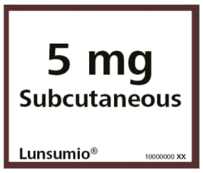
1. Retrieve one 5 mg or 45 mg Lunsumio vial from the refrigerator. DO NOT shake the vial.
2. Withdraw the required volume of Lunsumio solution from the vial into a syringe.
3. Label the syringe with the product name, dose (5 mg or 45 mg), date and time.
4. Apply the peel-off label from the package leaflet to the syringe.
5. Discard the vial and any unused portion of Lunsumio in accordance with the local requirements.

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 under 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.

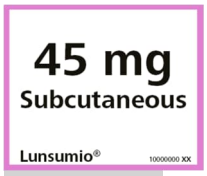
If using the 5 mg/0.5 mL configuration



Peel-off label

Peel and apply this label to the syringe

If using the 45 mg/mL configuration



Peel-off label

Peel and apply this label to the syringe