CLEAN PROFESSIONAL INFORMATION

WARNING: CYTOKINE RELEASE SYNDROME See full prescribing information for complete boxed warning. Cytokine release syndrome (CRS), including serious or life-threatening reactions, can occur in patients receiving LUNSUMIO. Initiate treatment with the LUNSUMIO step-up dosing schedule to reduce the risk of CRS. Withhold LUNSUMIO until CRS resolves or permanently discontinue based on severity. (2.1, 2.4, 5.1)

SCHEDULING STATUS

S4

NAME OF MEDICINE

Lunsumio 1mg/ 1 mL® Concentrate for solution for intravenous Infusion

Lunsumio 30 mg/ 30 mL® Concentrate for solution for intravenous Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Lunsumio contains Mosunetuzumab as the active substance

Mosunetuzumab is a full-length, humanized anti-CD20/CD3 T-cell dependent bispecific antibody of an immunoglobulin (Ig)G1 isotype that is produced in Chinese hamster ovary (CHO) cells.

Lunsumio 1 mg/2 mL concentrate for solution for infusion

Each vial contains 1 mg mosunetuzumab per 2 mL of liquid concentrate, corresponding to a concentration of 1 mg/mL before dilution.

Lunsumio 30mg/50 mL concentrate for solution for infusion

Each vial contains 30 mg mosunetuzumab per 50 mL of liquid concentrate, corresponding to a concentration of 1 mg/mL before dilution.

Contains sugar (sucrose) 82.1 mg for 1 mg/1 mL and 2462,4 mg for 30 mg/30 mL vial

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Lunsumio is provided as a sterile, colorless, preservative-free concentrate for solution for intravenous infusion formulated at 1 mg/mL mosunetuzumab in single-use vials.

4 CLINICAL PARTICULARS

4.1 Therapeutic indication

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

General

Substitution by any other biological medicinal product requires the consent of the prescribing physician.

Lunsumio must only be administered as an intravenous infusion under the supervision of a qualified physician with appropriate medical support to manage severe reactions such as cytokine release syndrome. (see Section 4.4 Special precautions and warnings).

Do not administer as an IV push or bolus.

Prophylaxis and premedication

Lunsumio should be administered to well-hydrated patients. Table 1 provides details on recommended premedication for cytokine release syndrome and infusion related reactions.

Table 1: Premedication to be administered to patients prior to Lunsumio Infusion

Patients requiring premedication	**Premedication**	**Dosage**	**Administration**
Cycles 1 and 2: all patients Cycles 3+: patients who experienced any grade CRS with previous dose	Corticosteroid	Dexamethasone 20 mg IV or methylprednisolone 80 mg IV	Complete at least 1 hour prior to infusion
	Anti-histamine	Diphenhydramine hydrochloride 50-100 mg or equivalent oral or IV anti-histamine	At least 30 minutes prior to infusion
	Anti-pyretic	Oral acetaminophen or paracetamol (500-1000 mg)	At least 30 minutes prior to infusion

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

Table 2: Dose of Lunsumio for patients with 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.
Cycle 3+	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

If any dose in cycle 1 is delayed for >7 days, the previous tolerated dose should be repeated prior to resuming the planned treatment schedule.

If a dose interruption occurs between cycles 1 and 2 that results in a treatment-free interval of ≥6 weeks, administer Lunsumio at 1 mg on Day 1, 2 mg on Day 8, then resume the planned cycle 2 treatment of 60 mg on Day 15.

If a dose interruption occurs that results in a treatment-free interval of ≥6 weeks between any cycles in cycle 3 onwards, administer Lunsumio at 1 mg on Day 1, 2 mg on Day 8, then resume the planned treatment schedule of 30 mg on Day 15.

Dose Modifications

Identify cytokine release syndrome (CRS) based on clinical presentation (see section 4.4 Warnings and Precautions). Evaluate for and treat 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, manage according to the recommendations in Table 3.

Table 3: CRS Grading1 and Management

CRS Grade	Current Infusion of Lunsumio	Management of CRS2	Next Scheduled Infusion of Lunsumio
Grade 1 Fever ≥38ºC	Interrupt infusion and treat symptoms.	Treat symptoms. If CRS event lasts > 48 hours after symptomatic management.	Ensure symptoms are resolved for 72 hours. Consider more frequent Monitoring.
	Re-start infusion at the same infusion rate when symptoms resolve. If symptoms recur with re-administration, discontinue current infusion. Resume treatment at the	consider dexamethasone and/or tocilizumab.	

	next scheduled infusion.		
Grade 2 Fever ≥38ºC and/or hypotension not requiring vasopressors and/or hypoxia requiring low-flow oxygen3 by nasal cannula or blow-by	Interrupt infusion and treat symptoms. Re-start infusion at 50% rate when symptoms resolve. If symptoms recur with re-administration, discontinue current infusion. Resume treatment at the next scheduled infusion	Treat symptoms. If no clinical improvement is observed after symptomatic management, consider dexamethasone4 and/or tocilizumab5. If there is no improvement within 24 hours or rapid progression of CRS, manage per Grade 3.	Ensure symptoms are resolved for 72 hours. Consider maximizing premedication as appropriate.7 Consider infusing the next dose at 50% rate, with more frequent monitoring.
Grade 3 Fever ≥38ºC and/or hypotension requiring a vasopressor (with or without vasopressin) and/or hypoxia requiring high flow oxygen6	Discontinue current infusion and treat symptoms. Do not resume the current infusion. Resume treatment at the next scheduled infusion	Treat symptoms. Administer tocilizumab5 and dexamethasone4. If there is no improvement or rapid progression of CRS, consider alternative anti-cytokine therapy and methylprednisolone 1000 mg/day IV.	Ensure symptoms are resolved for 72 hours. Hospitalize for the next infusion. Maximize premedication as appropriate.7 Administer the next infusion at 50% rate

by nasal cannula, face mask, non-rebreather mask, or Venturi mask			
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)	Discontinue current infusion and treat symptoms. Do not resume the current treatment.	Treat symptoms. Administer tocilizumab5 and dexamethasone4. If there is no improvement or rapid progression of CRS, consider alternative anti-cytokine therapy and methylprednisolone 1000 mg/day IV.	Permanently discontinue treatment.

[1] ASTCT = American Society for Transplant and Cellular Therapy.

[2] If CRS is refractory to management, consider other causes including hemophagocytic lymphohistiocytosis.

[3] Low-flow oxygen is defined as oxygen delivered at <6 L/minute.

[4] Dexamethasone should be administered at 10 mg IV every 6 hours (or equivalent).

[5] Tocilizumab should be administered at a dose of 8 mg/kg IV (8 mg/kg for participants at a weight of ≥30 kg only; 12mg/kg for participants at a weight of <30 kg; doses exceeding 800 mg per infusion are not recommended); repeat every 8 hours as necessary (up to a maximum of 4 doses).

[6] High-flow oxygen is defined as oxygen delivered at ≥6 L/minute.

[7] Refer to Table 1 for additional information.

Dose modifications for other clinically significant adverse reactions

Patients who experience grade 3 or 4 reactions should have treatment temporarily withheld until symptoms are resolved**.**

Pediatric Use

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

Geriatric Use

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

Renal impairment

No dose adjustment is required in patients with mild or moderate renal impairment. A recommended dose has not been determined for patients with CrCl <30 mL/min (see section 5.2 Pharmacokinetic properties).

Hepatic impairment

No dose adjustment of Lunsumio is required for patients with mild hepatic impairment [total bilirubin greater than upper limit of normal (ULN) and ≤ 1.5x ULN or aspartate transaminase greater than ULN]. (see section 5.2 Pharmacokinetic properties). A recommended dose has not been determined for Lunsumio in patients with moderate or severe hepatic impairment.

4.3 Contraindications

Lunsumio is contraindicated in patients with a known hypersensitivity to mosunetuzumab or any of the excipients.

4.4 Special warnings and precautions for use

General

In order to improve traceability of biological medicinal products, the trade name and the batch number of the administered product should be clearly recorded (or stated) in the patient file.

Sugar

Lunsumio contains D sucrose. Patients with the rare hereditary conditions of galactose intolerance lactase deficiency, glucose-galactose malabsorption intolerance should not take Lunsumio.
Lunsumio contains D sucrose which may have an effect on the glycaemic control of
patients with diabetes mellitus.

Cytokine Release Syndrome (CRS)

CRS, including life-threatening reactions, have occurred in patients receiving Lunsumio. 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.

Premedicate patients with corticosteroids, antipyretics and antihistamines at least through cycle 2. Ensure adequate hydration prior to the administration of Lunsumio. Monitor patients for signs or symptoms of CRS. Counsel patient to seek immediate medical attention should signs or symptoms of CRS occur at any time. Institute treatment with supportive care, tocilizumab and/or corticosteroids as indicated (see section 4.2 Psology and method of administration).

Serious infections

Serious infections such as pneumonia, bacteremia, and sepsis or septic shock have occurred in patients receiving Lunsumio some of which were life-threatening or fatal events. 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. Administer prophylactic antibacterial, antiviral and/or antifungal medications, as appropriate. Monitor patients for signs and symptoms of infection before and after Lunsumio administration and treat appropriately. In the event of febrile neutropenia, evaluate for infection and manage with antibiotics, fluids and other supportive care.

Tumor flare

Tumor flare has been reported in patients treated with Lunsumio. Manifestations included new or worsening pleural effusions, localized pain and swelling at the sites of lymphoma lesions and tumor inflammation. Consistent with the mechanism of action of Lunsumio tumor flare is likely due to the influx of T-cells into tumor sites following Lunsumio administration.

There are no specific risk factors for tumor flare that have been identified, however, there is a heightened risk of compromise and morbidity due to mass effect secondary to tumor flare in patients with bulky tumors located in close proximity to airways and/or a vital organ. Monitoring and evaluation for tumor flare at critical anatomical sites is recommended in patients treated with Lunsumio.

Tumor lysis syndrome (TLS)

TLS has been reported in patients receiving Lunsumio. Ensure adequate hydration prior tothe administration of Lunsumio. Administer prophylactic anti-hyperuricemic therapy (e.g allopurinol, rasburicase), as appropriate. Monitor patients for signs or symptoms of TLS, especially patients with

high tumor burden or rapidly proliferative tumors, and patients with reduced renal function. Monitor blood chemistries and manage abnormalities promptly.

Drug Abuse and Dependence

Lunsumio does not have the potential for abuse and dependence.

4.5 Interaction with other medicines and other forms of interaction

No dedicated pharmacokinetic drug-drug interaction studies have been conducted with mosunetuzumab. Physiologically based pharmacokinetics modeling and simulations based on IL-6 and cytochrome P450 (CYP) 3A interaction indicated a low risk of cytokine-mediated drug-drug interaction potential for mosunetuzumab. No dose adjustment for Lunsumio is recommended with co-administration of Lunsumio with small molecule drugs which are CYP3A substrates.

Upon initiation of Lunsumio in patients who are receiving concomitant drugs that are sensitive CYP3A substrates with a narrow therapeutic index, monitor for effect or drug concentration or dose adjust the CYP3A substrate accordingly, if warranted.

4.6 Fertility, pregnancy and lactation

Contraception

Women of childbearing potential should use contraception while receiving Lunsumio and for at least 3 months after the last infusion of Lunsumio (see section 5.2 Pharmacokinetic Properties, Elimination).

Pregnancy

Lunsumio should be avoided during pregnancy unless the potential benefit to the mother outweighs the potential risk to the fetus. There are no adequate and well-controlled data from studies in pregnant women; however transient peripheral B-cell depletion and lymphocytopenia have been

reported in infants born to mothers exposed to other anti-CD20 antibodies during pregnancy. (see section 5.3 Non clinical safety data)

Labor and Delivery

The safe use of Lunsumio during labor and delivery has not been established.

Breastfeeding

It is unknown whether Lunsumio is excreted in human breast milk or has any effect on the breastfed child and on milk production. Because human IgG is excreted in human milk, and the potential for mosunetuzumab absorption leading to B-cell depletion is unknown, women should be advised to discontinue breastfeeding during Lunsumio therapy.

Pediatric Use

The safety and efficacy of Lunsumio in children and adolescents (<18 years of age) has not been studied.

Geriatric Use

Among the 214 patients treated with Lunsumio92 (43%) were 65 years of age or older. No clinically important differences in safety or effectiveness of Lunsumio were observed between these patients and younger patients**.**

Renal Impairment

The safety and efficacy of Lunsumio in patients with renal impairment has not been formally studied. Patients with mild and moderate renal impairment were included in clinical trials. Lunsumio is a monoclonal antibody and cleared via catabolism (rather than renal excretion), and

a change in dose is not expected to be required for patients with renal impairment (see section 5.2 Pharmacokinetics properties).

Hepatic Impairment

The safety and efficacy of Lunsumio in patients with hepatic impairment has not been formally studied. Patients with mild hepatic impairment were included in clinical trials. Lunsumio is a monoclonal antibody and cleared via catabolism (rather than hepatic metabolism), and a change in dose is not expected to be required for patients with hepatic impairment (see section 5.2 Pharmacokinetic properties)

4.7 Effects on ability to drive and use machines.

Lunsumio may have a minor influence on the ability to drive and use machines.
Patients who experience events that impair consciousness should be evaluated and advised not to drive and refrain from operating heavy or potentially dangerous machinery until events are resolved.

4.8 Undesirable effects

Clinical Trials

The adverse drug reactions (ADRs) described in this section were identified from the clinical studies in patients treated at the recommended dose (n=214). The median number of cycles was 8, 37% received 8 cycles, and 15% received more than 8 cycles up to 17 cycles.

Table 4 summarizes the adverse drug reactions (ADRs) that have been reported in association with the use of Lunsumio.

MedDRA PT	Frequency category
Blood and lymphatic system disorders	
Neutropenia[1]	Very common

Anemia	Very common
Thrombocytopenia[2]	Very common
Febrile neutropenia	common
Gastrointestinal disorders	
Diarrhea	Very common
General disorders and administration site conditions	
Pyrexia	Very common
Immune system disorders	
Cytokine release syndrome[3]	Very common
Infections and infestations	
Upper respiratory tract infection	common
Urinary tract infection	common
Pneumonia	common
Investigations	
Alanine aminotransferase, increased	Very common
Aspartate aminotransferase increased	common
Metabolism and nutrition disorders	
Hypophosphatemia	Very common
Hypokalemia	Very common
Hypomagnesemia	Very common
Tumor lysis syndrome	Uncommon
Neoplasms benign, malignant and unspecified (including cysts and polyps)	

Tumor flare	common
Nervous system disorders	
Headache	Very common
Skin and subcutaneous tissue disorders	
Rash	Very common
Pruritus	Very common
Dry skin	Very common

[1] Neutropenia includes neutropenia and neutrophil count decreased

[2] Thrombocytopenia includes thrombocytopenia and platelet count decreased

3 By American Society for Transplant and Cellular Therapy

Additional information for selected adverse drug reactions

The data below reflect information for significant adverse reactions for Lunsumio.

Cytokine release syndrome

Cytokine release syndrome (ASTCT grading system) of any grade occurred in 39% (84/214) of patients, with grade 2 occurring in 15%, 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 and also experienced concurrent TLS. No patients had a fatal CRS event.

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% occurring in patients after the Cycle 2 and 2% 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 26 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 84 patients that experienced CRS, the most common signs and symptoms of CRS included pyrexia (96%), hypotension (36%), chills (33%), tachycardia (24%), hypoxia (23%) and headache (16%).

Sixteen percent (34/214) of patients received tocilizumab and/or a corticosteroid, 10% (21/214) received tocilizumab, 10% (22/214) received corticosteroids, and 4% (9/214) received both tocilizumab and corticosteroids.

In patients experiencing Grade 2 CRS, 48% (16/33) of patients were treated with symptomatic management without corticosteroids or tocilizumab, 33% (11/33) received corticosteroids, 30% (10/33) received tocilizumab, and 12% (4/33) received both corticosteroids and tocilizumab. Patients with grade 3 (n=5) or grade 4 (n=1) CRS received tocilizumab, corticosteroids, vasopressors and/or oxygen supplementation. Hospitalizations due to CRS occurred in 20% (43/214) of patients and the median duration of hospitalization was 5 days (range 0-28 days).

Neutropenia

Neutropenia of any grade occurred in 28% (59/214), including 24% Grade 3-4 events. The median time to onset of first neutropenia/neutrophil count decreased events was 46 days (range: 1-280 days), with median duration of 8 days (range: 1 - 314 days). Of the 59 patients who had neutropenia/neutrophil count decreased events 70% (41/59) received treatment G-CSF to treat the events.

Serious Infections

Serious infections of any grade occurred in 16% (35/214) of patients. Four (1.9%) patients experienced serious infections concurrently with Grade 3-4 neutropenia. The median time to onset of first serious infection was 40 days (range: 1-261 days), with median duration of 12 days (range: 2-174 days). Grade 5 events occurred in 0.9% (2/214) patients, which included pneumonia and sepsis.

Tumor Flare

Tumor flare (including pleural effusion and tumor inflammation) occurred in 4% (9/214) of patients, which included 1.9% grade 2 and 2.3% grade 3 events. The median time to onset was 13 days (range 5-84 days), and median duration was 10 days (range 1-77 days).

Tumor Lysis Syndrome

TLS occurred in 0.9% (2/214) 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.

Post marketing Experience

Not applicable

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the “6.04 Adverse Drug Reaction Report Form”, found online under SAHPRA’s publications:

https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Not applicable

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agent, ATC code: not yet assigned.

Mechanism of action

Mosunetuzumab is an anti-CD20/CD3 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.

Pharmacodynamic effects

Lunsumiocaused B-cell depletion (defined as CD19 B-cell counts < 0.07 x 109/L) and hypogammaglobulinemia (defined as IgG levels < 500 mg/dL).

Clinical / Efficacy Studies

An open-label, multicenter, multi-cohort study (GO29781) was conducted to evaluate
Lunsumio in patients with relapsed or refractory B-cell non-Hodgkin's lymphoma. 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.

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/hemophagocytic lympho histiocytosis, prior allogeneic stem cell transplant, or prior organ transplantation.

Patients received Lunsumio intravenously 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+ 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, 61% were male, 82% were white, 9% were Asian, 4% were Black, 100% had an Eastern Cooperative Oncology Group (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 as assessed by an independent review facility (according to standard criteria for NHL (Cheson 2007). The efficacy results are summarized in Table 5.

Table 5 Summary of efficacy in patients with FL

Efficacy parameter	Lunsumio

	N=90
Median observation time 12.9 months	
Complete Response (CR), n (%), (95% CI)	52 (57.8) (46.9, 68.1)
Objective Response Rate (ORR) n (%) (95% CI) Partial Response (PR) n (%) (95% CI)	71 (78.9) (69.0, 86.8) 19 (21.1) 13, 31
Duration of Response (DOR)1 Patients with event, n (%) Median, months (95% CI) K-M event-free proportion 12 months (95% CI) 9 months (95% CI)	20 (28.2) NR 65 (52.6, 78.1) 72 (60.9, 83.7)
Duration of Response in Patients who achieved CR (DORC)2 Patients with event, n (%) Median, months (95% CI) K-M 12-month event-free proportion, % (95% CI)	8 (15.4) NR 80.1 (67.4, 92.7)

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

[1] DOR is defined as the time from the initial occurrence of a documented PR or CR until documented disease progression or death due to any cause, whichever occurs first.

[2] DORC is defined as the time from the initial occurrence of a documented PR or CR until documented disease progression or death due to any cause, whichever occurs first.
Baseline levels in EORTC QLQ-C30 Physical Functioning, EORTC QLQ-C30 Fatigue and FACT-Lym Subscale were maintained during treatment (up to cycle 8).

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay.

Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of anti-Lunsumio antibodies in the study described below with the incidence of antibodies to other products may be misleading.

The immunogenicity of Lunsumio was evaluated using an enzyme-linked immunosorbent assay (ELISA). No patients tested positive for anti-Lunsumio antibodies in 418 ADA-evaluable patients who received Lunsumio single-agent IV treatments in Study GO27981. Based on the available information, the clinical relevance of anti-Lunsumio antibodies could not be assessed.

5.2 Pharmacokinetic properties

Lunsumio PK exposure increased in an approximately dose-proportional manner over the dose range studied. The population PK following intravenous administrations of Lunsumio was described by a 2-compartment PK model with time-dependent clearance, which was parameterized 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 Lunsumio was observed and characterized by inter-individual variability ranging from 18% to 86% clearance volume (CV) for mosunetuzumab PK parameters.

After the first two cycles (i.e., 42 days) of the dosing with mosunetuzumab, the serum

concentration reaches the C_{max} at the end of dose of cycle 2 Day 1 of the mosunetuzumab IV 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 246 day •µ g/mL with %CV of 46.9%

Absorption

Lunsumio vis administered intravenously.

Distribution

The population estimate of central volume of distribution for Lunsumio was 5.49 L with intravenous infusion of Lunsumio.

Metabolism

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

Elimination

Based on a population pharmacokinetic analysis, the estimated mean steady-state clearance (CL_{ss}) and baseline clearance ($CL_{baseline}$) 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 PK model estimates.

Special populations

No clinically meaningful baseline covariates were found for mosunetuzumab PK requiring dose adjustments.

Geriatric population

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

Paediatric Population

No studies have been conducted to investigate the pharmacokinetics of Lunsumioin pediatric patients (<18 years old).

Renal impairment

The population pharmacokinetic analysis of Lunsumio showed that creatinine clearance (CrCl) does not affect pharmacokinetics of Lunsumio. Pharmacokinetics of Lunsumio 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 dosage recommendations can be made. Lunsumiowas not studied in patients with end-stage renal disease and/or who are on dialysis.

Hepatic impairment

The population pharmacokinetic analysis of Lunsumio showed that hepatic impairment does not affect pharmacokinetics of Lunsumio. Pharmacokinetics of Lunsumio 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.

5.3 Non clinical safety data

Carcinogenicity

No carcinogenicity studies have been conducted with Lunsumio.

Genotoxicity

No genotoxicity studies have been conducted with Lunsumio. As an antibody, Lunsumio is not expected to interact directly with DNA.

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. Lunsumio had no effect on either male or female reproductive organs at exposures (AUC) approximately 5 times the AUC in patients receiving the recommended dose.

Reproductive toxicity

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

Other

Key nonclinical findings with Lunsumio 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 Cmax and AUC exposures over 50- and 20-times, respectively, higher than those in patients exposed to Lunsumio for the similar duration. No other neurological abnormalities were observed in any toxicity studies.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

L-histidine

L-methionine

Acetic acid

Sucrose

Polysorbate 20

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 diluents other than 0.9% or 0.45% sodium chloride solution to dilute Lunsumio since its use has not been tested.
- No incompatibilities have been observed between Lunsumio and IV 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).

6.3 Shelf life

24 months

6.4 Special precautions for storage

Vials

Store at 2°C-8°C.

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

Do not freeze. Do not shake.

This medicine should not be used after the expiry date (EXP) shown on the pack.

Shelf-life of the solution for infusion containing the product

The prepared infusion solution should be used immediately. If not used immediately, the infusion solution may be stored refrigerated at 2-8°C for up to 24 hours prior to administration and up to 24 hours at ambient temperature (9°C -30°C). Lunsumio does not contain antimicrobial preservatives. Therefore, care must be taken to ensure that the solution for infusion is not microbiologically compromised during preparation.

6.5 Nature and contents of container

Lunsumio 1 mg/vial: Pack of 1 vial. Colourless 2 mL, Type I, borosilicate glass vial with a flouroresin laminated gray rubber stopper, sealed with a 13 mm aluminium seal with plastic flip-off cap (dark grey).

Lunsumio 30 mg/vial: Pack of 1 vial. Colourless 50 mL, Type I, borosilicate glass vial with a flouroresin laminated gray rubber stopper, sealed with a 20 mm aluminium seal with plastic flip-off cap (light blue).

6.6 Special precautions for disposal and other handling

Lunsumio must be diluted into an infusion bag containing 0.9% or 0.45% sodium chloride solution by a healthcare professional using aseptic technique prior to administration.

Use sterile needle and syringe to prepare Lunsumio. The product contains no preservative and is intended for single-dose use only. 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.

Dilution

1. Withdraw a volume of 0.9% or 0.45% sodium chloride solution equal to the volume of the Lunsumio required for the patient's dose from the infusion bag according to the Table 6 below and discard.
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 6: Dilution of Lunsumio

Day of Treatment	**Dose of Lunsumio**		**Volume of Lunsumio in 0.9% or 0.45% sodium chloride solution**	**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+	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 insert to the infusion bag

Disposal of Unused/Expired Medicines

The release of pharmaceuticals in the environment should be minimized. Medicines 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. HOLDER OF CERTIFICATE OF REGISTRATION

Roche Products (Pty) Ltd

90 Bekker Road

Hertford Office Park

Building E

Vorna Valley

Midrand, 1685

South Africa

Roche Ethical Assistance Line (REAL) toll-free: 0800 21 21 25

8. REGISTRATION NUMBER(S)

Lunsumio 1mg/ mL: 57/30.1/0372

Lunsumio 30mg/ mL: 57/30.1/0373

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Registration: 18 March 2025

10. DATE OF REVISION OF THE TEXT

Last revision: 18 March 2025

Approved Manufacturer(s)

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