Lunsumio®

MOSUNETUZUMAB

Concentrate for Solution for Infusion

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

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 240-333 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) (see section 4.4).

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	Intravenous corticosteroids: dexamethasone 20 mg or methylprednisolone 80 mg	Complete at least 1 hour prior to Lunsumio infusion
Cycles 3 and beyond: patients who experienced any grade CRS with previous dose	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

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, Lunsumio should be administered 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, Lunsumio should be administered at 1 mg on Day 1, 2 mg on Day 8, then resume the planned treatment schedule of 30 mg on Day 15.

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).

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 3.

Table 3 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 • 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	The symptoms should be resolved for at least 72 hours prior to next infusion The patient should be monitored more frequently
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 maximized 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	If CRS occurs during infusion: • The current infusion should be discontinued • The symptoms should be treated	The symptoms should be resolved for at least 72 hours prior to next infusion Patients should be

vasopressor (with or without vasopressin) and/or hypoxia requiring high flow oxygen[8] by nasal cannula, face mask, non-rebreather mask, or Venturi mask	• 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	hospitalized for the next infusion Premedication should be maximized 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) and/or hypoxia requiring oxygen by positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation)	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: • Alternative immunosuppressants[9] and methylprednisolone 1 000 mg/day intravenously should be administered until clinical improvement	

[1] ASTCT = American Society for Transplant 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 hemophagocytic 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)

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 and adolescents 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). Haemophagocytic lymphohistiocytosis (HLH), including fatal cases, has 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.

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.

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.

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 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 to refrain from operating heavy or potentially dangerous machines until events are resolved.

4.8 Undesirable effects

Summary of safety profile

The adverse reactions (ARs) described in this section were identified from the pivotal clinical trial GO29781 in patients treated at the recommended dose (n=218). Patients had follicular lymphoma (41.3%), diffuse large B-cell lymphoma/transformed follicular lymphoma (40.4%) mantle cell lymphoma (11.5%), Richter's transformation (6.4%), and other histologies (0.5%). The median number of cycles of Lunsumio received was 8 (range 1 -17), 37% of patients received 8 cycles, and 15% received more than 8 cycles up to 17 cycles.

The most common adverse reactions (≥ 20%) observed were cytokine release syndrome, neutropenia, pyrexia, hypophosphatemia and headache. The most common serious adverse reactions (≥ 2%) observed included cytokine release syndrome (CRS) (21% by ASTCT grading system), pyrexia (5%), and pneumonia (3%). Nine of 218 patients (4.1%) discontinued Lunsumio due to an adverse event. 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 4 Adverse reactions occurring in patients treated with Lunsumio

System organ class / preferred term or adverse reaction	**All grades**	**Grade 3 – 4**
Infections and infestations		
Upper respiratory tract infection	Common	Common
Urinary tract infection	Common	Common
Pneumonia	Common	Common
Neoplasms benign, malignant and unspecified (including cysts and polyps)		
Tumour flare	Common	Common
Blood and lymphatic system disorders		
Neutropenia[1]	Very common	Very common
Anaemia	Very common	Common
Thrombocytopenia[2]	Very common	Common
Febrile neutropenia	Common	Common
Haemophagocytic lymphohistiocytosis	Uncommon	Uncommon
Immune system disorders		
Cytokine release syndrome[3]	Very common	Common
Metabolism and nutrition disorders		
Hypophosphataemia	Very common	Very common
Hypokalaemia	Very common	Common
Hypomagnesaemia	Very common	Very rare
Tumour lysis syndrome	Uncommon	Uncommon
Nervous system disorders		
Headache	Very common	Uncommon
Gastrointestinal disorders		

System organ class / preferred term or adverse reaction	All grades	Grade 3 – 4
Diarrhoea	Very common	Very rare
Skin and subcutaneous tissue disorders		
Rash	Very common	Uncommon
Pruritus	Very common	Very rare
Dry skin	Very common	Very rare
General disorders and administration site conditions		
Pyrexia	Very common	Common
Chills	Very common	Uncommon
Investigations		
Alanine aminotransferase, increased	Very common	Common
Aspartate aminotransferase, increased	Common	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

Description of selected adverse reactions

Cytokine release syndrome (CRS)

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.

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

Neutropenia

Neutropenia of any grade occurred in 28% of patients, including 24% Grade 3-4 events. The median time to onset of first neutropenia/neutrophil count decreased events was 48 days (range: 1-280 days), with median duration of 8 days (range: 1-314 days). Of the 60 patients who had neutropenia/neutrophil count decreased events 68% received treatment G-CSF to treat the events.

Serious infections

Serious infections of any grade occurred in 17% of patients. 1.8% of patients experienced serious infections concurrently with grade 3-4 neutropenia. The median time to onset of first serious infection was 50 days (range: 1-561 days), with median duration of 12 days (range: 2-174 days). Grade 5 events occurred in 0.9% of patients, which included pneumonia and sepsis.

Tumour flare

Tumour flare (including pleural effusion and tumour inflammation) occurred in 4% of patients, which included 1.8% 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).

Tumour Lysis Syndrome (TLS)

TLS occurred in 0.9% 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 4 and 6 days, respectively.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form sideeffects.health.gov.il/

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 antineoplastic agents; monoclonal antibodies, 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 < 0.07 x 10^9/L) and hypogammaglobulinemia (defined as IgG levels < 500 mg/dL).

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 / hemophagocytic 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 5.

Table 5 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 (%)	18 (20.0)
(95% CI)	(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.

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 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 mosunetuzumab was observed and characterized 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•µg/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

Sucrose
L-histidine
L-methionine
Polysorbate 20 (E 432)
Acetic acid (pH adjustment)
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

The expiry date of the product is indicated on the packaging materials.

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 butyl 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 butyl 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

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 6 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 6: 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 Pharmaceuticals (Israel) Ltd., P.O.Box 6391 Hod Hasharon 4524079.

8. MARKETING AUTHORISATION NUMBER(S)

172-15-37418-00

9. MANUFACTURER

F. Hoffmann-La Roche Ltd. Basel, Switzerland

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