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INJ-LUN-2024 08

Lunsumio®

Mosunetuzumab

1. DESCRIPTION

1.1 THERAPEUTIC / PHARMACOLOGIC CLASS OF DRUG

Antineoplastic agents
ATC code: L01FX25

1.2 TYPE OF DOSAGE FORM

Concentrate for solution for Infusion

1.3 ROUTE OF ADMINISTRATION

Intravenous (IV) Infusion

1.4 STERILE / RADIOACTIVE STATEMENT

Sterile Product

1.5 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient(s): mosunetuzumab

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 is provided as a sterile, colorless, preservative-free concentrate for solution for intravenous infusion formulated at 1 mg/mL mosunetuzumab in colorless type I borosilicate single-use glass vials with fluororesin-laminated latex-free rubber stopper and aluminium seal with plastic flip-off cap.

- 1 mg in a 2 mL vial
- 30 mg in a 50 mL vial

Excipients: Glacial acetic acid, L-histidine, L-methionine, polysorbate 20, sucrose and water for injection.

The pH of lunsumio is between 5.5 to 6.1 and the osmolality is between 240 to 333 mOsm/kg.

2. CLINICAL PARTICULARS

2.1 THERAPEUTIC INDICATION(S)

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

2.2 DOSAGE AND ADMINISTRATION

General

Lunsumio must only be administered as an intravenous infusion under the supervision of a qualified healthcare professional with appropriate medical support to manage severe reactions such as cytokine release syndrome and neurologic toxicity. *(see Section 2.4 Warnings and Precautions).*

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 antihistamine	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 Doses

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

Cytokine Release Syndrome

Identify cytokine release syndrome (CRS) based on clinical presentation (see section 2.4 *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[1] Grading and Management

CRS Grade	CRS Management[2]	Next Scheduled Infusion of Lunsumio
Grade 1 Fever ≥38ºC	If CRS occurs during infusion: • Interrupt infusion and treat symptoms • Re-start infusion at the same rate when symptoms resolve • If symptoms recur with re-administration, discontinue current infusion If CRS occurs post-infusion: • Treat symptoms If CRS lasts >48 hours after symptomatic management: • Consider dexamethasone[3] and/or tocilizumab[4,5]	Ensure symptoms are resolved for at least 72 hours prior to next infusion Monitor patient 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: • Interrupt infusion and treat symptoms • Re-start infusion at 50% rate when symptoms resolve • If symptoms recur with re-administration, discontinue current dose If CRS occurs post-infusion: • Treat symptoms If no improvement occurs after symptomatic management: • Consider dexamethasone[3] and/or tocilizumab[4,5]	Ensure symptoms are resolved for at least 72 hours prior to next infusion Maximize premedication as appropriate[7] Consider infusing the next dose at 50% rate, with more frequent monitoring[8]
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: • Discontinue current infusion • Treat symptoms • Administer dexamethasone[3] and tocilizumab[4,5] If CRS occurs post-infusion: • Treat symptoms • Administer dexamethasone[3] and tocilizumab[4,5] If CRS is refractory to dexamethasone and tocilizumab[4,5]: • Consider alternative immunosuppressants[8] and methylprednisolone 1000 mg/day IV until clinical improvement	Ensure symptoms are resolved for at least 72 hours prior to next infusion. Hospitalize for the next infusion. Maximize premedication as appropriate.[7] Administer the next infusion at 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: • Permanently discontinue treatment with Lunsumio • Treat symptoms • Administer dexamethasone[3] and tocilizumab[4,5] If CRS is refractory to dexamethasone and tocilizumab: • Consider alternative immunosuppressants[9] and methylprednisolone 1000 mg/day IV	

[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 IV 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)

Neurologic Toxicity Including Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)

Management recommendations for neurologic toxicity, including ICANS, is summarized in Table 4. At the first sign of neurologic toxicity, including ICANS, withhold Lunsumio for grade 2 and above and consider neurology evaluation. Rule out other causes of neurologic symptoms. Provide supportive therapy, which may include intensive care.

Table 4 Recommendations for Management of Neurologic Toxicity (including ICANS)

Adverse Reaction	Grade[a,b]	Actions
Neurologic Toxicity[a] (Including ICANS[b])	Grade 1	• Continue Lunsumio and monitor neurologic toxicity symptoms. • If Grade 1 ICANS,[b] consider a single dose of dexamethasone 10 mg, if not taking other corticosteroids
	Grade 2	• Withold Lunsumio until neurologic toxicity symptoms improve to Grade 1 or baseline,[c,d] Provide supportive therapy and consider neurologic consultation and evaluation. • If Grade 2 ICANS,[b] treat with dexamethasone 10 mg intravenously every 12 hours, if not taking other corticosteroids, until improvement to Grade 1, then taper.
	Grade 3	• Withold Lunsumio until neurologic toxicity symptoms improve to Grade 1 or baseline for at least 7 days.[d,e] • For Grade 3 neurologic events lasting more than 7 days, consider permanently discontinuing Lunsumio. • Provide supportive therapy, which may include intensive care, and consider neurologic consultation and evaluation. • • If Grade 3 ICANS,[b] 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.
	Grade 4	• Permanently discontinue Lunsumio. • Provide supportive therapy, which may include intensive care, and consider neurologic consultation and evaluation. • If Grade 4 ICANS,[b] 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.

a. Neurologic toxicity grading per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03.
b. American Society for Transplantation and Cellular Therapy (ASTCT) consensus grading criteria.
c. Consider the type of neurologic toxicity before deciding to withhold Lunsumio.
d. See *Delayed or Missed Doses* for guidance on restarting Lunsumio after dose delay.
e. Evaluate benefit/risk before restarting Lunsumio.

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.

2.2.1 Special Dosage Instructions

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 2.5.5 *Use in Special Populations, Geriatric Use*).

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 sections 2.5.6 *Renal Impairment* and 3.2.5 *Pharmacokinetics in Special Populations*).

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 2.5.7 Hepatic Impairment* and *3.2.5 Pharmacokinetics in special populations*). A recommended dose has not been determined for Lunsumio in patients with moderate or severe hepatic impairment.

2.3 CONTRAINDICATIONS

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

2.4 WARNINGS AND PRECAUTIONS

2.4.1 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.

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 *2.3 Dosage and Administration*).

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.

Neurologic Toxicity Including Immune Effector Cell-Associated Syndrome (ICANS)

Lunsumio can cause serious neurologic toxicity, including serious and life-threatening ICANS.

The most frequent neurologic toxicities were headache, peripheral neuropathy, dizziness, and mental status changes (including confusional state, disturbance in attention, cognitive disorder, delirium, encephalopathy, and somnolence).

Coadministration of Lunsumio with other products that cause dizziness or mental status changes may increase the risk of neurologic toxicity.

Monitor patients for signs and symptoms of neurologic toxicity during treatment. At the first sign of neurologic toxicity, including ICANS, immediately evaluate the patient, consider neurology evaluation as appropriate, and provide supportive therapy based on severity; withhold or permanently discontinue Lunsumio based on severity and follow management recommendations.

Patients who experience neurologic toxicity such as tremors, dizziness, insomnia, severe neurotoxicity, or any other adverse reactions that impair consciousness should be evaluated, including potential neurology evaluation, and patients at increased risk should be advised not to drive and to refrain from operating heavy or potentially dangerous machinery until resolution.

Hemophagocytic lymphohistiocytosis

Hemophagocytic lymphohistiocytosis (HLH), including fatal cases, has occurred in patients receiving Lunsumio, in the setting of disease progression and/or viral infections. HLH is a hyperinflammatory syndrome with potentially life-threatening complications, characterized by fever, hepatomegaly and cytopenias. HLH, including Immune Effector Cell Associated HLH-like Syndrome (IEC-HS), should be considered when the presentation of CRS is atypical or prolonged. Patients should be monitored

for clinical signs and symptoms of HLH. For suspected HLH, Lunsumio must be interrupted and treatment for HLH initiated per current practice guidelines.

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 to the 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.

2.4.2 Drug Abuse and Dependence
Lunsumio does not have the potential for abuse and dependence.

2.4.3 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, including ICANS, should be evaluated and advised not to drive and refrain from operating heavy or potentially dangerous machinery until events are resolved.

2.5 USE IN SPECIAL POPULATIONS
2.5.1 Females and Males of Reproductive Potential
No text (see section *3.3.3 Impairment of Fertility*).

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 *3.2.4 Pharmacokinetic Properties, Elimination*).

2.5.2 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 *3.3.4 Nonclinical Safety, Reproductive Toxicity*)

Labor and Delivery
The safe use of Lunsumio during labor and delivery has not been studied.

2.5.3 Lactation
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.

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

2.5.5 Geriatric Use
Among the 218 patients treated with Lunsumio, 94 (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.

2.5.6 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 3.2.5 Pharmacokinetics in Special Populations, Renal Impairment)*.

2.5.7 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 3.2.5 Pharmacokinetics in Special Populations, Hepatic Impairment)*.

2.6 UNDESIRABLE EFFECTS
2.6.1 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=218). The median number of cycles was 8, 37% received 8 cycles, and 15% received more than 8 cycles up to 17 cycles.

Table 5 summarizes the adverse drug reactions (ADRs) that have been reported in association with the use of Lunsumio.

Table 5 Summary of Adverse Drug Reactions Occurring in Patients Treated with Lunsumio

MedDRA PT	All grades (%)	Grade 3 – 4 (%)	Frequency Category
Blood and lymphatic system disorders			
Neutropenia[1]	27.5	24.3	Very common
Anemia	15.1	8.3	Very common
Thrombocytopenia[2]	11.5	6.9	Very common
Febrile neutropenia	2.3	2.3	Common
Gastrointestinal disorders			
Diarrhea	17.4	0	Very common
General disorders and administration site conditions			
Pyrexia	24.3	1.8	Very common
Chills	10.6	0.5	Very common
Immune system disorders			
Cytokine release syndrome[3]	39.4	2.8	Very common
Hemophagocytic lymphohistiocytosis	0.2	0.1	Uncommon
Infections and infestations			
Upper respiratory tract infection	9.6	1.4	Common
Urinary tract infection	6.9	1.4	Common
Pneumonia	5.5	2.3	Common
Investigations			
Alanine aminotransferase, increased	10.6	4.6	Very common
Aspartate aminotransferase, increased	6.9	3.2	Common
Metabolism and nutrition disorders			
Hyperglycaemia	7.8	5.5	Very common
Hypophosphatemia	22.5	14.7	Very common
Hypokalemia	15.6	1.8	Very common
Hypomagnesemia	13.3	0	Very common
Tumor lysis syndrome	0.9	0.9	Uncommon
Neoplasms benign, malignant and unspecified (including cysts and polyps)			
Tumor flare	1.8	1.4	Common
Nervous system disorders			
Headache	20.2	0.5	Very common
Immune effector cell-associated neurotoxicity syndrome[4]	2.1	0.1	Common
Skin and subcutaneous tissue disorders			
Rash	19.3	0.9	Very common
Pruritus	14.2	0	Very common
Dry skin	12.4	0	Very common

[1] Neutropenia includes neutropenia and neutrophil count decreased
[2] Thrombocytopenia includes thrombocytopenia and platelet count decreased
[3] American Society for Transplant and Cellular Therapy
[4] Neurologic toxicity with the consistent medical concept of ICANS according to American Society for Transplant and Cellular Therapy includes confusional state, lethargy and ICANS.

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% (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. Recurrent CRS occurred in 11% of patients. 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 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%).

Sixteen percent (34/218) of patients received tocilizumab and/or a corticosteroid, 10% (21/218) received tocilizumab, 10% (22/218) received corticosteroids, including 4% (9/218) who 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% (44/218) of patients and the median duration of hospitalization was 5 days (range 0-30 days).

Neutropenia
Neutropenia of any grade occurred in 28% (60/218), 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% (41/60) received G-CSF treatment to treat the events.

Serious Infections
Serious infections of any grade occurred in 17% (37/218) of patients. Four (1.8%) 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% (2/218) patients, which included pneumonia and sepsis.

Immune Effector Cell-Associated Neurotoxicity Syndrome
Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) occurred in 2.1 % (20/949) of patients, and included confusional state, lethargy and ICANS. 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).

Hemophagocytic Lymphohistiocytosis
HLH occurred in 0.2% (2/949) of patients. One patient experienced a Grade 4 event in the setting of disease progression with onset on day 8, the patient died on day 17 due to disease progression without recovering from HLH. One patient experienced a Grade 5 event in the setting of disease transformation and concurrent EBV and CMV infection with onset on day 20.

Tumor Flare
Tumor flare (including pleural effusion and tumor inflammation) occurred in 4% (9/218) 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).

Tumor Lysis Syndrome (TLS)
TLS occurred in 0.9% (2/218) 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.

2.6.2 Post marketing Experience
Not applicable

2.7 OVERDOSE
Not applicable

2.8 INTERACTIONS WITH OTHER MEDICINAL PRODUCTS 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 coadministration 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.

3. PHARMACOLOGICAL PROPERTIES AND EFFECTS
3.1 PHARMACODYNAMIC PROPERTIES
3.1.1 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 activated T cell induce B-cell lysis leading to cell death.

3.1.2 Pharmacodynamic Effects
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).

3.1.3 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 lymphohistiocytosis, prior allogeneic stem cell transplant, or prior organ transplantation.

Patients received Lunsumio intravenously as follows:
- Cycle 1 Day 1 – 1mg
- 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: 29-90 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 6.

Table 6 Summary of efficacy in patients with FL

Efficacy parameter	Lunsumio N=90
	Median observation time 18.3 months
Complete Response (CR), n (%) (95% CI)	54 (60.0) (49.1, 70.2)
Objective Response Rate (ORR), n (%) Partial Response (PR), n (%) (95% CI)	72 (80.0) (70.3, 87.7) 18 (20.0) (12.3, 29.8)
Duration of Response (DOR)[1] Patients with event, n (%) Median, months (95% CI) K-M event-free proportion 12 months (95% CI) 18 months (95% CI)	 29 (40.3) 22.8 (9.7, NR) 61.8 (50.0, 73.7) 56.9 (44.1, 69.6)
Duration of Response in Patients who achieved CR (DORC)[2] Patients with event, n (%) Median, months (95% CI) K-M event-free proportion 12 months (95% CI) 18 months (95% CI)	 16 (29.6) 22.8 (18.7, NR) 76.4 (64.6, 88.1) 70.2 (56.7, 83.8)

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, in patients with a best overall response of CR

Baseline levels in EORTC QLQ-C30 Physical Functioning, EORTC QLQ-C30 Fatigue and FACT-Lym Subscale were maintained during treatment (up to cycle 8).

3.1.4 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.

3.2 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% coefficient of variation (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 126 day·mg/mL with %CV of 44.4%.

3.2.1 Absorption
Lunsumio is administered intravenously.

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

3.2.3 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.

3.2.4 Elimination
Based on a population pharmacokinetic analysis, the estimated mean steady-state clearance (CL_{ss}) and baseline clearance ($CL_{baseline}$) were 0.584 L/day and 1.08 L/day, respectively. The terminal half-life estimate was 16.1 days at steady state based on population PK model estimates.

Pharmacokinetics in Special Populations
No clinically meaningful baseline covariates were found for mosunetuzumab PK requiring dose adjustments.

Pediatric Population
No studies have been conducted to investigate the pharmacokinetics of Lunsumio in pediatric patients (<18 years old).

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.

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. Lunsumio was 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 × ULN, any AST, n=2) and no patients with severe hepatic impairment have been studied.

3.3 NONCLINICAL SAFETY

3.3.1 Carcinogenicity
No carcinogenicity studies have been conducted with Lunsumio.

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

3.3.3 Impairment of Fertility
Male and female fertility was investigated as part of the 26-week GLP study in cynomolgus monkeys. No mosunetuzumab-related findings were observed in male and female reproductive endpoints up to the highest dose tested (0.5 mg/kg), at exposures (AUC) similar to exposure (AUC) in patients receiving the recommended dose.

3.3.4 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 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 fetal loss. Transient CRS associated with Lunsumio administration may also be harmful to pregnancy.

3.3.5 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 C_{max} 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.

4. PHARMACEUTICAL PARTICULARS

4.1 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.

Shelf life
As registered locally
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
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.

Lunsumio does not contain antimicrobial preservatives. Therefore, care must be taken to ensure that the solution for infusion is not microbiologically compromised during preparation.

4.2 SPECIAL INSTRUCTIONS FOR USE, HANDLING AND DISPOSAL
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 7 below and discard.
2. Withdraw the required volume of Lunsumio from the vial using a sterile syringe and needle and dilute into the infusion bag. Discard any unused portion left in the vial.

Table 7 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	250 mL
Cycle 2	Day 1	60 mg	60 mL	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.

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).

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.

4.3 PACKS
Vials 1mg/ml 1
Vials 30mg/30ml 1

Medicine: keep out of reach of children

Current at Aug 2024

F. Hoffmann-La Roche Ltd, Basel, Switzerland