swissmedic

Date: 3 May 2023
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Lunsumio

International non-proprietary name: mosunetuzumab

Pharmaceutical form: concentrate for solution for infusion

Dosage strength(s): 30 mg/30 mL, 1 mg/1 mL

Route(s) of administration: intravenous

Marketing authorisation holder: Roche Pharma (Schweiz) AG

Marketing authorisation no.: 68314

Decision and decision date: temporary authorisation in accordance with Art. 9a TPA approved on 9 February 2023

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

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1 Terms, Definitions, Abbreviations

1L	First-line
2L	Second-line
ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ASTCT	American Society for Transplantation and Cellular Therapy
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CR	Complete remission
CRS	Cytokine release syndrome
CYP	Cytochrome P450
DCO	Data cut-off
DDI	Drug-drug interaction
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
FL	Follicular lymphoma
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
ICANS	Immune effector cell-associated neurotoxicity syndrome
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
MTD	Maximum tolerated dose
N/A	Not applicable
NCCN	National Comprehensive Cancer Network
NO(A)EL	No observed (adverse) effect level
ORR	Objective response rate
OS	Overall survival
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PFS	Progression-free survival
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PR	Partial response
PSP	Paediatric study plan (US FDA)

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RMP	Risk management plan
R/R	Refractory or relapsing
SAE	Serious adverse event
SD	Stable disease
SOC	System Organ Class
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

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2 Background Information on the Procedure

2.1 Applicant's Request(s)

New active substance status
The applicant requested new active substance status for mosunetuzumab in the above-mentioned medicinal product.

Orphan drug status
The applicant requested orphan drug status in accordance with Article 4 a^{decies} no. 2 of the TPA.
Orphan drug status was granted on 19 August 2021.

Authorisation as human medicinal product in accordance with Article 13 TPA
The applicant requested a reduced assessment procedure in accordance with Article 13 TPA.

Temporary authorisation for human medicinal products
The applicant requested a temporary authorisation in accordance with Article 9a TPA.

2.2 Indication and dosage

2.2.1 Requested indication

Mosunetuzumab 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.

2.2.2 Approved indication

Lunsumio is indicated as a monotherapy for the treatment of adult patients with relapsed or refractory follicular lymphoma (FL) who have received at least two prior systemic lines of therapy, including a monoclonal anti-CD20 antibody and an alkylating agent (see "Clinical efficacy" section).
The results on the efficacy and safety of Lunsumio in patients with prior anti-CD19 directed CAR-T cell therapy are limited (see "Warnings and precautions" section).

2.2.3 Requested dosage

Summary of the requested standard dosage:

Premedication prior to Lunsumio infusion:

- intravenous corticosteroid: dexamethasone 20 mg or methylprednisolone 80 mg
- anti-histamine: 50-100 mg diphenhydramine hydrochloride or equivalent oral or intravenous anti-histamine
- anti-pyretic: 500-1000 mg paracetamol

The proposed dose for Lunsumio is step-up dosing in Cycle 1 administered at 1 mg, 2 mg, 60 mg on days 1, 8, 15, followed by 60 mg on Cycle 2 Day 1, and 30 mg from Cycle 3 onwards (q3w).

In the absence of unacceptable toxicity or disease progression, patients initially receive 8 cycles of mosunetuzumab (where each cycle is 21 days).

Patients who achieve a CR after receiving 8 cycles of treatment do not receive any additional cycles of mosunetuzumab. Patients who achieve a partial response (PR) or maintained stable disease (SD) after receiving 8 cycles of treatment continue single-agent mosunetuzumab for a total of 17 cycles unless progressive disease or unacceptable toxicity is observed.

2.2.4 Approved dosage

(see appendix)

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2.3 Regulatory history (milestones)

Application	10 May 2022
Formal control completed	13 May 2022
List of Questions (LoQ)	12 July 2022
Response to LoQ	29 September 2022
Preliminary decision	15 November 2022
Response to preliminary decision	5 December 2022
Labelling corrections	22 December 2022
Response to labelling corrections	18 January 2023
2nd Labelling corrections	2 February 2023
Response to 2nd labelling corrections	7 February 2023
Final decision	9 February 2023
Decision	approval (temporary authorisation in accordance with Art. 9a TPA)

Swissmedic has only assessed parts of the primary data submitted with this application. As regards the remaining data, Swissmedic relies for its decision on the assessment of the foreign reference authority the EMA. This SwissPAR relates to the publicly available assessment report of Lunsumio, EMEA/H/C/005680/0000, 22 April 2022 issued by the EMA.

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3 Medical context

Follicular lymphoma (FL) is the most common indolent non-Hodgkin's lymphoma and the second most common lymphoma in Europe (Mounier et al. Lancet Haematol. 2015 Nov; 2(11):481-91). Patients with refractory or relapsing FL (R/R FL) after ≥ 2 prior lines of therapy including anti-CD20 and chemotherapeutic regimens have a poor prognosis. Progression-free survival (PFS) and overall survival (OS) shorten with each subsequent relapse and line of therapy, with median PFS ranges from 1- 1.1 years for third-line patients and median OS of 4.8-8.8 years (Rivas-Delgado et al. Br J Haematol 2019 Mar;184(5):753-759; Batlevi et al. Blood Cancer J. 2020 Jul 17;10(7):7).

4 Quality aspects

Swissmedic has not assessed the primary data relating to quality aspects submitted with this application and relies on the assessment of the foreign reference authority, the EMA. The SwissPAR relating to quality aspects refers to the publicly available assessment report Lunsumio, EMEA/H/C/005680/0000, 22 April 2022 issued by the EMA.

5 Nonclinical aspects

Swissmedic has not assessed the primary data relating to nonclinical aspects submitted with this application and relies on the assessment of the foreign reference authority, the EMA. The preclinical aspects in this SwissPAR refer to the publicly available assessment report Lunsumio, EMEA/H/C/005680/0000, 22 April 2022 issued by the EMA.

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6 Clinical and clinical pharmacology aspects

6.1 Clinical pharmacology

This application was submitted according to Article 13 TPA. Swissmedic has not assessed the primary data relating to clinical pharmacology aspects of this application and its decision relies on the results of the assessment of the foreign reference authority, the EMA. Regarding clinical pharmacology aspects, the SwissPAR refers to the European Public Assessment Report for Lunsumio.

6.2 Dose finding and dose recommendation / Efficacy

This application was submitted according to Article 13 TPA, and the evaluation is partly based on the assessment of the foreign reference authority, the EMA. The current SwissPAR relating to clinical aspects refers to the publicly available EMA Assessment Report for Lunsumio. Swissmedic focused its evaluation on efficacy and safety depending on previous therapy, subgroup efficacy analyses, treatment duration and indication wording.

The applicant submitted one pivotal study, GO29781, for evaluation of efficacy and safety of mosunetuzumab in patients with relapsed or refractory follicular lymphoma (R/R FL) and ≥ 2 prior lines of systemic therapy including previous therapy with an anti-CD20 antibody and an alkylating agent. For details of study design and study population please refer to the “Clinical efficacy” section of the attached information for healthcare professionals.

The included patient population is representative of the intended population. However, patients with various concomitant health conditions (ECOG ≥2, cardiac conditions, moderate-severe renal and hepatic impairment) were excluded.

The study was primarily designed to evaluate the efficacy and safety of mosunetuzumab applied for 8 cycles. Patients with a partial response (PR) or stable disease (SD) could receive additional 9 cycles of mosunetuzumab up to a maximum of 17 cycles. However, results for efficacy and safety are limited, with 16 patients (18% of patients) who received ≥ 8 cycles mosunetuzumab.

The evaluation of efficacy and safety was focused on the cohort B11 FL RP2D (n=90), including patients who had R/R FL and received the recommended Phase II dose 1/2/60/30 mg of mosunetuzumab (for details please refer to the “Dosage/Administration” section of the attached information for healthcare professionals).

At data cut-off (DCO) August 2021 the objective response rate (ORR) was 80% and complete remission (CR) was 60% in the B11 FL RP2D cohort.

The Independent Review Committee (IRC) assessed progression-free survival (PFS) was not fully mature (46.7% events) and overall survival (OS) was immature (8.9%) for cohort B11 FL RP2D. The median PFS was estimated to 17.9 months and OS was not estimable.

In patients in the B11 FL RP2D group, only three patients had had prior CAR-T therapy and no valid conclusion on efficacy and safety in this population is possible.

6.3 Safety

The most common adverse events (AEs, ≥20%) in cohort B11 RP2D were cytokine release syndrome (CRS), neutropenia/neutrophil count decreased, fatigue, hypophosphatemia, and pyrexia.

Serious AEs were reported in 50.9% of patients in cohort B11 RP2D, the most frequent being CRS (20.6% by ASTCT 2019 grading criteria). Other SAEs reported at a frequency of ≥ 2% were pyrexia and pneumonia.

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Overall, six deaths in patients with R/R NHL (group B, n=414) were due to AEs, of which four occurred in cohort B11 RP2D. Five of these were due to infections.

CRS events in the overall group B as well as cohort B11 RP2D were predominantly grade 1 or 2 in severity and occurred primarily in Cycle 1, with decreasing frequencies in the subsequent treatment cycles. However, CRS events were also observed in the following cycles, and 11% of patients had recurrent CRS.

Neurologic AEs (NAEs) including serious NAEs and immune effector cell-associated neurotoxicity syndrome (ICANS) are a further relevant safety risk in patients treated with mosunetuzumab. SAEs reported in more than one patient were confusional state, encephalopathy, syncope, subdural hematoma, and neurotoxicity and herpes.

6.4 Final clinical and clinical pharmacology benefit-risk assessment

Follicular lymphoma remains an incurable disease with currently available therapies. In patients who progress from front-line therapies, the disease-free intervals and DOR become progressively shorter, with increased refractoriness with each subsequent progression/relapse. These patients have a high unmet medical need for new therapies in order to increase overall survival with acceptable or lower toxicity as compared to SOC.

The efficacy of mosunetuzumab in R/R FL having received ≥2 prior lines of systemic therapies is promising based on the CR rate. Given the limitations associated with the uncontrolled single-arm design of the pivotal study and given the primary endpoint, CR, not being an established surrogate endpoint in R/R FL, mature PFS and OS results are necessary for confirmation.

The overall safety is manageable, and the most relevant safety risks of CRS and neurological toxicity including ICANS are described in the information for healthcare professionals.

To confirm a clinical benefit as a condition of temporary authorisation, the applicant is conducting a randomised Phase 3 trial (CELESTIMO / GO42909) of mosunetuzumab plus lenalidomide versus rituximab plus lenalidomide in patients with R/R FL after at least one prior systemic therapy regimen. The first results are expected in 2024 and will therefore be available before expiry of the temporary authorisation.

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7 Risk management plan summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

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8 Appendix

Approved Information for healthcare professionals

Please be aware that the following version of the information for healthcare professionals for Lunsumio was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the information for healthcare professionals approved in one of the official Swiss languages.

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▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.
Lunsumio has been granted temporary authorisation, see section "Indications/Uses".

Lunsumio®

Composition

Active substances

Mosunetuzumab (produced using genetically engineered CHO [Chinese hamster ovary] cells).

Excipients

L-histidine, L-methionine, acetic acid (to adjust the pH), sucrose, polysorbate 20 (E 432) (produced from genetically engineered maize), water for injections.

Pharmaceutical form and active substance quantity per unit

Concentrate for solution for infusion (1 mg/ml).
Clear, colourless liquid, pH 5.8 and osmolality of 240-333 mOsm/kg.

1 mg/1 ml concentrate in a single dose vial

30 mg/30 ml (1 mg/ml) concentrate in a single dose vial

Indications/Uses

Lunsumio is indicated as a monotherapy for the treatment of adult patients with relapsed or refractory follicular lymphoma (FL) who have received at least two prior systemic lines of therapy, including a monoclonal anti-CD20 antibody and an alkylating agent (see section "Clinical efficacy").
The results on the efficacy and safety of Lunsumio in patients with prior anti-CD19 directed CAR-T cell therapy are limited (see section "Warnings and precautions").

This indication is granted temporary authorisation (article 9a TPA) due to the incomplete data at the time of the assessment. The temporary authorisation is subject to the timely fulfilment of obligations. Once these have been fulfilled, the temporary authorisation can be converted into a standard authorisation.

Dosage/Administration

Lunsumio must only be administered under the supervision of a healthcare professional qualified in the use of anti-cancer therapies, in a setting with appropriate medical support to manage severe reactions such as cytokine release syndrome (CRS) and of neurological toxicities including immune

effector cell associated neurotoxicity syndrome (ICANS) (see section "Warnings and precautions"). Intensive monitoring of patients is to be undertaken for the next administration of Lunsumio if CRS (grade ≥2) or clinically relevant neurological toxicity (i.e. serious or life-threatening neurological toxicity including ICANS) associated with the administration of Lunsumio was observed during the previous administration. In such cases, inpatient monitoring should be carried out over at least 72 hours and patients should be monitored on a daily basis for signs and symptoms of cytokine release syndrome (CRS), as well as for neurological and other toxicities, over a period of up to 7 days after administration of Lunsumio. In addition, the patients should be advised to stay in the vicinity of a treatment centre during this period. Any ongoing monitoring is at the discretion of the physician.

To ensure traceability of biotechnological medicinal products, documentation of the trade name and batch number is recommended for each treatment.

Prophylaxis and premedication

Lunsumio should be administered to well-hydrated patients.

Table 1 provides details on recommended premedication to reduce the risk of CRS and infusion-related reactions.

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

Patients requiring premedication	Premedication	Administration
Cycles 1 and 2: all patients Cycles 3 and beyond: patients who experienced any grade CRS with a previous dose	Intravenous corticosteroids: 20 mg dexamethasone or 80 mg methylprednisolone	Administer at least 1 hour prior to Lunsumio infusion
	Antihistamine: 50-100 mg diphenhydramine hydrochloride or equivalent oral or intravenous antihistamine	Administer at least 30 minutes prior to Lunsumio infusion
	Antipyretic: 500-1000 mg paracetamol	

Table 2 gives the recommended dose of Lunsumio for each 21-day cycle.

Table 2: Lunsumio dose for patients with relapsed or refractory follicular lymphoma

Day of treatment		Lunsumio dose	Infusion rate
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 a period of 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 is required beyond 8 cycles. 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 (i.e. a total of 17 cycles) should be administered, unless a patient experiences unacceptable toxicity or disease progression (see "Undesirable effects"). The median number of cycles was 8 in the pivotal clinical trial (GO29781, see "Clinical efficacy"), 59% of patients received 8 cycles, 18% (16 patients) received more than 8 and up to 17 cycles.

Dose adjustment following undesirable effects/interactions

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

Cytokine release syndrome (CRS)

CRS should be identified based on clinical presentation (see section "Warnings and precautions"). Patients should be examined 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, then patients should be managed according to the recommendations in Table 3 and, in addition, in accordance with the Consensus Guidelines.

Table 3: CRS grading[1] and management

CRS grade	CRS management[2]	Next scheduled infusion of Lunsumio
Grade 1 Fever ≥ 38 °C	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	The symptoms should have resolved for at least 72 hours prior to the next infusion. The patient should be monitored more frequently.

	If CRS persists for > 48 hours after symptomatic management: • Treatment of CRS in accordance with the Consensus Guidelines	
Grade 2 Fever ≥ 38 °C and/or hypotension not requiring vasopressors and/or hypoxia requiring low-flow oxygen[3] 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% of 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: • Treatment of CRS in accordance with the Consensus Guidelines	The symptoms should have resolved for at least 72 hours prior to the next infusion. Premedication should be maximised as appropriate[4]. Consideration should be given to administration of the next infusion at 50% of the rate. Inpatient monitoring should be carried out over at least 72 hours for the next infusion.
Grade 3 Fever ≥ 38 °C and/or hypotension requiring a vasopressor (with or without vasopressin) and/or hypoxia requiring high-flow oxygen[5] by nasal cannula, face mask, non-rebreather mask or Venturi mask	If CRS occurs during infusion: • The current infusion should be discontinued • The symptoms should be treated • Treatment of CRS in accordance with the Consensus Guidelines If CRS occurs post-infusion: • The symptoms should be treated • Treatment of CRS in accordance with the Consensus Guidelines	The symptoms should have resolved for at least 72 hours prior to the next infusion. Inpatient monitoring should be carried out over at least 72 hours for the next infusion. Premedication should be maximised as appropriate[4]. Permanently discontinue treatment with Lunsumio in the event of recurrent Grade 3 CRS.
Grade 4 Fever ≥ 38ºC and/or hypotension requiring multiple vasopressors (excluding vasopressin) and/or hypoxia requiring oxygen administered 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 • Treatment of CRS in accordance with the Consensus Guidelines	

[1] ASTCT = American Society for Transplant and Cellular Therapy. Premedication may mask fever. Please therefore follow these management guidelines if clinical presentation is consistent with CRS.

[2] If CRS is refractory to treatment, consider other causes including haemophagocytic lymphohistiocytosis.

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

[4] Refer to Table 1 for additional information.

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

Neurological toxicities and ICANS

Patients who suffer neurological events should be treated in accordance with Table 4.
For patients who experience serious or life-threatening neurological toxicity including ICANS, inpatient monitoring should be carried out over at least 72 hours for the next infusion.

Table 4: Recommendations for the treatment of neurological events (including ICANS)

Adverse reaction	Severity	Measures
Neurotoxicity (including ICANS)	Grade 2	• Discontinue Lunsumio until the symptoms of neurotoxicity have abated to Grade 1 for at least 72 h or have returned to the situation prevailing beforehand. • Administer supportive treatment. In the presence of ICANS: treatment in accordance with the Consensus Guidelines.
	Grade 3	• Discontinue Lunsumio until the symptoms of neurotoxicity have abated to Grade 1 for at least 72 h or have returned to the situation prevailing beforehand. • Administer supportive treatment (which may include intensive care) and consider a neurological evaluation. In the presence of ICANS: treatment in accordance with the Consensus Guidelines. • Permanently discontinue Lunsumio in the event of a recurrence.
	Grade 4	• Permanently discontinue Lunsumio. • Administer supportive treatment (which may include intensive care) and consider a neurological evaluation. In the presence of ICANS: treatment in accordance with the Consensus Guidelines.

1. Based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.0.
2. Based on American Society for Transplantation and Cellular Therapy (ASTCT) 2019 grading for ICANS.

Special dosage instructions

Patients with hepatic disorders

Lunsumio has not been studied in patients with hepatic impairment. Dose adjustments are not considered necessary based on its pharmacokinetics (see section "Pharmacokinetics").

Patients with renal disorders

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 its pharmacokinetics (see section "Pharmacokinetics").

Elderly patients

No dose adjustment of Lunsumio is required in patients aged ≥ 65 years (see section "Pharmacokinetics").

Children and adolescents

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

Delayed administration

If a 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, administration of Lunsumio should be continued at a dose of 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 from 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.

Mode of administration

Lunsumio is for intravenous use only.

Lunsumio must be diluted under sterile conditions and under the supervision of a healthcare professional. The intravenous infusion should be administered through a dedicated infusion line. Do not use an in-line filter. Drip chamber filters can be used.

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

Lunsumio must not be administered as an IV push or bolus.

For instructions on dilution of the medicinal product before administration, see section "Instructions for Handling".

Contraindications

Hypersensitivity to the active substance or to any of the ingredients listed in the section "Composition, Excipients".

Warnings and precautions

Cytokine Release Syndrome (CRS)
CRS, including life-threatening reactions, have occurred in patients receiving Lunsumio (see section "Undesirable effects"). 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 doses administered on Day 1 and Day 15; however, CRS events also occurred during subsequent cycles (see section "Adverse effects"). Recurrent CRS occurred in 11% of patients.

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. In cases of Grade 2 CRS or higher, physicians should start treatment with supportive measures (this may also include intensive care in cases of serious or life-threatening CRS) in accordance with Consensus Guidelines and temporarily or permanently discontinue Lunsumio based on the severity. Other aetiologies should be considered in cases of treatment-refractory CRS, including haemophagocytic lymphohistiocytosis or capillary leak syndrome (see section "Dosage/Administration").

Neurological events

Lunsumio may cause serious or life-threatening neurological toxicities, including immune effector cell-associated neurotoxicity syndrome (ICANS) (see "Undesirable effects").
Concomitant treatment with Lunsumio and other medicinal products that may cause dizziness or an altered state of consciousness can increase the risk of neurological toxicity.
Patients should be monitored for signs and symptoms of neurotoxicity during treatment. The patient must be examined immediately at the first signs of neurotoxicity (including ICANS), a neurological evaluation should potentially be considered and, depending on severity, supportive care provided; Lunsumio should be temporarily or permanently discontinued depending on severity and the recommendations for treatment are to be adhered to (see "Dosage/Administration").

Serious infections
Serious infections such as pneumonia, bacteraemia, sepsis or septic shock, as well as opportunistic infections, have occurred in patients receiving Lunsumio, some of which were life-threatening or fatal events (see section "Undesirable effects"). Febrile neutropenia was observed in some patients after receiving a 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 infection), with underlying conditions that may predispose them to infections or who have had significant prior immunosuppressive treatment. Patients should be given prophylactic antibacterial, antiviral and/or antifungal medicinal products, as appropriate. Patients should be monitored for signs and symptoms of infection, before and after Lunsumio is administered, and treated accordingly. In the event of febrile neutropenia, patients should be examined for infection and treated with antibiotics, fluids and other supportive care, according to local guidelines.

Cytopenia

Lunsumio can cause serious or severe cytopenia, including neutropenia, anaemia and thrombocytopenia (see section "Undesirable effects").
Blood parameters must be monitored throughout treatment with Lunsumio. Lunsumio is to be interrupted or permanently discontinued based on the severity of the cytopenia (see "Dosage/Administration").

Hepatitis B Reactivation

Hepatitis B virus (HBV) reactivation, can occur in patients treated with drugs directed against B cells, which may lead to hepatitis taking a fulminant course, liver failure and death in some cases. Patients in whom a positive HBV serology was determined should be monitored for clinical symptoms, which may be signs of HBV reactivation, and undergo laboratory tests during treatment with Lunsumio and for at least six months after completion of treatment.

Tumour flare

Tumour flare has been reported in patients treated with Lunsumio (see section "Undesirable effects"). 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 to be attributed to the influx of T cells into tumour sites following the administration of Lunsumio.

No specific risk factors have been identified for tumour flare, however, there is a heightened risk of compromise and morbidity due to the 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 "Undesirable effects"). Patients must be adequately hydrated prior to the administration of Lunsumio. Patients should be given prophylactic anti-hyperuricemic therapy (e.g. allopurinol, rasburicase), as appropriate. Patients should be monitored for signs or symptoms of TLS, especially patients with a high tumour burden or rapidly

proliferative tumours, and patients with impaired renal function. Patients should be monitored with blood tests and any abnormalities should be treated immediately.

Hepatotoxicity

Lunsumio can cause hepatotoxicity that may potentially take a fatal course.
Elevated liver enzymes have been reported in patients receiving Lunsumio (see section "Undesirable effects"). Liver enzymes and bilirubin should be monitored at the start and during treatment, as clinically indicated. Treatment must adhere to local treatment protocols/guidelines. Lunsumio is to be interrupted or permanently discontinued depending on severity (see section "Dosage/Administration").

Prior CAR-T cell therapy

A total of 3 patients with relapsed/refractory follicular lymphoma receiving treatment with Lunsumio had undergone prior CAR-T cell therapy. These data are too limited to make a reliable statement on the efficacy of Lunsumio. In the safety population, including all patients with FL and other histologies (n = 416), 49 patients had undergone prior CAR-T cell therapy. These patients had more aggressive NHL histology (83.6% had DLBCL or transformed FL), heavier disease burden, worse ECOG PS at baseline, and more lines of prior therapy compared to patients without prior CAR-T therapy. Patients with prior CAR-T therapy exhibited more grade 5 adverse reactions, serious adverse reactions and grade 3-4 adverse reactions when compared with patients without prior CAR-T cell therapy.

Immunisation

Live and/or live-attenuated vaccines should not be given concurrently with Lunsumio. No studies have been conducted in patients who had recently received live vaccines.

Patient card

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

Interactions

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 result in 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 necessary.

Pregnancy, lactation

Women of childbearing age/Contraception
Women of childbearing age should use effective contraception during treatment with Lunsumio and for at least 3 months after the final infusion of Lunsumio.

Pregnancy

There are no data on the use of Lunsumio in pregnant women. No adequate animal studies have been conducted on reproductive toxicity (see section "Preclinical data").
Lunsumio is not recommended during pregnancy and in women of childbearing age who are not using contraception.

Lactation

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.

Fertility

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

Effects on ability to drive and use machines

Patients who experience CRS or neurological adverse reactions, such as tremors, dizziness, insomnia, severe neurotoxicity or any other adverse reactions that impair consciousness, should be evaluated, in particular, including a potential neurological examination, and such patients should be advised not to drive and to refrain from operating heavy or potentially dangerous machinery until the adverse reactions have resolved.

Undesirable effects

Summary of the safety profile
The adverse reactions (ARs) described in this section were identified in the pivotal clinical trial GO29781 in patients treated with the recommended dose (n = 218). These patients had follicular lymphoma (41.3%) or other B-cell non-Hodgkin’s lymphoma histologies (58.7%). The median number of cycles of Lunsumio was 8 (range 1 -17), 37% of patients received 8 cycles and 15% received more than 8 and up to 17 cycles.

The most common adverse reactions (≥ 20%) observed in the 218 patients were cytokine release syndrome, neutropenia, pyrexia, hypophosphataemia and headache. The most common serious adverse reactions (≥ 2%) included cytokine release syndrome (CRS) (21% based on the 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 of treatment in more than one patient (2 patients [0.9%]).

List of adverse reactions

The adverse reactions of all degrees of severity listed below are based on pooled data from patients of clinical studies (n = 526) in whom Lunsumio was administered as monotherapy.

The adverse reactions are arranged according to MedDRA system organ classes and the conventional frequencies, as follows:
"very common" (≥1/10)
"common" (≥1/100, <1/10)
"uncommon" (≥1/1,000, <1/100)
"rare" (≥1/10,000, <1/1,000)
"very rare" (<1/10,000)
"not known" (frequency cannot be estimated from the available data)
Within each frequency grouping, adverse reactions are presented in order of decreasing severity.

Table 5: Summary of adverse reactions in patients treated with Lunsumio monotherapy in clinical studies

	Lunsumio monotherapy n = 526
Infections and Infestations	
Very Common	Upper respiratory tract infection[1] (all grades 17.9%, grade 3-4 2.1%)
Common	Urinary tract infection[2], Pneumonia[3] (all grades 7.8%, grade 3-4 3.2%)*, Sepsis[4], COVID-19 (all grades 1.4%, grade 3-4 0.9%)*, Epstein-Barr viraemia[5] (all grades 1.4%, grade 3-4 0.5%)*
Neoplasms Benign, Malignant and Unspecified (including Cysts and Polyps)	
Common	Tumour flare
Blood and Lymphatic System Disorders	
Very Common	Neutropenia[6] (all grades 27.5%, grade 3-4 24.3%)*, Anaemia[7] (all grades 16.5%, grade 3-4 8.7%)*, Thrombocytopenia[8] (all grades 11.5%, grade 3-4 6.9%)*
Common	Lymphopenia[9], Febrile neutropenia, Leukopenia[10]
Immune System Disorders	
Very Common	Cytokine release syndrome[11] (all grades 39.4%, grade 3-4 2.8%)*

Metabolism and Nutrition Disorders	
Very Common	Hypophosphataemia[12] (all grades 22.5%, grade 3-4 15.1%)*, Hypokalaemia (all grades 15.6%, grade 3-4 1.8%)*, Hypomagnesaemia (all grades 13.3%, grade 3-4 0%)*
Common	Hyperglycaemia (all grades 7.8%, grade 3-4 5.5%)*, Hyperuricaemia
Uncommon	Tumor lysis syndrome
Psychiatric Disorders	
Very common	Insomnia (all grades 10.6%, grade 3-4 0%)*
Common	Anxiety
Nervous System Disorders	
Very Common	Headache[13] (all grades 20.6%, grade 3-4 0.5%)*, Peripheral neuropathy[15] (all grades 13.3%, grade 3-4 0.5%)*, Dizziness[14] (all grades 11.0%, grade 3-4 0.6%)
Common	Mental status change[16], Motor dysfunction[17]
Uncommon	Immune effector cell-associated neurotoxicity syndrome, Seizure, Aphasia
Respiratory, Thoracic, and Mediastinal Disorders	
Very Common	Cough[18] (all grades 19.7%, grade 3-4 0%)*
Common	Dyspnoea[19], Pneumonitis
Gastrointestinal Disorders	
Very Common	Diarrhoea[20] (all grades 19.0%, grade 3-4 0.6%), Nausea (all grades 17.4%, grade 3-4 0.5%)*, Abdominal pain[21] (all grades 13.3%, grade 3-4 0.6%)
Investigations	
Very common	Alanine aminotransferase increased (all grades 10.6%, grade 3-4 4.6%)*
Common	Aspartate aminotransferase increased, Gamma-glutamyltransferase increased
Skin and Subcutaneous Tissue Disorders	
Very Common	Rash[22] (all grades 34.4%, grade 3-4 2.3%)*, Pruritus (all grades 14.2%, grade 3-4 0%)*, Dry skin (all grades 12.4%, grade 3-4 0%)*
Common	Skin exfoliation (all grades 6.0%, grade 3-4 0%)*
Musculoskeletal and Connective Tissue Disorders	
Very Common	Musculoskeletal pain[23] (all grades 21.7%, grade 3-4 1.1%)

Common	Arthralgia
Renal and Urinary Disorders	
Very Common	Renal insufficiency[24] (all grades 10.1%, grade 3-4 2.8%)*
General Disorders and Administration Site Conditions	
Very Common	Fatigue[25] (all grades 36.2%, grade 3-4 0.9%)*, Pyrexia (all grades 24.3%, grade 3-4 1.8%)*, Oedema[26] (all grades 20.2%, grade 3-4 0.5%)*, Chills (all grades 10.6%, grade 3-4 0.5%)*

* Frequency derived from patients who received the recommended dose in Study GO29781 (n = 218).

[1] Upper respiratory tract infection includes infections of the upper respiratory tract, nasopharyngitis, pharyngitis, rhinovirus infection, sinusitis, chronic sinusitis, laryngitis, rhinitis, parainfluenzae virus infection and viral upper respiratory tract infection.

[2] Urinary tract infection includes urinary tract infections, acute pyelonephritis and pyelonephritis.

[3] Pneumonia includes pneumonia, pneumocystis jirovecii pneumonia, mycoplasmal pneumonia, staphylococcal pneumonia, pneumonia haemophilus, lung infiltration, atypical pneumonia, aspiration pneumonia and pneumonia viral.

[4] Sepsis includes sepsis, candida sepsis, urosepsis and septic shock.

[5] Epstein-Barr viraemia includes Epstein-Barr viraemia and Epstein-Barr virus infection.

[6] Neutropenia includes neutropenia and neutrophil count decreased.

[7] Anaemia includes anaemia, haemolytic anaemia and iron deficiency anaemia.

[8] Thrombocytopenia includes thrombocytopenia and platelet count decreased.

[9] Lymphopenia includes lymphopenia and lymphocyte count decreased.

[10] Leukopenia includes leukopenia and leukocyte count decrease.

[11] According to the American Society for Transplant and Cellular Therapy.

[12] Hypophosphataemia includes hypophosphataemia and blood phosphate concentration decreased.

[13] Headaches include headache and migraine.

[14] Dizziness includes dizziness, vertigo and syncope.

[15] Peripheral neuropathy includes peripheral neuropathy, burning sensation, dysaesthesia, hypaesthesia, neuralgia, paraesthesia, peripheral motor neuropathy, peripheral sensory neuropathy and toxic neuropathy.

[16] Mental status change includes cognitive disorders, attention deficit disorders, encephalopathy, neurotoxicity, somnolence, confusion and delirium.

[17] Motor dysfunction includes gait disorders, ataxia, balance disorders, muscle spasms, dysphonia and tremor.

[18] Cough includes coughs, productive coughs and upper respiratory tract cough syndrome.

[19] Dyspnoea includes dyspnoea and exercise dyspnoea.

[20] Diarrhoea includes diarrhoea and viral diarrhoea.

[21] Abdominal pain includes abdominal pain, abdominal complaints, lower abdominal pain and upper abdominal pain.

[22] Rash includes rash, pustular rash, dermatitis, acneiform dermatitis, erythema, exfoliative rash, palmar erythema, erythematous rash, macular rash, maculopapular rash, papular rash, follicular rash and pruriginous rash.

[23] Musculoskeletal pain includes musculoskeletal pain, back pain, musculoskeletal chest pain, non-cardiac chest pain, pain in an extremity, myalgia and pain in the back of the neck.

[24] Renal insufficiency includes blood creatinine increased, acute kidney injury, azotaemia and kidney dysfunction.

[25] Fatigue includes fatigue, asthenia and lethargy.

[26] Oedema includes oedema, facial oedema, generalised oedema, localised oedema, peripheral oedema, peripheral swelling, facial swelling, hyperhydration, fluid retention, lymphoedema and pulmonary oedema.

Description of specific adverse reactions and additional information

Cytokine release syndrome (CRS)

CRS (ASTCT grading system) (all grades of severity) occurred in 39% (86/218) of patients treated with Lunsumio, with grade 2 CRS developing in 14%, grade 3 CRS developing in 2.3%, and grade 4 CRS developing in 0.5% of patients. The one patient with grade 4 CRS was a patient with FL in the leukaemic phase, who also experienced concurrent TLS.

CRS (all grades of severity) occurred in 15% of patients after the Day 1 dose in Cycle 1; in 5% after the Day 8 dose in Cycle 1; in 33% after the Day 15 dose in Cycle 1, 5% occurred in patients after Cycle 2 and 1% in Cycles 3 and beyond. Median time to onset of CRS after the start of the infusion was 5 hours (range: 1-73 hours) on Day 1 of Cycle 1, 28 hours (range: 5-81 hours) on Day 8 of Cycle 1, 25 hours (range: 0.1-391 hours) on Day 15 of Cycle 1, and 46 hours (range: 12-82 hours) on Day 1 of Cycle 2. Median duration of CRS events was 3 days (range 1-29 days). CRS was reversible in all patients.

In the 86 patients who experienced CRS, the most common signs and symptoms of CRS were pyrexia (98%), chills (36%), hypotension (35%), tachycardia (24%), hypoxia (22%) and headache (16%).
In 6% of patients, neurological adverse reactions occurred simultaneously, including headache, confusion and anxiety.

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

Neutropenia

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

Neurological events

Neurological events (reported as nervous system disorders) occurred in 39% of patients, with Grade 3 neurological events occurring in 3% of patients. Median duration to the first occurrence of neurological events was 17 days (range: 1 – 331 days), median duration of the events was 4 days (range: 1 – 344 days).

The most common neurological events were headaches (21%), peripheral neuropathy (13%) and dizziness (11 %). ICANS was reported as a neurological event in 0.5% of patients who received the recommended dose of Lunsumio in the clinical study.

Serious infections
Serious infections (all grades of severity) occurred in a total of 17% of patients, including opportunistic infections (e,g pneumocystis jiroveci pneumonia) and reactivated viral infections (e.g. Epstein-Barr viraemia). 1.8% of patients developed serious infections concurrently with grade 3-4 neutropenia. A grade 3-4 infection was observed in 14% and a grade 5 infection in 0.9% of patients. The most common infections ≥ grade 3 were pneumonia, sepsis and upper respiratory tract infections.
Median time to the first occurrence of a serious infection was 50 days (range: 1-561 days), with a median duration of 12 days (range: 2-174 days). Grade 5 events occurred in 0.9% of patients, which included pneumonia and sepsis.

Cytopenia
Out of patients who were given the recommended dosage of Lunsumio in clinical studies, 24.3% exhibited grade 3-4 neutropenia, 8.7% Grade 3-4 anaemia and 6.9% Grade 3-4 thrombocytopenia. Febrile neutropenia was observed in 2.3%.

Tumour flare
Tumour flare (including pleural effusion and tumour inflammation) occurred in 4% of patients, including 1.8% with grade 2 and 2.3% with grade 3 events. Median time to onset of such an event 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 who developed grade 4 TLS was in the leukaemic phase. TLS occurred on Days 2 and 24, and resolved within 4 and 6 days, respectively.

Hepatotoxicity
Hepatic events occurred in 13.3% of patients, including 2.3% with grade 2, 4.1% grade 3 and 1.8% grade 4 events. Serious AEs occurred in 1.4% of patients. The median time to onset of the first event was 6 days (range 1-399 days) and the median duration was 6.5 days (range 2-56 days).

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

In cases of an overdose, patients should be closely monitored for signs or symptoms of adverse reactions, and appropriate symptomatic treatment instituted.

Properties/Effects

ATC code

L01F

Mechanism of action

Mosunetuzumab is a bispecific anti-CD20/CD3 antibody that targets B cells expressing CD20. It is a conditional agonist; targeted killing of B cells only occurs 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. The subsequent direct release of perforin and granzymes due to T cell activation through the immunologic synapsis induces B cell lysis, thereby leading to cell death.

Lunsumio caused B cell depletion (defined as CD19 B cell counts < 0.07 x 10^9/l) and hypogammaglobulinaemia (defined as IgG levels < 500 mg/dl).

Clinical efficacy

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 Grade 3b FL and patients with transformed FL at study entry were excluded from the FL cohort; 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 an Eastern Cooperative Oncology Group (ECOG) performance status $\geq$ 2, significant cardiovascular disease (such as New York Heart Association Class III or IV cardiac disease, myocardial infarction within the last 6 months, unstable arrhythmia, or unstable angina), significant active pulmonary disease, impaired renal function (creatinine clearance [CrCl] < 60 ml/min with elevated serum creatinine levels), active autoimmune disease requiring immunosuppressive therapy, active infections (i.e., chronic active EBV, acute or chronic hepatitis C, hepatitis B, HIV), progressive multifocal leukoencephalopathy, current or a history of CNS lymphoma

or CNS disease, a history of macrophage activation syndrome/haemophagocytic lymphohistiocytosis, prior allogeneic stem cell transplant, or prior organ transplantation.

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

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

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

The median age was 60 years (range 29 to 90 years), with 31% aged > 65, and 7.8% aged ≥ 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 previous therapies was 3 (range: 2-10), with 38% having received 2 prior therapies, 31% having been given 3 prior therapies and 31% having received more than 3 prior therapies.

All patients had been given prior anti-CD20 and alkylating agent therapies, 21% had received an autologous stem cell transplant, 19% PI3K inhibitors, 9% prior rituximab plus lenalidomide therapy, and 3% had received a CAR-T therapy. Seventy-nine percent of patients were refractory to prior anti-CD20 monoclonal antibody therapy and 53% were refractory to both therapy with an anti-CD20 monoclonal antibody and alkylating agents. Sixty-nine percent of patients were refractory to the last previous therapy and 52% experienced disease progression within 24 months of the 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 6.

Table 6: Summary of efficacy in patients with relapsed/refractory FL

Efficacy parameter	**Lunsumio n = 90**
Median observation time: 18.3 months (range 2 – 27 months)	
Complete Response (CR), n (%), (95% CI)	54 (60.0) (49.1, 70.2)
Objective Response Rate (ORR), n (%) (95% CI)	72 (80.0) (70.3, 87.7)
Partial Response (PR) n (%) (95% CI)	18 (20.0) (12.3, 29.8)
Duration of Response (DOR)[1] Median, months (95% CI) Rate of Continued Response[2] At 12 months, (95% CI) At 18 months, (95% CI)	 22.8 (9.7, NR) 62 (50, 74) 57 (44, 70)

CI = confidence interval; NR = not reached.

Clinical cut-off: 27 August 2021.

Hypothesis testing was conducted on the primary endpoint, CR rate, assessed by the IRF.

[1] DOR is defined as the time from the initial occurrence of a documented partial response (PR) or complete response (CR) until the patient experiences an event (documented disease progression or death due to any cause, whichever occurs first), among patients who achieved a PR or CR.

[2] Kaplan-Meier estimate.

The median follow-up for DOR was 14.9 months and 40.3% of responders had a DOR event. Median progression-free survival was 17.9 months (95% CI: 10.1 not reached). Data on overall survival were not yet mature at the time of the analysis with 8.9% of patients having an overall survival event.

Further information

Immunogenicity

The immunogenicity of mosunetuzumab was evaluated using an enzyme-linked immunosorbent assay (ELISA). None of the 418 patients who were available for analysis in relation to anti-drug antibodies (ADA) and who received Lunsumio single-agent intravenous treatment in study GO29781 tested positive. The clinical relevance of anti-mosunetuzumab antibodies could not be assessed based on the available data.

Pharmacokinetics

Mosunetuzumab pharmacokinetic (PK) exposure increased in an approximately dose-proportional manner over the dose range that was investigated, from 0.05 to 60 mg. The population pharmacokinetics following intravenous administrations of Lunsumio was described by a 2-compartment PK model with time-dependent clearance. Clearance was reduced from a baseline

value ($CL_{baseline}$) at the start of treatment, with a transitional half-life of 16.3 days, to a steady-state plateau (CL_{ss}). Moderate to high pharmacokinetic variability was observed for mosunetuzumab and characterized by inter-individual variability (IIV) with a CV (coefficient of variation) ranging from 18% to 86% for different pharmacokinetic parameters: IIV was estimated for $CL_{baseline}$ (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 treatment with Lunsumio, the serum concentration reaches a mean maximum concentration of 17.9 µg/ml and a %CV of 49.6% at the end of the Day 1 dose of the intravenous infusion of Lunsumio in Cycle 2. The mean total AUC for mosunetuzumab exposure was 126 day•µg/ml with %CV of 44.4% over two cycles (42 days).

Absorption

Lunsumio is administered intravenously.

Distribution

The population estimate of the central volume of distribution for mosunetuzumab was 5.49 l after an intravenous infusion of Lunsumio. Because mosunetuzumab is an antibody, protein binding studies were not conducted.

Metabolism

The metabolic pathway of mosunetuzumab has not been studied directly. Like other protein-based therapeutic agents, mosunetuzumab is assumed 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 ($CL_{baseline}$) were 0.584 l/day and 1.08 l/day, respectively. The estimated terminal half-life was 16.1 days at steady state. The results obtained in study GO29781 indicate that the serum mosunetuzumab concentration reaches the C_{max} at the end of the intravenous infusion and declines in a bi-exponential fashion thereafter.

Kinetics in specific patient groups

Hepatic impairment

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

The population pharmacokinetic analysis of mosunetuzumab revealed that hepatic impairment has no

effect on the pharmacokinetics of mosunetuzumab. The 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.

Renal impairment

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

The population pharmacokinetic analysis of mosunetuzumab revealed that creatinine clearance (CrCl) has no effect on the pharmacokinetics of mosunetuzumab. The 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 from 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.

Elderly patients

Age had no effect on the pharmacokinetics of mosunetuzumab based on a population pharmacokinetic analysis conducted in patients aged 19-96 years (n = 439). No clinically relevant difference was observed in the pharmacokinetics of mosunetuzumab for patients in this age group.

Children and adolescents

No studies have been conducted to investigate the pharmacokinetics of mosunetuzumab in children and adolescents (aged < 18 years).

Bodyweight

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

Gender

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

Ethnic origin

Ethnic origin (Asian vs. non-Asian) was not identified as a covariate that influences the pharmacokinetics of mosunetuzumab.

Preclinical data

Repeated dose toxicity

Key non-clinical findings for mosunetuzumab that were identified in single- and repeat-dose toxicity studies of up to 26-weeks in duration included transient post-dose CRS, primarily occurring after the first dose, vascular/perivascular inflammatory cell infiltrates that primarily occurred in the CNS and infrequently in other organs and could probably be attributed to cytokine release and immune cell activation, as well as increased susceptibility to infection following chronic dosing due to sustained B cell depletion.

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

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

Reproductive toxicity

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

Other information

Incompatibilities

- Do not mix Lunsumio with other medicinal products or administer it through the same infusion line.
- Do not use solvents other than 9 mg/ml (0.9%) or 4.5 mg/ml (0.45%) sodium chloride solution for infusion to dilute Lunsumio as their use has not been tested.

- No incompatibilities have been observed between Lunsumio and intravenous infusion bags made from polyvinyl chloride (PVC) or polyolefins (PO), such as polyethylene (PE) and polypropylene (PP) that come into contact with the product. In addition, no incompatibilities have been observed with infusion sets or infusion aids made from PVC, PE, polyurethane (PUR), polybutadiene (PBD), silicone, acrylonitrile butadiene styrene (ABS), polycarbonate (PC), polyetherurethane (PEU), fluorinated ethylene propylene (FEP) or polytetrafluorethylene (PTFE) that come into contact with the product, or with a drip chamber filter membrane composed of polyamide (PA).
- Do not use an in-line filter.

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the pack.

Shelf life after opening

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 perspective, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user and should normally be no longer than 24 hours at 2 °C to 8 °C, unless dilution has taken place under controlled and validated aseptic conditions.

Special precautions for storage

Keep out of the reach of children.
Store in the refrigerator (2-8 °C).
Do not shake.
Do not freeze.
Keep the container in the outer carton in order to protect the contents from light.

Instructions for handling

General precautions

Lunsumio contains no preservative and is intended as a single dose only. This medicinal product must be handled under aseptic conditions throughout. Do not shake.

Instructions for dilution

Prior to administration, Lunsumio must be diluted under aseptic conditions by a healthcare professional into a PVC or polyolefin (PO), e.g., polyethylene (PE) and polypropylene, infusion bag containing a 9 mg/ml sodium chloride solution for infusion (0.9%) or a 4.5 mg/ml sodium chloride solution for infusion (0.45%).

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

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 9 mg/ml (0.9%) or 4.5 mg/ml (0.45%) sodium chloride solution for infusion equal to the volume of the Lunsumio required for the patient's dose from the infusion bag according to Table 7 below.
2. Withdraw the required volume of Lunsumio from the vial using a sterile syringe and dilute into the infusion bag. Discard any unused residue left in the vial.

Table 7: Dilution of Lunsumio

Day of treatment		Lunsumio dose	Volume of Lunsumio in 0.9% or 0.45% sodium chloride solution for infusion	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 contents of 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 package leaflet to the infusion bag.

For storage conditions of the infusion bags, see section "Other information/Shelf life".

Disposal

The release of pharmaceuticals into the environment should be minimised. Medicinal products should not be disposed of via wastewater and disposal in 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.

Peel-off label

Authorisation number

68314 (Swissmedic).

Packs

Vial containing 1 mg/1 ml: 1 [A]
Vial containing 30 mg/30 ml: 1 [A]

Type I glass-vial with a butyl rubber stopper and an aluminium seal with a plastic dark grey flip-off cap (1 mg/1 ml dose strength) or light blue flip-off cap (30 mg/30 ml dose strength).

Marketing authorisation holder

Roche Pharma (Switzerland) Ltd., Basel.

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February 2023.