NATIONAL PHARMACEUTICAL REGULATORY AGENCY
MINISTRY OF HEALTH MALAYSIA

TECHNICAL EVALUATION SUMMARY FOR NEW REGISTRATION APPLICATION (CONDITIONAL REGISTRATION)

PRODUCT NAME:
Lunsumio 1mg/ml Concentrate for Solution for Infusion (MAL24096026ARZ)

ACTIVE INGREDIENT:
Mosunetuzumab 1mg/mL; Mosunetuzumab 30mg/30mL

PRODUCT REGISTRATION HOLDER:
Roche (Malaysia) Sdn Bhd

PRODUCT MANUFACTURER:
Genentech INC, US

APPROVAL DATE:
5 September 2024 (DCA 400)

1.0 BACKGROUND INFORMATION

1.1 Approved Indication:

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

This indication is approved under conditional approval based on response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

1.2 Approved Posology:

General
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).

Posology
Prophylaxis and premedication
Lunsumio should be administered to well-hydrated patient

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

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

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

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

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

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

Duration of treatment
Lunsumio should be administered for 8 cycles, unless a patient experiences unacceptable toxicity or disease progression.

For patients who achieve a complete response, no further treatment beyond 8 cycles is required. For patients who achieve a partial response or have stable disease in response to treatment with Lunsumio after 8 cycles, an additional 9 cycles of treatment (17 cycles total) should be administered, unless a patient experiences unacceptable toxicity or disease progression.

Delayed or missed dose

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

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

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

Dose modification

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

CRS should be identified based on clinical presentation (see section 4.4). Patients should be evaluated and treated for other causes of fever, hypoxia, and hypotension, such as infections/sepsis. Infusion related reactions (IRR) may be clinically indistinguishable from manifestations of CRS. If CRS or IRR is suspected, patients should be managed according to the recommendations in Table 3.

Table 3 CRS grading[1] and management

CRS grade	CRS management[2]	Next scheduled infusion of Lunsumio
Grade 1 Fever ≥ 38ºC	If CRS occurs during infusion: ● The infusion should be interrupted and symptoms treated ● The infusion should be re-started at the same rate once the symptoms resolve ● If symptoms recur with re-administration, the current infusion should be discontinued If CRS occurs post-infusion: ● The symptoms should be treated If CRS lasts > 48 hours after symptomatic management: ● Dexamethasone[3] and/or tocilizumab[4,5] should be considered	The symptoms should be resolved for at least 72 hours prior to next infusion The patient should be monitored more frequently
Grade 2 Fever ≥ 38ºC and/or hypotension not requiring vasopressors and/or hypoxia requiring low-flow oxygen[6] by nasal cannula or blow-by	If CRS occurs during infusion: ● The infusion should be interrupted and symptoms treated ● The infusion should be re-started at 50% the rate once the symptoms resolve ● If symptoms recur with re-administration, the current infusion should be discontinued If CRS occurs post-infusion: ● The symptoms should be treated If no improvement occurs after symptomatic management: ● Dexamethasone[3] and/or tocilizumab[4,5] should be considered	The symptoms should be resolved for at least 72 hours prior to next infusion Premedication should be maximized as appropriate[7] Consideration should be given to administration of the next infusion 50% rate, with more frequent monitoring of the patient

Grade 3 Fever ≥ 38ºC and/or hypotension requiring a vasopressor (with or without vasopressin) and/or hypoxia requiring high flow oxygen[8] by nasal cannula, face mask, non-rebreather mask, or Venturi mask	If CRS occurs during infusion: ● The current infusion should be discontinued ● The symptoms should be treated ● Dexamethasone[3] and tocilizumab[4, 5] should be administered If CRS occurs post-infusion: ● The symptoms should be treated ● Dexamethasone[3] and tocilizumab[4, 5] should be administered If CRS is refractory to dexamethasone and tocilizumab: ● Alternative immunosuppressants[9] and methylprednisolone 1 000 mg/day intravenously should be administered until clinical improvement	The symptoms should be resolved for at least 72 hours prior to next infusion Patients should be hospitalized for the next infusion Premedication should be maximized as appropriate[7] The next infusion should be administered at a 50% rate
Grade 4 Fever ≥ 38ºC and/or hypotension requiring multiple vasopressors (excluding vasopressin) and/or hypoxia requiring oxygen by positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation)	If CRS occurs during or post-infusion: ● Treatment with Lunsumio should be permanently discontinued ● The symptoms should be treated ● Dexamethasone[3] and tocilizumab[4, 5] should be administered If CRS is refractory to dexamethasone and tocilizumab: ● Alternative immunosuppressants[9] and methylprednisolone 1 000 mg/day intravenously should be administered until clinical improvement	

[1] ASTCT = American Society for Transplant and Cellular Therapy. Premedication may mask fever, therefore if clinical presentation is consistent with CRS, please follow these management guidelines.
[2] If CRS is refractory to management, consider other causes including hemophagocytic lymphohistiocytosis
[3] Dexamethasone should be administered at 10 mg intravenously every 6 hours (or equivalent) until clinical improvement
[4] In study GO29781, tocilizumab was administered intravenously at a dose of 8 mg/kg (not to exceed 800 mg per infusion), as needed for CRS management
[5] If no clinical improvement in the signs and symptoms of CRS occurs after the first dose, a second dose of intravenous tocilizumab 8 mg/kg may be administered at least 8 hours apart (maximum 2 doses per CRS event). Within each time period of 6 weeks of Lunsumio treatment, the total amount of tocilizumab doses should not exceed 3 doses
[6] Low-flow oxygen is defined as oxygen delivered at < 6 L/minute.
[7] Refer to Table 1 for additional information
[8] High-flow oxygen is defined as oxygen delivered at ≥ 6 L/minute
[9] Riegler L et al. (2019)

Special populations

Elderly

No dose adjustment of Lunsumio is required in patients ≥ 65 years of age.

Renal impairment

Lunsumio has not been studied in patients with severe renal impairment. Dose adjustments are not considered necessary in patients with mild to moderate renal impairment based on pharmacokinetics.

Hepatic impairment

Lunsumio has not been studied in patients with hepatic impairment. Dose adjustments are not considered necessary based on pharmacokinetics.

Paediatric population

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

Method of administration

Lunsumio is for intravenous use only.

Lunsumio must be diluted using aseptic technique under the supervision of a healthcare professional.

It should be administered as an intravenous infusion through a dedicated infusion line. Do not use an in-line filter to administer Lunsumio. Drip chamber filters can be used to administer Lunsumio.

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

Lunsumio must not be administered as intravenous push or bolus.

For instructions on dilution of the medicinal product before administration, see section Special precautions for disposal and other handling.

1.3 Route of Administration:

Intravenous infusion

1.4 Pharmacological Aspects:

Pharmacodynamic Properties

Mechanism of action

Mosunetuzumab is an anti-CD20/CD3 T-cell engaging bispecific antibody targeting CD20-expressing B-cells. It is a conditional agonist; targeted B-cell killing is observed only upon simultaneous binding to CD20 on B-cells and CD3 on T-cells. Engagement of both arms of mosunetuzumab results in the formation of an immunologic synapse between a target B cell and a cytotoxic T cell leading to T-cell activation. Subsequent directed release of perforin and granzymes from T-cell activation through the immunologic synapsis induce B-cell lysis leading to cell death.

Lunsumio caused B-cell depletion (defined as CD19 B-cell counts < 0.07 x 10^9/L) and hypogammaglobulinemia (defined as IgG levels < 500 mg/dL).

2.0 SUMMARY REPORT

2.1 Quality

2.1.1 Active Substance

- The active substance of Lunsumio is mosunetuzumab, a humanised full-length anti-CD20/CD3 T-cell-dependent bispecific IgG1 monoclonal antibody, formed from the assembly of two half-antibodies, KTWE4644 (derived from the murine anti-CD20 monoclonal antibody 2H7) and HTHR4765 (derived from the murine anti-CD3 monoclonal antibody 40G5c).
- The manufacturing process of mosunetuzumab involved independent cell culture and harvest of each half antibody, followed by purification and virus inactivation to form an adjusted affinity pool. The adjusted affinity pool from both half antibodies are combined and assembled to produce the biologically active bispecific antibody (mosunetuzumab) which is then further purified downstream and formulated before filling into the stainless steel or Hastelloy vessel to be frozen.
- Process validation of mosunetuzumab has been conducted using more than three batches and the satisfactory results obtained have confirmed that the process could deliver mosunetuzumab with the expected product quality consistently.
- Primary stability data of three batches placed at the long-term stability condition of -20°C and accelerated conditions of 5°C were able to support the proposed shelf-life of mosunetuzumab for 48 months.
- The manufacturing site has been inspected by the USFDA and concluded as satisfactory.

2.1.2 Finished Product

- The manufacturing process of finished product (Lunsumio) only involved sterile filtration, filling into vials (1mg/vial and 30mg/vial), capping and crimping, final visual inspection as well as secondary packaging and cold storage.
- The results of process validation using commercial scale batches of Lunsumio (1 mg/vial and 30 mg/vial) were satisfactory and demonstrated that the manufacturing process was well controlled.
- The primary stability studies conducted using at least 3 commercial scale batches for up to 36 months in long term storage conditions (2°C-8°C, protected from light) and for up to 6 months in accelerated conditions (25°C ± 2°C/ 60% RH ± 5% RH) have demonstrated satisfactory results. Hence, the proposed shelf-life of 36 months at 2°C-8°C for Lunsumio is acceptable. Additionally, Lunsumio is also stable in a range of commercially available 0.45% and 0.9% saline infusion bags with a PVC infusion set without in-line filters during 24 hours at 2°C-8°C followed by 24 hours at 9°C-30°C with subsequent infusion over 480 minutes covering the proposed in-use period. As Lunsumio does not contain preservatives, from a microbiological point of view, the product should be used immediately.
- Lunsumio is presented as a concentrate for solution for infusion in single use vial with two different fill volume presentations (1 mg [each vial contains 1 mg of mosunetuzumab in 1 mL] and 30 mg [each vial contains 30 mg of mosunetuzumab in 30 mL]). The container closure system consists of a Type 1 clear glass vial with a butyl rubber stopper and aluminium overseal with a plastic flip-off cap (dark grey for 1 mg strength and light blue for 30 mg strength).
- Lunsumio finished product is manufactured at Genentech, Inc., 1 DNA Way South San Francisco (SSF), CA 94080, USA. The site has been inspected by the USFDA and concluded as satisfactory.
- The product has passed the laboratory evaluation for the analytical protocol and validation.

2.2 Non-Clinical Studies

- The pivotal toxicology and safety pharmacology studies intended to support human clinical trials were conducted in a country that is a member of the OECD Mutual Acceptance of Data (MAD) program under OECD Principles of Good Laboratory Practice (GLP).
- Non-clinical studies in human CD20/CD3 transgenic mice and cynomolgus monkeys showed potent, dose-dependent B-cell depletion, T-cell activation, and cytokine release.
- Safety pharmacology evaluations revealed transient, reversible cardiovascular effects primarily related to cytokine release. There were no drug-related effects on respiratory or neurological safety pharmacology endpoints.
- The key mosunetuzumab-related toxicities following IV administration were attributed to cytokine release and included clinical signs (emesis, diarrhea, hypoactivity/hunched posture), hypotension, tachycardia, fever, indicators of inflammation consistent with acute phase reactions with minimal activation of the coagulation system, and minimal hepatocellular degeneration and single-cell hepatocyte necrosis with associated minimal increases in ALT/AST possibly due to cytokine-mediated hepatocyte damage. All findings were transient and generally limited to the first dose.
- Reproductive toxicity studies indicated no significant effects on male or female reproduction, with a low risk for teratogenicity based on available data.
- No genotoxicity or carcinogenicity studies were conducted.
- Overall, mosunetuzumab demonstrated robust pharmacological activity and an acceptable safety profile in preclinical models, supporting its clinical development.

2.3 Clinical Study

- The proposed indication is supported by one phase I/II clinical study (GO29781).

2.3.1 Efficacy

Table 1: Summary of Clinical Studies Conducted

<table>
<tr><th>Study Type & Design (N)</th><th>Objectives of the Study</th><th>Results</th></tr>
<tr><td>Study GO29781
single arm, multicenter, open-label, ongoing phase I/II, dose escalation and dose expansion study

Lihua E Budde et al; GO29781 study. Safety and efficacy of mosunetuzumab, a bispecific antibody, in patients with relapsed or refractory follicular lymphoma: a single-arm, multicentre, phase 2 study. Lancet Oncol. 2022;23:1055-65. doi: 10.1016/ S1470-2045(22)00335-7.</td><td>To evaluate the efficacy and safety of mosunetuzumab monotherapy in patients with relapsed/refractory (R/R) follicular lymphoma (FL) who have received at least two prior systemic therapies.</td><td>Primary Endpoints:
Independent Review facility (IRF)-assessed complete response (CR) rate according to standard NHL response criteria (Cheson et al. 2007)

Results
<table>
<tr><td>Cohort</td><td rowspan="2">B11 FL RP2D cohort</td></tr>
<tr><td>Best Overall Response</td></tr>
<tr><td>Objective Response Rate (ORR; CR or PR), n (%), (95% CI)</td><td>72 (80.0%) (70.3, 87.7)</td></tr>
<tr><td>Complete Response, n (%), (95% CI)</td><td>54 (60.0%) (49.1, 70.2)</td></tr>
<tr><td>Partial Response, n (%),</td><td>18 (20.0%)</td></tr>
</table>
</td></tr>
</table>

Study Type & Design (N)	Objectives of the Study	Results
N = 90 Dose of mosunetuzumab is 21 day-cycle Cycle 1: Day 1 = 1mg, day 8 = 2mg, day 15 = 60mg Cycle 2: Day1 = 60mg Cycle 3+: Day1 = 30mg		**Conclusion** Mosunetuzumab IV monotherapy induces high ORR and CR in patients with R/R FL who have received at least 2 prior therapies.

2.3.2 Safety

- The most commonly reported adverse events were cytokine release syndrome (CRS) (39.4%), fatigue (32.1%), pyrexia (24.3%), hypophosphatemia (22.5%), headache (20.2%), rash (19.3), neutropenia/neutrophil count decreased (27.5%), diarrhea (17.4%), nausea (17.4%) and constipation (16.5%).
- The most commonly reported serious adverse events were cytokine release syndrome (20.6%), malignant neoplasm progression (12.8%) and pyrexia (4.6%).
- Generally, the adverse events are manageable; in particular the risk of cytokine release syndrome requires careful training of hospital staff in relation to observation and management and furthermore easy access to an ICU. Risk minimisation measures including a patient card have been implemented.

3.0 CONCLUSION:

In summary, the data provided in early phase study confirms a positive benefit/risk profile for the use of Lunsumio in the treatment of adult subjects with relapsed or refractory follicular lymphoma (FL) who have received at least two prior systemic therapies. There is an unmet medical need for this group of patients. Furthermore, Lumsumio provides a novel mechanism of action, has a potential therapeutic advantage compared to available treatments, and provides clinically meaningful ORR, CR and DOR, while having a clinically manageable safety profile.

Hence, Drug Control Authority (DCA) on the 400th meeting on 5th September 2024 has decided to approve this product with conditional registration for 2 years with the following indication:

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

This indication is approved under conditional approval based on response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

With the following conditions:

1. To submit data based on confirmatory trial which is the GO42909 trial, a randomized Phase III trial of mosunetuzumab plus lenalidomide versus rituximab plus lenalidomide in patients with R/R FL after at least one prior systemic therapy regimen, to verify the predicted clinical benefit.

2. Implementation of Risk Management Plan for Lunsumio including conducting enhanced post-market surveillance and reporting.

3. To submit the updated Periodic Benefit-Risk Evaluation Report (PBRER) for Lunsumio

4. The PRH shall apply for its renewal at least six months before its expiry (a conditional registration is valid for two years) and shall provide the NPRA with an interim report on the fulfillment of the specific conditions through variation application.