NCPE Assessment

Technical Summary

Mosunetuzumab (Lunsumio®)

23023

24 March 2025

Applicant: Roche Products Ireland Ltd.

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

NCPE
National Centre for Pharmacoeconomics, Ireland

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of mosunetuzumab (Lunsumio®). Following assessment of the Applicant's submission, the NCPE recommends that mosunetuzumab (Lunsumio®) not be considered for reimbursement*.

The Health Service Executive (HSE) asked the NCPE to carry out an evaluation of the Applicant's (Roche Products Ireland Ltd) Health Technology Assessment of mosunetuzumab (Lunsumio®). The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes comparative clinical effectiveness and health related quality of life benefits, which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified.

Following the recommendation from the NCPE, the HSE examines all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs the NCPE recommendation is also considered by the National Cancer Control Programme (NCCP) Technology Review Group.

About the National Centre for Pharmacoeconomics

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

Summary

In February 2024, Roche Products Ireland Ltd submitted a dossier which investigated the comparative clinical effectiveness, cost-effectiveness and budget impact of mosunetuzumab (Lunsumio®) as monotherapy for the treatment of adult patients with relapsed or refractory follicular lymphoma who have received at least two prior systemic therapies. Roche Products Ireland Ltd is seeking reimbursement of mosunetuzumab on the Oncology Drug Management System. Mosunetuzumab is an anti-CD20/CD3 T-cell engaging bispecific antibody targeting CD20-expressing B-cells. Mosunetuzumab is administered as an intravenous (IV) infusion. Each treatment cycle is 21 days. The dose of mosunetuzumab is titrated upwards in Cycle One, with 1mg administered on Day One, 2mg administered on Day Eight and 60mg administered on Day 15. Thereafter, mosunetuzumab is administered on Day One only of each 21-day cycle; 60mg is administered on Day One of Cycle Two and 30mg is administered on Day One of Cycle Three and on Day One of each subsequent 21-day cycle. Patients receive mosunetuzumab for eight treatment cycles, after which their treatment response is assessed. If a complete response is attained, no further treatment is required. If a partial response or stable disease is observed, an additional nine treatment cycles should be administered (maximum of 17 treatment cycles), unless a patient experiences unacceptable toxicity or disease progression.

Follicular lymphoma typically presents as a slow-growing or indolent form of non-Hodgkin's lymphoma. Follicular lymphoma is considered a chronic disease, characterised by repeated relapses over the patient's lifetime. Mosunetuzumab is positioned as a third-line or later treatment for relapsed or refractory follicular lymphoma. There is no universal standard-of-care (SOC) for relapsed and/or refractory follicular lymphoma at this line of therapy in the Irish setting, with the choice of therapy depending on prior treatments received and the kinetics of relapse. Commonly used regimens include rituximab-based regimens, obinutuzumab in combination with bendamustine and idelalisib. Stem cell transplant may also be considered for suitable patients, although the Applicant did not consider this to be a relevant comparator. Tisagenlecleucel has been assessed by the NCPE for this indication and is currently under consideration by the HSE. As such, tisagenlecleucel is a potential future comparator.

1. Comparative effectiveness of mosunetuzumab

The efficacy and safety data for mosunetuzumab is from an ongoing, Phase I/II, single-arm, open-label study, GO29781. The clinical evidence for this indication is from 90 participants in the licensed population with relapsed or refractory follicular lymphoma from Group B11 RP2D who had received the recommended Phase II dose of mosunetuzumab monotherapy during the dose expansion stage of the study. Participants had to have relapsed after or failed to respond to at least two prior lines of systemic therapy including an anti-CD20-directed therapy and an alkylating agent. The primary efficacy endpoint was Complete Response Rate (CRR) as assessed by independent review committee (IRF-CRR), compared with a pre-specified threshold of 14% from a historical control. Response was assessed based on the 2007 Cheson et al. criteria. Progression-Free Survival (PFS) and Overall Survival (OS) were key secondary endpoints. At the primary efficacy analysis (clinical cut-off date March 2021), the IRF-CRR was 58%, which was significantly higher than the pre-specified value of 14%. PFS or OS data from the March 2021 clinical cut-off were not provided. The Applicant instead provided updated data from more recent datacuts. At both the May 2022 and May 2023 data-cuts, the investigator-assessed CRR (60%) was consistent with the prior datacut (March 2021). The median investigator-assessed PFS, at the most recent datacut (May 2023), was 24 months (95% confidence interval 12 months to not reached). OS data from the May 2023 datacut remains immature at 83.3%.

Due to the single-arm nature of the GO29781 study, unanchored indirect treatment comparisons (ITCs) were required to inform the comparisons between mosunetuzumab and SOC therapies. The Applicant conducted unanchored matched adjusted indirect comparisons (MAICs) between mosunetuzumab and the following therapies (comparator data sources listed in brackets): idelalisib (DELTA); rituximab in combination with lenalidomide (AUGMENT) and tisagenlecleucel (ELARA). Propensity score analysis ITCs were conducted for comparisons with: obinutuzumab plus bendamustine (GADOLIN); bendamustine plus rituximab (CONTRALTO); rituximab in combination with cyclophosphamide, vincristine and prednisolone (R-CHOP, EORTC 20981) and the Flatiron-treatment basket (informed by real-world data from the Flatiron Database in the US).

The results of the unanchored ITCs should be interpreted with a high level of caution due to several limitations. Limitations include: heterogeneity across studies; a lack of adjustment for several key baseline characteristics in the unanchored ITCs, and also that the most up-to-date datacuts for mosunetuzumab were not used (a January 2022 datacut was used). Specifically, for the comparison with the Flatiron-treatment basket, there were differences in study design, outcome assessment and study populations. The unadjusted, naïve comparison with R-CHOP was not considered robust for decision-making due to population heterogeneity. The results of the unanchored ITCs do not demonstrate a treatment benefit for mosunetuzumab over comparators.

2. Safety of mosunetuzumab

The safety of mosunetuzumab was assessed in all patients with relapsed or refractory non-Hodgkins lymphoma who received mosunetuzumab at the Phase II dose (Group B11 RP2D; n=218) and in the licensed population (n=90) with relapsed or refractory follicular lymphoma. All participants in the relapsed or refractory follicular lymphoma cohort experienced at least one adverse event (AE). Based on the August 2021 datacut, 46.67% experienced a serious AE (SAE), with 71.4% (n=30) of SAEs deemed to be treatment related. Grade ≥ 3 AEs were experienced by 70% of the population with relapsed or refractory follicular lymphoma.

The Summary for Product Characteristics outlines risk minimisation procedures regarding cytokine release syndrome.

3. Cost effectiveness of mosunetuzumab

The de novo partitioned-survival model for cost effectiveness assessment includes three mutually exclusive health states; Progression-Free, Post-Progression and Death. Key efficacy inputs were PFS and OS. The modelled population is based on participants in the licensed population with relapsed or refractory follicular lymphoma (n=90) from Group B11 RP2D of the GO29781 trial. Treatment effects were based on the Applicant's unanchored ITC analyses.

Treatment effects for most comparisons were modelled using independent parametric

survival models fit separately to OS and PFS data for the respective comparator and mosunetuzumab arms (adjusted data for each comparison). Proportional hazards were assumed to hold for the comparison with obinutuzumab plus bendamustine. The Review Group considered that the proportional hazards assumption was not met for any of the comparisons. The Review Group considered that the most relevant comparison for decision-making is likely the comparison to the Flatiron treatment basket. This comparator is most reflective of the basket of therapies that are used for the treatment of relapsed or refractory follicular lymphoma in the third-line or later treatment setting in Ireland. The Applicant base case extrapolation for the Flatiron-treatment basket OS curve results in a quality adjusted life year (QALY) loss for mosunetuzumab versus the Flatiron-treatment basket. This is because of crossing of the extrapolated OS curves towards the end of the model time horizon. There is no robust evidence to demonstrate a treatment benefit for mosunetuzumab over the Flatiron-treatment basket. Additionally, the longer-term treatment effects of mosunetuzumab are uncertain. The model was sensitive to changes in the OS extrapolations. Due to limitations with the unanchored ITCs, there is a high risk of bias and substantial uncertainty in estimates of treatment effectiveness and therefore cost-effectiveness.

EQ-5D-3L data collected in the G029781 trial is used to inform health-state utility values in the cost-effectiveness analysis. The Review Group considered Post-Progression utility values to be highly uncertain due to the small number of participants contributing observations.

Results

The results of the Applicant base case deterministic cost-effectiveness analysis versus the Flatiron-treatment basket are presented in Table 2. The Flatiron-treatment basket is considered the main comparator of relevance as it is most reflective of the basket of treatments that are used for the treatment of relapsed or refractory follicular lymphoma in the third-line or later treatment setting in Ireland. Analyses for other comparators were presented by the Applicant.

Table 2: Applicant base case incremental cost-effectiveness results

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
Mosunetuzumab versus Flatiron basket treatment[a]					

Flatiron basket treatment	110,371	7.39	-	-	
Mosunetuzumab	165,108	6.81	54,737	-0.58	Dominated[b] (mosunetuzumab is more costly, less effective)

Note: Figures in the table are rounded, and so calculations may not be directly replicable. 4% discount rate appliced to costs and outcomes.

[a]Corresponding probabilistic ICER using 1,000 iterations=Mosunetuzumab is dominated. While the ITC between mosununetuzumab and the Flatiron treatment basket indicate a possible overall survival benefit for mosunetuzumab, the use of different parametric extrapolations of overall survival in each treatment arm causes the curves to cross each other. This results in mosunetuzumab having relatively worse overall survival over the cost-effectiveness model time horizon.

[b]The Applicant stated they wished to revert to their original base case assumption of proportional hazards for the comparison between mosunetuzumab and the Flatiron treatment basket in the post-FAC stage of the assessment process. For transparency, the ICER for mosunetuzumab in this scenario is €26,317/QALY. The Review Group do not consider proportional hazards to be appropriate.

[h] A commercial in confidence PAS is in place for idelalisib and obinutuzumab (PAS offer), not included in this Table.

The Review Group have a number of concerns regarding the reliability of results presented in the Applicant base case. The Review Group considered that the limitations of the evidence base underpinning cost-effectiveness estimates cannot be overcome by making adjustments to a NCPE adjusted base case. As such, the Review Group did not consider it appropriate to present an adjusted NCPE base case.

Sensitivity analysis

The Review Group did not consider that the probabilistic sensitivity analysis captured the uncertainty in estimates of cost effectiveness. The results are thus not presented here.

The Review Group noted that the ICER for the comparison to the Flatiron basket treatment arm varies substantially. Either QALY gain or loss is possible, depending on survival extrapolations selected or if proportional hazards are assumed. The Review Group considered that cost-effectiveness results for all comparisons are uncertain given the substantial uncertainty in the unachored ITCs.

4. Budget impact of mosunetuzumab

The price-to-wholesaler (PtW) of one 1mL vial (1mg mosunetuzumab) is €244.11, while the PtW of one 30mL vial (30mg mosunetuzumab) is €7,326.80. Assuming the mean number of 21-day treatment cycles is 8.4, the mean treatment course cost of mosunetuzumab is estimated to be €87,701 (including VAT).

The Applicant estimated that 10 patients will be treated with mosunetuzumab in Year One,

rising to 14 in Year Five. The Review Group considered that patient population estimates are underestimated as only incident patients with relapsing or refractory follicular lymphoma are considered, with prevalent patients excluded. Patient population estimates are considerably smaller when compared with estimates in the NCPE evaluation of tisagenlecleucel.

The Review Group estimated that the five-year cumulative gross drug budget impact of mosunetuzumab is €7.34 million (including VAT). The cumulative net drug budget impact of mosunetuzumab was estimated to be €5.10 million (including VAT). Budget impact estimates are highly uncertain and likely underestimated.

5. Patient Organisation Submission

No patient organisation submissions were received during the course of the assessment

6. Conclusion

The NCPE recommends that mosunetuzumab not be considered for reimbursement*.

*This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.