Cost effectiveness of polatuzumab vedotin (Polivy®) in combination with bendamustine and rituximab for the treatment of adult patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) who are not candidates for haematopoietic stem cell transplant (HSCT)

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost effectiveness of polatuzumab vedotin (Polivy®)**.** Following assessment of the Applicant's submission, the NCPE recommends that polatuzumab vedotin (Polivy®) be considered for reimbursement if cost effectiveness can be improved relative to existing treatments. This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.

The HSE asked the NCPE to carry out an assessment of the Applicant's (Roche products Ireland) economic dossier on the cost effectiveness of polatuzumab vedotin (Polivy®). The NCPE uses a decision framework to systematically assess whether a technology is cost effective. This includes clinical effectiveness and health-related quality of life benefits, which the new treatment may provide and whether the cost requested by the Applicant 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.

National Centre for Pharmacoeconomics **February 2021**

Summary

In July 2020, Roche products Ireland submitted a dossier of clinical, safety and economic evidence in support of polatuzumab vedotin in combination with bendamustine and rituximab (Pola+BR) for the treatment of adult patients with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL) who are not candidates for haematopoietic stem cell transplant (HSCT). Final data submitted by the Applicant was received in November 2020.

Polatuzumab vedotin is an antibody-drug conjugate (ADC) composed of the anti-mitotic agent monomethylauristatin E (MMAE) covalently conjugated, via a cleavable linker, to a CD79b-directed monoclonal antibody. It kills dividing cells by inhibiting cell division and inducing apoptosis. Polatuzumab vedotin is formulated as a powder for concentrate for solution for infusion. It is available as a 140mg vial and a 30mg vial, each containing 20mg/ml of polatuzumab vedotin in its reconstituted form. The recommended dose of polatuzumab is 1.8mg/kg administered as an intravenous infusion (IV) on day 1 of each 21-day cycle for 6 cycles. It should be administered in combination with bendamustine. The recommended dose of bendamustine is 90mg/m^2/day on day 1 and day 2 of each 21-day cycle. The recommended dose of rituximab is 375mg/m^2 on day 1 of each 21-day cycle. Dose modifications based on severity and clinical presentation of adverse events are permitted, as outlined in the summary of product characteristics.

It is anticipated that polatuzumab vedotin will be used to treat the following patient cohorts:

- patients with R/R DLBCL who are clear non-candidates for HSCT,
- patients with R/R DLBCL who are treated with salvage chemotherapy with intent to HSCT but do not respond to salvage chemotherapy (and are therefore, HSCT ineligible),
- patients with R/R DLBCL who relapse following HSCT.

This is in line with the licensed indication and with clinical opinion obtained by the Review Group.

Clinical opinion also highlighted that Pola+BR might be considered as treatment to bridge patients to HSCT and CAR T-cell therapy. The Review Group note that this is not a licensed indication. Clinical efficacy and cost effectiveness for this indication have not been evaluated.

There is no universal standard-of-care for patients with R/R DLBCL who are not candidates for HSCT. The Applicant considered BR (bendamustine in combination with rituximab) to be the base case comparator. BR is not used in Irish clinical practice. The Review Group do not consider it to be a relevant comparator and therefore, do not report the cost-effectiveness outputs here. A comparison with R-GemOx (rituximab, gemcitabine, oxaliplatin) was submitted as scenario analysis. R-GemOx is a commonly used regimen for this indication in Ireland. The Review Group consider this to be the base case comparator. The Applicant also considered CAR T-cell therapies to be relevant comparators; however, these are not currently reimbursed in Ireland. Clinical opinion obtained by the Review Group indicated that other regimens such as R-GDP (rituximab, gemcitabine, dexamethasone, cisplatin), and R-ICE (rituximab, ifosfamide, carboplatin, etoposide) are also used. These were not considered by the Applicant.

1. **Comparative effectiveness of polatuzumab vedotin**

Clinical evidence for polatuzumab vedotin came from the GO29365 trial. This comprised a phase Ib safety run-in phase and a randomised phase II multi-centre, open-label expansion phase. The target population was patients aged 18 years of age and over, with histologically confirmed DLBCL, and who had received at least one prior therapy for DLBCL. Patients must have relapsed or become refractory to a prior regimen. Patients who received prior HSCT or were eligible for HSCT were excluded. A total of 80 patients were enrolled into the phase II portion of GO29365 and randomised to receive either Pola+BR (Arm C; n=40) or BR (Arm D; n=40). All treatments were administered on a 21-day cycle for a maximum of six cycles or until disease progression, whichever occurred first.

The primary endpoint was complete response as determined by an independent review committee at the primary response assessment using a PET-CT scan. Secondary endpoints included objective response rate, best objective response, and independent review committee-assessed progression free survival. Overall survival was an exploratory endpoint. As no superiority or non-inferiority hypotheses were pre-specified in the study protocol, the study was exploratory in nature. Data on health-related quality of life (HRQOL) were not collected; however, patient-reported outcomes, evaluating peripheral neuropathy, were

assessed by means of the Therapy-Induced Neuropathy Assessment Score (TINAS) instrument.

Imbalances in baseline characteristics between the arms indicated that patients in the BR arm had worse prognosis at baseline. These imbalances included a higher proportion of patients with bulky disease (37.5% versus 25.0%) and a high prognostic risk (IPI) score of 4-5 (42.5% versus 22.5%).

As of the March 2019 data cut-off analysis, median duration of follow up was 30 months. The primary endpoint of complete response was higher in the Pola+BR arm, 57.5% (95% CI 40.9 to 70.3), compared to the BR arm, 20% (95% CI 9.1 to 35.7). The median progression-free survival, as assessed by the independent review committee, was 9.5 months (95% CI 6.2 to 13.9) in the Pola+BR arm and 3.7 months (95% CI 2.1 to 4.5) in the BR arm. Median overall survival was 12.4 months (95% CI 9.0 to N.E.) in the Pola+BR arm and 4.7 months (95% CI 3.7 to 8.3) in the BR arm. The risk of bias in reported outcomes is high in this exploratory analysis. Data collected using the TINAS instrument indicated that, overall, peripheral neuropathy symptoms were mild.

Data from Arm C (n=40) of GO29365 were generated using the liquid formulation of polatuzumab vedotin; however, it is the lyophilised formulation that will be available in clinical practice. Two additional arms (Arm G and Arm H) were subsequently added to GO29365; patients in both arms received lyophilised Pola+BR. Data from these arms indicated that patients who received the lyophilised formulation had a lower median progression-free survival (independent review committee-assessed) and overall survival than those who received the liquid formulation. The Review Group noted that differences between Arm C (liquid formulation) and Arm G and Arm H (lyophilised formulation) may partly be explained by differences in the length of follow-up. No major concerns, in terms of comparability of the liquid and lyophilised formulations, were highlighted by the EMA and pharmacokinetic analysis supported comparability. Overall, the Review Group concluded that although uncertainty exists, it is reasonable to utilise data of the liquid formulation (Arm C) to represent the lyophilised formulation (Arm G and Arm H).

In the absence of direct comparative evidence of Pola+BR versus R-GemOx, the feasibility of conducting an indirect treatment comparison was explored, using conventional network meta-analysis methods and matching-adjusted indirect comparison methods (MAICs). Neither of these approaches was deemed feasible due to the limitations in the existing evidence base. Instead, the efficacy of R-GemOx was assumed to be equal to that of BR. Clinical opinion obtained by the Review Group indicated that R-GemOx is likely to be more effective than BR; however, limited evidence is available to support this. The validity of this assumption is uncertain.

2. Safety of polatuzumab vedotin

The population included in the safety analysis of GO29365 consisted of 45 patients who received at least one dose of Pola+BR during phase Ib and phase II and 39 patients who received BR in phase II. Based on the April 2018 data-cut, all patients in the Pola+BR arm experienced at least one adverse event, while 97.4% of patients in the BR arm experienced at least one adverse event. A higher proportion of patients in the Pola+BR arm experienced adverse events of grade 3-4 severity (84.4% versus 71.8%). The safety profile of Pola+BR was characterised mainly by myelosuppression. The most common adverse events experienced by patients included neutropenia (46.7%), anaemia (46.7%), and thrombocytopenia (46.7%). These occurred at a higher incidence in the Pola+BR arm. The proportion of patients experiencing these adverse events at grade 3-4 severity ranged from 24.2% (anaemia) to 40% (neutropenia; thrombocytopenia).

Peripheral neuropathy, including peripheral sensory and motor neuropathy, is an identified risk of polatuzumab vedotin, consistent with the mechanism of action of MMAE. A total of 40% of patients in the Pola+BR arm experienced peripheral neuropathy, compared to 7.7% in the BR arm. No cases were fatal, serious or led to study withdrawal. All events were grade 1-2 in severity.

Overall, the EMA concluded that the safety profile of Pola+BR was not negligible, yet manageable in the context of the severity of disease.

3. Cost effectiveness of polatuzumab vedotin

For the cost-effectiveness analysis, the key effectiveness inputs were overall survival and progression free survival. Clinical efficacy inputs for Pola+BR and BR were derived from the randomised phase II (Arm C and Arm D) portion of GO29365. Efficacy of R-GemOx was assumed to be equal to that of BR. Cost effectiveness was based on a cost-utility partitioned survival model with a time horizon of 45 years and cycle length of one week. The model included three health states: progression-free, post-progression, and death.

In the Applicant base case, survival outcomes (progression free survival and overall survival) were extrapolated to the full time horizon of the model using a log-normal mixture cure model for both treatment arms. General population overall survival curves were calculated from Central Statistics Office Irish Life tables and adjusted for a 14% excess hazard of death. The Review Group concluded that the data available from GO29365 were not sufficiently mature or robust to support an assumption of cure. As such, for the NCPE-adjusted base case, the Review Group selected the standard parametric log-normal distribution for progression-free survival and overall survival extrapolations in both the Pola+BR and R-GemOx arms.

Health state-specific utility values were applied to the progression-free and post-progression health states. Utility values were obtained from the ZUMA-1 trial, which examined axicabtagene ciloleucel in R/R DLBCL. Despite limitations associated with the ZUMA-1 data (including very small sample size and differences in patient populations between ZUMA-1 and GO29365), the Review Group considered these values to be the most appropriate, of the identified values, to inform the model. For patients who remained in the progression-free health state at two years, the Applicant assumed that these would revert to a HRQOL equivalent to similarly aged persons from the general population. In light of the limited evidence provided, in the NCPE-adjusted base case, the Review Group assumed that patients remaining in the progression-free health state do not revert to general population utilities. Treatment-specific disutility values for adverse events were obtained from the literature. The cost components considered in the model included: drug acquisition and administration costs, follow-up and monitoring costs, adverse event costs, subsequent

treatment costs, and end-of-life costs. These were generally considered appropriate by the Review Group.

Analyses presented in this document are based on the list prices of Pola+BR and R-GemOx. The NCPE Review Group implemented a number of changes to the Applicant base case to reflect the most plausible assumptions. The most notable of these include: the use of standard parametric log-normal distribution to extrapolate survival data, the reduction of the number of cycles of R-GemOx received from eight to six, and assuming a flat administration cost of €557 per administration day, regardless of the length of infusion or number of infusions received on a particular day. The NCPE-adjusted base case ICER versus R-GemOx is presented in Table 1.

Table 1 NCPE-adjusted base case results

Technology	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	Pairwise ICERs (€/QALY)
R-GemOx	46,002	0.65			
Pola+BR	107,139	1.65	61,137	1.00	61,236

Note: Figures in table are rounded and so, will not be directly replicable.
Pola+BR: Polatuzumab vedotin in combination with bendamustine and rituximab; **R-GemOx**: Rituximab, gemcitabine, oxaliplatin.

In the NCPE-adjusted base case analysis, Pola+BR had a probability of cost effectiveness, versus R-GemOx, of 19% at a willingness-to-pay threshold of €45,000 per QALY. The probability of cost effectiveness at a willingness-to-pay threshold of €20,000 per QALY was 0%. The Applicant base case ICER is presented in Table 2.

Table 2 Applicant base case results

Technology	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	Pairwise ICERs (€/QALY)
R-GemOx	44,629	0.68			
Pola+BR	103,625	2.12	58,996	1.45	40,809

Note: Figures in table are rounded and so, will not be directly replicable.
Pola+BR: Polatuzumab vedotin in combination with bendamustine and rituximab; **R-GemOx**: Rituximab-gemcitabine, oxaliplatin.

In the Applicant base case analysis, Pola+BR had a probability of cost effectiveness, versus R-GemOx, of 58% at a willingness-to-pay threshold of €45,000 per QALY. The probability of cost effectiveness at a willingness-to-pay threshold of €20,000 per QALY was 0%.
It should be noted that ICERs may be underestimated due to the assumption of equal efficacy of BR and R-GemOx.

4. Budget impact of polatuzumab vedotin

The Applicant applied for reimbursement of polatuzumab vedotin under the Oncology Drugs Management System (ODMS). Polatuzumab vedotin is available as a 140mg and 30mg vial. The price to wholesaler of the 140mg vial is €9,800, while that of the 30mg vial is to be confirmed. When rebate is accounted for, and assuming a weighted average patient weight from the GO29365 trial, the total cost of polatuzumab vedotin to the HSE per each treatment cycle is €10,553.13 (excluding VAT) and €13,121.62 (including VAT). Incorporating the costs of bendamustine and rituximab, the total regimen cost to the HSE per each treatment cycle is €13,032.43 (excluding VAT) and €16,173.32 (including VAT). Based on the assumption that all patients receive six cycles of Pola+BR, the total cost of treatment with Pola+BR is €78,194.61 (excluding VAT) and €97,039.95 (including VAT). Patients who do not respond to treatment may not receive the full six cycles, potentially resulting in a reduced cost.

Based on population estimates obtained from National Cancer Registry Ireland (NCRI) data and clinical opinion, a total of 528 patients are expected to be eligible for treatment with Pola+BR over five years. Based on a predicted market share of 60% in year 1 and rising by 5% each year to year 5, a total of 371 patients are expected to be treated with Pola+BR over 5 years. Estimates were considered reasonable by the Review Group. The subsequent 5-year gross budget impact of Pola+BR is estimated to be €36,009,472. The 5-year net drug budget impact, based on displacement of R-GemOx, is estimated to be €30,774,902. As R-GemOx is the only comparator considered in the net drug budget impact, the true net drug budget impact, due to displacement of other comparators, is unknown.

5. Patient submissions

No patient organisation submissions were received during this assessment.

6. Conclusion

Following assessment of the Applicant's submission, the NCPE recommends that polatuzumab vedotin (Polivy®) be considered for reimbursement if cost effectiveness can be improved relative to existing treatments.*

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