NCPE Assessment

Technical Summary

Polatuzumab vedotin (Polivy®)

HTA ID: 22043

05 December 2023

Applicant: Roche Products Ireland Ltd

Polatuzumab vedotin in combination with rituximab, cyclophosphamide, doxorubicin, and prednisolone (Pola+R-CHP) for the treatment of adult patients with previously untreated diffuse large B-cell lymphoma.

NCPE
National Centre for Pharmacoeconomics, Ireland

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of polatuzumab vedotin (Polivy®) for this indication.

Following assessment of the Applicant's submission, the NCPE recommends that polatuzumab vedotin (Polivy®) not be considered for reimbursement unless cost-effectiveness can be improved relative to existing treatments*.

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 polatuzumab vedotin (Polivy®). 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 January 2023, Roche Products Ireland Ltd submitted a dossier which investigated the comparative clinical effectiveness, cost-effectiveness and budget impact of polatuzumab vedotin (Polivy®) in combination with rituximab, cyclophosphamide, doxorubicin, and prednisolone (Pola+R-CHP) for the treatment of adult patients with previously untreated diffuse large B-cell lymphoma (DLBCL). Roche Products Ireland Ltd is seeking reimbursement of Pola+R-CHP on the Oncology Drugs Management System.

Polatuzumab vedotin is a CD79b-targeted antibody-drug conjugate. 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 vedotin is 1.8mg/kg administered as an intravenous (IV) infusion on day 1 of each 21-day cycle for six cycles. It should be administered in combination with rituximab 375mg/m^2 IV for eight cycles, cyclophosphamide 750mg/m^2 IV for six cycles, doxorubicin 50mg/m^2 IV for six cycles (each administered on day 1 of each 21-day cycle), and prednisolone 100mg orally on days 1 to 5 of each 21-day cycle for six cycles.

The Applicant anticipates that Pola+R-CHP will be used for the treatment of adult patients with previously untreated DLBCL, who have an International Prognostic Index (IPI) score of 2 to 5. The Review Group noted that the licensed indication does not specify a restriction regarding IPI score. However, clinical opinion obtained by the Review Group indicated that Pola+R-CHP is likely to be used in line with the Applicant's proposed positioning. This is aligned with the inclusion criteria of the pivotal POLARIX trial. Rituximab in combination with cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP) is considered to be standard-of-care for this patient population and is the comparator of relevance to this assessment.

1. Comparative effectiveness of Pola+R-CHP

The safety and efficacy of Pola+R-CHP was investigated in the phase III, randomised, placebo-controlled, double-blind, multi-centre trial; POLARIX. In this trial, patients with previously untreated DLBCL were randomised 1:1 to receive either Pola+R-CHP (n=440) or R-

CHOP (n=439). Patients were required to have an IPI score of 2 to 5 and an ECOG performance status of 0 to 2. Investigator-assessed progression-free survival (PFS) was the primary endpoint. Overall survival (OS) was a secondary endpoint. Results, based on the data cuts from June 2021 (primary analysis) and June 2022 (supportive analysis), were presented by the Applicant.

At the June 2022 data cut, median duration of follow up was 39.7 months. At this data cut, treatment with Pola+R-CHP was associated with a statistically significant improvement in PFS versus R-CHOP (hazard ratio 0.76; 95% CI 0.60 to 0.97). These data were immature; 26.8% of patients in the Pola+R-CHP arm and 32.6% in the R-CHOP arm experienced a PFS event. Median PFS was not reached in either arm. There was no statistically significant difference in OS between the Pola+R-CHP and R-CHOP arms (hazard ratio 0.94; 95% CI 0.67 to 1.33). OS data were also immature; 14.5% of patients in the Pola+R-CHP arm and 15.3% of patients in the R-CHOP arm had died. Median OS was not reached in either arm.

The Review Group considered the immaturity of the available efficacy data to be a major source of uncertainty regarding the comparative effectiveness of Pola+R-CHP. Notably, the study was not adequately powered for OS, even for the final analysis. It was further highlighted that a considerable duration of follow-up will be required to demonstrate any differences in OS, if any, between the two treatment arms. Results should therefore be interpreted with caution.

2. Safety of Pola+R-CHP

The adverse event (AE) profile of Pola+R-CHP observed in POLARIX was aligned with the established AE profile of each individual component of the regimen. No new safety concerns were raised. Pola+R-CHP is associated with a high incidence of grade ≥3 AEs and serious AEs (mainly myelosuppression and infections). The incidence of infection events, grade 3 to 4 infections and serious infections was higher in the Pola+R-CHP arm compared to the R-CHOP arm (49.7% versus 42.7%; 14.0% versus 11.2%; and 14.0% versus 10.3%, respectively). The most common grade ≥3 AEs in either arm included neutropenia (28.3% Pola+R-CHP versus 30.8% R-CHOP), febrile neutropenia (13.8% versus 8.0%), and anaemia (12.0% versus 8.4%).

3. Cost effectiveness of Pola+R-CHP

Methods

A de novo partitioned survival model was used to evaluate the cost effectiveness of Pola+R-CHP. This model included three mutually exclusive health states; progression-free, post-progression and death. Direct evidence for Pola+R-CHP versus R-CHOP was available from the POLARIX trial (June 2022 data cut). A mixture cure model approach was used to extrapolate the PFS and OS data. The mixture cure model assumes that a proportion of patients ('cure fraction') will not progress and will have OS in line with the general population. Due to the immaturity of the data from POLARIX, the Applicant used external data to support the modelling of a 'more accurate' long-term cure fraction. The R-CHOP arm of the GOYA trial was used by the Applicant to achieve this. GOYA is a multicentre, open-label, randomised, phase III study, which examined the efficacy of obinutuzumab-CHOP (n = 706) versus R-CHOP (n = 712). Inclusion criteria and patient characteristics were generally aligned between the POLARIX and GOYA trials. Propensity score matching was used to match patients who received R-CHOP in GOYA with patients in POLARIX (both Pola+R-CHP and R-CHOP arms). For each patient from POLARIX, from 42 months onwards, the time in PFS was assumed to continue as that of the matched patients from the R-CHOP arm of GOYA. Thus, 'extending' the POLARIX PFS data. OS data were not extended, as the OS Kaplan-Meier curves of the R-CHOP arms of GOYA and POLARIX were not aligned. The Review Group had concerns regarding the post-hoc approach taken to extend the POLARIX PFS data. The Review Group did not consider it appropriate to artificially stabilise such data in an attempt to estimate a cure fraction.

Utility data were derived from EQ-5D-3L data collected during the GOYA trial. The Applicant assumed that patients who remain progression-free at 2.4 years (0.4 years of treatment plus 2 years progression-free) have utility equivalent to that of the general population. The Review Group considered utility values derived from POLARIX to be more methodologically robust. Additionally, the assumption that long-term survivors have utility equal to that of the general population is not supported by the literature.

The model included drug acquisition, administration, monitoring, AE, and subsequent treatment costs. To align with the assumption of cure, patients in the progression-free

health state incurred no health-state monitoring costs from 2.4 years onwards. Additionally, once the proportion of patients remaining in the progression-free health state reached the cure fraction, no further post-progression (once-off) or subsequent treatment costs were applied. The Review Group had concerns regarding the Applicant's approach to modelling health-state monitoring costs, with post-progression costs likely overestimated. Due to the model structure, the impact of the approach taken could not be fully investigated.

The Review Group identified a number of limitations in the Applicant's base case, which were explored in the NCPE-adjusted base case. The most notable of these included removal of the GOYA 'extension' from the POLARIX PFS data, application of a standardised mortality ratio to long-term survivors to account for excess mortality, application of progression-free health-state monitoring costs until five years, and assuming that post-progression (once-off) and subsequent treatment costs are incurred throughout the time horizon of the model.

Results

Analyses presented in this document are based on the list prices of interventions. Results of the Applicant's base case deterministic cost-effectiveness analysis are presented in Table 1. Results of the NCPE-adjusted base case are presented in Table 2. The Review Group considered the results to be highly uncertain, due to uncertainty in the clinical evidence and concerns regarding the modelling of health-state monitoring costs.

Table 1 Applicant base case incremental cost-effectiveness results[a]

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
R-CHOP	146,022	8.69	-	-	-
Pola+R-CHP[b]	157,070	8.98	11,048	0.30	37,352

ICER: Incremental cost-effectiveness ratio; **Pola+R-CHP:** Polatuzumab vedotin, rituximab, cyclophosphamide, doxorubicin, prednisolone; **QALY:** Quality-adjusted life year; **R-CHOP**: Rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone.
[a] Corresponding probabilistic ICER using 1,000 iterations =€35,838/QALY. Figures in the table are rounded, and so calculations may not be directly replicable. Costs and QALYs discounted (4%).
[b]A commercial in confidence patient access scheme is in place for polatuzumab vedotin; not included in this table.

Table 2 NCPE-adjusted base case incremental cost-effectiveness results[a]

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
R-CHOP	138,582	8.42	-	-	-
Pola+R-CHP[b]	160,758	8.65	22,177	0.23	97,744

ICER: Incremental cost-effectiveness ratio; **Pola+R-CHP:** Polatuzumab vedotin, rituximab, cyclophosphamide, doxorubicin, prednisolone; **QALY:** Quality-adjusted life year; **R-CHOP**: Rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone.
[a] Corresponding probabilistic ICER using 1,000 iterations =€95,462/QALY. Figures in the table are rounded, and so calculations may not be directly replicable. Costs and QALYs discounted (4%).
[b]A commercial in confidence patient access scheme is in place for polatuzumab vedotin; not included in this table.

Sensitivity analysis

The probabilities of cost effectiveness, for Pola+R-CHP versus R-CHOP, under the NCPE-adjusted base case assumptions were 1% at the €20,000 per QALY threshold and 11% at the €45,000 per QALY threshold. Deterministic one-way sensitivity analysis indicated that the most influential parameters in the NCPE-adjusted base case were progression-free and post-progression utility values. In the Applicant base case, the most influential parameters related to per cycle post-progression health state costs.

A price-ICER analysis, conducted using the NCPE-adjusted base case, indicated that a 39.2% and 29.3% reduction in the price-to-wholesaler of polatuzumab vedotin was required to meet the €20,000 per QALY and €45,000 per QALY thresholds, respectively. A commercial-in-confidence patient access scheme is currently in place for polatuzumab vedotin. This is not considered in these estimates.

4. Budget impact of Pola+R-CHP

The price-to-wholesaler of the 140mg vial of polatuzumab vedotin is €9,800, while that of the 30mg vial is €2,090. The total cost, per patient, per treatment course of Pola+R-CHP, using the mean number of treatment cycles from POLARIX, was €80,303 (€64,359 excluding VAT).

The eligible population is defined as patients with previously untreated DLBCL with an IPI score of 2 to 5. Based on population estimates obtained from the National Cancer Registry Ireland and clinical opinion, a total of 1,666 patients are expected to be eligible for treatment over a five-year period. Assuming a market share of 10% (year one) to 20% (year two onwards), the total number of patients expected to receive treatment with Pola+R-CHP over a five-year period is 301. Considering the heterogeneous nature of DLBCL, and the lack of published epidemiological data in Ireland, the population of eligible patients and the proportion expected to receive treatment with Pola+R-CHP is difficult to accurately estimate. The uncertainty is highlighted.

Based on these assumptions, the cumulative five-year gross drug budget impact was

estimated to be €20.8million (€16.7million excluding VAT). The cumulative five-year net drug budget impact was estimated to be €17.5million (€14.0million excluding VAT). The Review Group conducted a scenario, whereby the full weight distribution of patients in POLARIX was used to calculate drug costs. This is in contrast to the mean weight and mean body surface area used in the Applicant base case. In this scenario, the five-year cumulative gross drug budget impact was €24.2million (€19.4million excluding VAT). The cumulative five-year net drug budget impact was €20.1million (€16.2million excluding VAT).

5. Patient Organisation Submission

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

6. Conclusion

The NCPE recommends that Pola+R-CHP not be considered for reimbursement unless 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.*