Cost-effectiveness of Obinutuzumab (Gazyvaro®) for the First Line Treatment of Follicular Lymphoma

The NCPE has issued a recommendation regarding the cost-effectiveness of obinutuzumab (Gazyvaro®). Following NCPE assessment of the applicant's submission, the NCPE recommends that obinutuzumab (Gazyvaro®) for this indication should 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.

The HSE asked the National Centre for Pharmacoeconomics (NCPE) to carry out an assessment of the applicant's (Roche) economic dossier on the cost effectiveness of obinutuzumab (Gazyvaro®). 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 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

National Centre for Pharmacoeconomics **May 2018**

Summary

In November 2017, Roche submitted a dossier for obinutuzumab (Gazyvaro®). Roche are seeking reimbursement for obinutuzumab (Gazyvaro®) in the hospital setting for an extension of the product license to allow previously untreated advanced follicular lymphoma (FL). Therefore, obinutuzumab is indicated in combination with chemotherapy (O-chemo), followed by obinutuzumab maintenance in patients achieving a response, for previously untreated advanced FL. Obinutuzumab is formulated as a 1000mg concentrate for solution for infusion.

The recommended dose of obinutuzumab in cycle 1, in combination with chemotherapy, is 1,000 mg administered on Day 1, Day 8 and Day 15 of the first 21 or 28-day treatment cycle. The recommended dose in cycles 2-6 (or 8) in combination with chemotherapy, is 1,000 mg administered on Day 1 of each 21-day treatment cycle (8 cycles in total), or on Day 1 of each 28-day treatment cycle (6 cycles in total). Patients who respond to induction treatment (i.e. the initial 6-8 treatment cycles) should continue to receive obinutuzumab 1,000 mg as single agent maintenance therapy once every 2 months for two years or until disease progression (whichever occurs first).

Obinutuzumab is an orphan drug. It is a recombinant monoclonal humanised and glycoengineered Type II anti-CD20 antibody of the IgG1 isotype.

1. **Comparative effectiveness of obinutuzumab (Gazyvaro®)**

- Rituximab in combination with chemotherapy (R-chemo) as an induction treatment followed by rituximab maintenance /monotherapy is the most appropriate comparator and therefore the chosen comparator in the comparative effectiveness analysis.
- The evidence used to support efficacy was from the GALLIUM trial. GALLIUM is an open-label, international, multicentre, randomised, 2-arm, phase III trial to evaluate the efficacy and safety of O-chemo followed by obinutuzumab maintenance therapy for responders compared with R-chemo followed by rituximab maintenance therapy for responders, in previously-untreated patients with CD20-positive advanced B-cell indolent Non-Hodgkin's lymphoma (iNHL), including both FL and marginal zone lymphoma (MZL) patients, who had a life expectancy of greater than 12-months and

an ECOG status of 0-2. The primary efficacy endpoint was progression-free survival as assessed by the investigator (PFS-INV) among patients with FL. Secondary efficacy endpoints included; PFS assessed by independent review committee (PFS-IRC), overall survival (OS), overall response (OR), overall response rate (ORR) and safety outcomes. Health related quality of life (HRQoL) assessments were performed using the FACT-Lym instrument and the EQ-5D-3L. The interim analysis (clinical cut-off date January 2016) was considered by the Applicant as the primary analysis for efficacy as the pre-specified boundary for the primary endpoint, PFS-INV in the FL population had been met.

- The median time for PFS was not reached in either treatment arm. The hazard ratio for PFS-INV was 0.66 (95% CI 0.51, 0.85) and PFS-IRC was 0.68 (95% CI 0.54, 0.87) at the January 2016 clinical cut-off. Based on KM estimates, at the later September 2016 cut-off, 75.0% (95% CI 71.0, 78.5) of patients in the R-chemo arm and 81.5% (95% CI 77.9, 84.6) of patients in the O-chemo arm were progression-free at three years, based on investigator assessment. The median OS was not estimable in either treatment arm, HR=0.82 (95% CI 0.54, 1.22) at the September 2016 clinical cut-off. Based on KM estimates the probability of being alive at three years were 92.2% (95% CI 89.7, 94.1) in the R-chemo arm and 93.9% (95% CI 91.6, 95.6) in the O-chemo arm at the September 2016 data cut-off. However, less than 20% of patients had been followed for survival for more than 4-years. The NCPE review team has concerns regarding the immaturity of the survival data (PFS and OS), resulting in uncertainty in interpreting the effect of treatment with O-chemo on both PFS and OS.
- Comparative clinical data derived from the GALLIUM trial were used in the economic model.

2. **Safety of obinutuzumab (Gazyvaro®)**

- Adverse events occurring more frequently on the O-chemo treatment arm in the GALLIUM trial included infusion-related reactions, neutropenia, constipation and diarrhoea. Serious adverse events and grade 3-5 adverse events occurring more frequently in the O-chemo treatment arm included febrile neutropenia, infusion-related reactions and neutropenia.

- Adverse events and serious adverse events were generally less common during maintenance therapy than during the induction phase (except for infections and infestations). With neutropenia being the most common adverse event of grade 3 to 5 and pneumonia the most common serious adverse event in the maintenance phase.

3. **Cost effectiveness of obinutuzumab (Gazyvaro®)**

Methods

- A cost-utility analysis comparing O-chemo followed by obinutuzumab maintenance therapy with R-chemo followed by rituximab maintenance therapy was submitted by the company. The perspective of the HSE (payer) was presented.
- The model was a multi-state cost-utility Markov model, incorporating four health states: progression-free, early progressive disease (within the first two years), late progressive disease (subsequent years) and death.
- The time horizon was 50-years (reflecting a life-time horizon), with cycle lengths of 1 month.
- Health benefit was measured in quality adjusted life years (QALYs). EQ-5D-3L data collected in the GALLIUM trial was used to inform utilities in the PFS stage of the model. EQ-5D-3L data were transformed into utility values using the EQ-5D UK tariff values. A regression was fitted to predict utility including age, baseline utility, ECOG score, gender and FLIPI score as co-variates. Values obtained from the literature were used to inform the progressed health states as EQ-5D-3L values were only collected at the first assessment after progression in the GALLIUM trial.
- Costs in the model included, drug acquisition, drug administration and monitoring costs, health-state costs and costs of adverse events.
- The exponential distribution was used to extrapolate PFS data beyond the observation period in the GALLIUM trial to inform treatment effectiveness in the model. Post-progression survival was analysed separately for patients who progressed before and after two years, using data from the GALLIUM trial for early progressors and the PRIMA trial of rituximab maintenance versus observation for late progressors. OS was calculated through the model based on the proportion of

patients in the PFS and progressed disease states and was therefore an output of the survival model.

- The NCPE review team identified several key issues and uncertainties with the economic model including the use of PFS-INV in preference to PFS-IRC, the use of the exponential model in preference to the Weibull, the assumption of an 11-year duration of treatment effectiveness based on the length of follow-up of the PRIMA trial, pooling of data from both treatment arms to inform survival probabilities and assumptions surrounding the proportions of companion chemotherapies.

Results (specifically state the incremental cost and QALY gain alongside the ICER)

- The base case incremental cost-effectiveness results indicate that O-chemo results in an additional 0.72 life-years, equating to 0.79 additional QALYs compared with R-chemo, at an additional cost of €42,209. This results in an **ICER of €53,249 per QALY.**
- The NCPE did not consider that the Applicant's submitted model and resulting ICER are a complete reflection of the cost-effectiveness of obinutuzumab. Several changes were implemented in the model by the NCPE including increasing the average age of patients to that observed in Irish clinical practice, using the Weibull to extrapolate PFS, using PFS-IRC in preference to PFS-INV and assuming equal hazard for treatment effect beyond 5-years. Implementation of these changes resulted in increases in the ICER up to €95,606/QALY (incremental costs €43,809; incremental QALYs 0.458).

Sensitivity analysis

- One-way sensitivity analyses were performed with model input parameters varied across their plausible ranges. These analyses showed that the model is most sensitive to decreasing time horizon, discount rate for effects, utility values in the maintenance phase and duration of treatment effect.
- Two further scenario analyses were presented, one varying the cost and market share of the biosimilar rituximab and a second using the proportions of companion chemotherapy regimens based on those observed in clinical practice in preference to those observed in the GALLIUM trial. Neither analysis had a significant effect on the final ICER.

- The probability of the applicant base case ICER being below a willingness-to-pay threshold of €45,000 and €20,000 is 28.2% and 0% respectively.

4. Budget impact of obinutuzumab (Gazyvaro®)

- The list price of obinutuzumab is €3,479.37 per 1,000mg vial. The total treatment cost of obinutuzumab (excluding the companion chemotherapy cost) per patient after induction therapy and 2-years of maintenance, including all rebates and VAT, is estimated as €81,765 for patients receiving O-benda and €89,942 for patients receiving O-CHOP or O-CVP.
- The Applicant estimated that the eligible population would increase from 37 patients in Year 1 increasing to 109 in Year 5. The projected gross budget impact including acquisition costs only for obinutuzumab (excluding the companion chemotherapy cost) was estimated as €1,845,440 (year 1), €3,950,077 (year 2), €6,289,379 (year 3), €7,969,654 (year 4) and €9,005,619 (year 5). This results in a cumulative gross budget impact of €29.1M over 5-years.
- The Applicant provided a net budget impact of the incremental impact of including O-chemo induction and maintenance therapy in preference to R-chemo induction and maintenance therapy. The net budget impact was estimated to increase from €1.32 million in year 1 to €6.23 million in Year 5 (cumulative 5-year net budget impact €20.2 million).

5. Patient submissions

- No patient submissions were received in support of the application.

6. Conclusion

- Following assessment of the company submission, the NCPE recommends that obinutuzumab (Gazyvaro®) in combination with chemotherapy followed by obinutuzumab maintenance therapy for this indication should 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.