Cost-effectiveness of Obinutuzumab (Gazyvaro®) for the 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, obinutuzumab (Gazyvaro®) is not considered cost-effective for the treatment of follicular lymphoma and therefore is not recommended for reimbursement at the submitted price.

The HSE asked the National Centre for Pharmacoeconomics (NCPE) to carry out an assessment of the applicant's (Roche Products Ireland Ltd) 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 **January 2017**

Summary

In July 2016, Roche submitted a dossier for obinutuzumab (Gazyvaro®). Obinutuzumab in combination with bendamustine followed by obinutuzumab maintenance is indicated for the treatment of patients with follicular lymphoma (FL) who did not respond or who progressed during or up to 6 months after treatment with rituximab or a rituximab-containing regimen. Obinutuzumab is a recombinant monoclonal humanised and glycoengineered antibody.

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

- At present bendamustine monotherapy is the only licenced treatment for patients with rituximab refractory indolent non-Hodgkin's lymphoma (iNHL) (of which FL is the main sub-type) in Ireland. Consequently, bendamustine monotherapy is the chosen comparator in the comparative effectiveness analysis.
- The evidence to support efficacy was an open-label, multicentre, randomised, phase III study to investigate the efficacy and safety of obinutuzumab combined with bendamustine followed by obinutuzumab maintenance compared with bendamustine alone, in patients with iNHL who are refractory to rituximab or a rituximab-containing regimen, had a life expectancy of about 5 years and an ECOG status of 0-2. The primary endpoint was independent review committee (IRC) assessed progression-free survival (PFS). Secondary efficacy endpoints included; investigator assessed PFS, overall survival (OS), best overall response, best response of complete response, and overall response rate. Health related quality of life (HRQoL) assessments were performed using the FACT-Lym instrument and the EQ-5D-3L. The study was reported at the planned interim efficacy analysis because the primary endpoint of statistically significantly improved PFS in the iNHL population was met.
- In the FL sub-group in the GADOLIN study, the median IRC-PFS was not reached in the obinutuzumab plus bendamustine arm, however in the bendamustine monotherapy arm the median IRC-PFS was 13.8 months, HR=0.48 (95% CI 0.34, 0.68). A median time was reached in the later cut-off (01 May 2015) of 29.2 months vs 13.8 months in the bendamustine monotherapy arm at the same data cut-off. The

median investigator assessed PFS was 29.2 months in the obinutuzumab plus bendamustine arm and 13.7 months in the bendamustine monotherapy arm, HR=0.48 (95% CI 0.35, 0.67). In addition, 34.8% of obinutuzumab plus bendamustine patients and 54.2% of bendamustine monotherapy patients had a PFS event including disease progression, relapse or death. The median OS was not estimable in either treatment arm, however at the latest data cut-off (01 May 2015), 18.3% of obinutuzumab plus bendamustine and 28.1% of bendamustine monotherapy patients had died, HR=0.62 (95% CI 0.39, 0.98). The NCPE review team has concerns that the relative immaturity of the PFS and OS data mean that definitive conclusions regarding the effect of treatment with obinutuzumab plus bendamustine on PFS and OS cannot be drawn.

- Comparative clinical data derived from the GADOLIN study were used in the economic model.

2. Safety of obinutuzumab (Gazyvaro®)

- Treatment-related adverse events that occurred more frequently in FL patients in the obinutuzumab plus bendamustine treatment arm included; hypotension, neutropenia, fatigue and infusion related reactions. Cardiac events were also increased in the obinutuzumab plus bendamustine arm (11.3%) compared to the bendamustine monotherapy arm (5.6%) in the entire iNHL population.
- The most common AEs reported during the obinutuzumab maintenance phase were neutropenia and infections.

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

Methods

- A cost-utility analysis comparing obinutuzumab plus bendamustine with bendamustine monotherapy was submitted by the company. The perspective of the HSE (payer) was presented.
- The model was a multi-state cost-utility Markov model, incorporating three health states: progression-free, progressed-disease and death.
- The time horizon was 25-years (reflecting a life-time horizon), with cycle lengths of 1

month.

- Health benefit was measured in quality adjusted life years (QALYs). Utility values for the progression-free and progressed-disease health states were identified from a systematic review of the literature and used in preference to the utility values obtained from the GADOLIN study. The NCPE review team has some concerns regarding the choice of this approach. Utility decrements for adverse events, including infusion related reactions, febrile neutropenia and hypoxia were not included in the model base case but were included in a sensitivity analysis.
- Costs in the model included; drug acquisition, administration and monitoring, health-state costs, costs of pre-medications for obinutuzumab and costs of AEs.

Results

- The base case incremental cost-effectiveness results indicate that obinutuzumab plus bendamustine results in an additional 1.38 life-years, equating to 1.15 additional QALYs compared with bendamustine monotherapy, at an additional cost of €60,142. This results in an **ICER per QALY of €52,248.**

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 a decreasing time horizon and the parametric distributions used to estimate PFS and post-progression survival. The model was also fairly sensitive to variations in discount rate.
- Several scenario analyses were performed. Use of alternative utility data both from the GADOLIN study and alternative data from the literature resulted in marginally increased ICERs.
- Scenario analyses which decreased the final ICER included, use of the actual treatment duration observed in the GADOLIN study and using a separate PPS curve for each treatment arm.
- The probability of the ICER being below a willingness-to-pay threshold of €45,000 per QALY is approximately 24%.

4. Budget impact of obinutuzumab (Gazyvaro®)

- The list price of obinutuzumab is €3,580.69 per 40ml (1,000mg) vial. The total cost per patient for 6-months induction treatment with obinutuzumab plus bendamustine is €33,635. The cost per patient of obinutuzumab maintenance therapy for 2 years is €42,968. Both costs exclude VAT and rebate and assume a body surface area of 1.82m^2.
- The projected gross budget impact (including VAT and rebates), based on company estimates of market share is €724,056 (year 1), €1,174,918 (year 2), €1,399,667 (year 3), €1,424,639 (year 4) and €1,424,639 (year 5). This results in a cumulative gross budget impact of €6.15m over 5-years.
- The company also presented a net budget impact of the incremental impact of including obinutuzumab plus bendamustine as induction and obinutuzumab maintenance therapy in preference to bendamustine monotherapy as induction with no maintenance therapy. The cumulative 5 year net budget impact is estimated at €5.6m.

5. Patient submissions

- No patient submissions were received in support of the application

6. Conclusion

Following NCPE assessment of the company submission, obinutuzumab (Gazyvaro®) in combination with bendamustine followed by obinutuzumab maintenance is not considered to be cost-effective at the submitted price for the treatment of adult patients with follicular lymphoma who did not respond or who progressed during or up to 6 months after treatment with rituximab or a rituximab-containing regimen, at a threshold of €45,000 per QALY.