Cost effectiveness of obinutuzumab (Gazyvaro®) (in combination with chlorambucil) for the treatment of adult patients with previously untreated chronic lymphoytic leukaemia and with comorbidities making them unsuitable for full-dose fludarabine based therapy

The NCPE has issued a recommendation regarding the use of obinutuzumab (in combination with chlorambucil) for this indication. The NCPE does not recommend reimbursement of this drug.

The HSE has asked the National Centre for Pharmacoeconomics (NCPE) to evaluate the manufacturer's (Roche Products (Ireland) Ltd) economic dossier on the cost effectiveness of obinutuzumab (in combination with chlorambucil). 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 that the new treatment may provide and whether the cost requested by the pharmaceutical company is justified.

Following the recommendation from the NCPE, the HSE examine all the evidence that 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 **02 April 2015**

Background

Obinutuzumab (Gazyvaro®) is a recombinant monoclonal antibody targeting the CD20 transmembrane antigen on the surface of non-malignant and malignant pre-B and mature B-lymphocytes.

Roche Products (Ireland) Ltd submitted a dossier to examine the cost effectiveness of obinutuzumab (in combination with chlorambucil) for the treatment of adult patients with previously untreated chronic lymphoytic leukaemia (CLL) and with comorbidities making them unsuitable for full-dose fludarabine based therapy.

The recommended dose of obinutuzumab is 1,000 mg administered on Day 1-2 (100 mg on day 1, 900 mg on day 2) and 1000mg on Day 8 and Day 15 of the first 28 day treatment cycle followed by 1,000 mg administered on Day 1 only for each subsequent treatment cycle (Cycles 2-6). If the 100mg dose on Day 1 (Cycle 1) is given without the need for infusion rate modifications/interruptions, the 900mg dose can be administered on the same day [1].

The comparative regimens used in Ireland for this indication are rituximab + bendamustine, rituximab + chlorambucil and chlorambucil monotherapy.

1. Comparative Effectiveness

CLL11 was an international, multicentre, open label, randomised Phase III trial [2]. Here 781 patients with previously untreated CLL and a Cumulative Illness Rating Scale score > 6 or an estimated creatinine clearance of 30 - 69 ml/min were randomly (2:2:1) assigned to obinutuzumab (+ chlorambucil), rituximab (+ chlorambucil) or chlorambucil monotherapy.

Median progression free survival (investigator assessed) was 26.7 months with obinutuzumab (+ chlorambucil) versus 11.1 months with chlorambucil; stratified hazard ratio 0.18; 95% CI, 0.13-0.24; and 16.3 months with rituximab (+ chlorambucil) vs. 11.1 months with chlorambucil; stratified hazard ratio 0.44; 95% CI, 0.34-0.57. This benefit was seen in all analysed subgroups, except in del(17p). Obinutuzumab (+ chlorambucil) prolonged progression free survival (investigator assessed) compared to rituximab (+ chlorambucil); stratified hazard ratio 0.39; 95% CI, 0.31-0.49.

Treatment with obinutuzumab (+ chlorambucil) prolonged overall survival compared to chlorambucil; stratified hazard ratio for death 0.41; 95% CI, 0.23-0.74. No significant benefit in overall survival was seen with obinutuzumab (+ chlorambucil) compared to rituximab (+ chlorambucil); stratified hazard ratio 0.66; 95% CI, 0.41-1.06.

This was an open label trial where the primary outcome was investigator assessed progression free survival; there may be a risk of bias. However, the Independent Review Committee assessment of progression free survival was reflective of that assessed by investigator.

Safety analysis was performed on data from all patients who had at least one dose of study medication. The obinutuzumab (+ chlorambucil) arm has an inferior safety profile relative to the comparators. The most common treatment-related Grade 3 to 5 adverse events were infusion-related reaction, neutropenia, and thrombocytopenia.

Patients from the chlorambucil arm were allowed to cross over to obinutuzumab (+ chlorambucil) after progression. This was not adjusted for in the economic model. However, this approach is expected to be conservative when determining the cost effectiveness of obinutuzumab (+ chlorambucil).

The dose of chlorambucil used in the trial is lower than that used in routine clinical practice in Ireland.

The Applicant estimated a hazard ratio (progression free survival) for obinutuzumab (+ chlorambucil) versus rituximab + bendamustine of 0.41 from a Bayesian network meta-analysis. This network included trials that enrolled patients eligible for fludarabine and also several trials were needed to link rituximab + bendamustine to obinutuzumab (+ chlorambucil). These limitations make this comparison less stable. For the submission made to NICE [3], a hazard ratio of 0.76 was estimated using the interim results from the MaBLe study (a randomised study comparing rituximab + bendamustine to rituximab (+ chlorambucil) in patients with CLL who are ineligible for fludarabine) [4]. The MaBLe study has now been completed[4], when it is published it will be possible to compare obinutuzumab (+ chlorambucil) to rituximab + bendamustine (in patients ineligible for fludarabine) using the rituximab (+ chlorambucil) arms of MaBLe and CLL11 as the common comparator. In the

interim, the Review Groups considers it pragmatic to use the most conservative hazard ratio (0.76) in basecase analyses.

Other hazard ratios (progression free survival) estimated from this network and used in the economic model are: obinutuzumab (+ chlorambucil) versus chlorambucil; HR 0.19, 95% CI: 0.15, 0.25, adjusted for age) and obinutuzumab (+ chlorambucil) versus rituximab (+ chlorambucil); HR 0.45, 95% CI: 0.36, 0.57, adjusted for age).

The overall survival data from CLL11 is immature; the indirect treatment comparisons were only performed for progression free survival. Instead the economic model estimated overall survival by applying post-progression survival data from the CLL5 study (a randomised controlled trial that compared fludarabine to chlorambucil in untreated CLL) [5]. The CLL5 trial recruited patients from 1999 to 2004. It may therefore not reflect current clinical practice. The model assumes that treatments do not affect survival beyond progression.

2. Comparative Safety

An analysis of comparative safety was not provided. For the economic model, frequencies of adverse events were taken directly from the CLL11[2] trial (for obinutuzumab (+ chlorambucil), rituximab (+ chlorambucil) or chlorambucil monotherapy) and from CLL10 [6] (for the rituximab + bendamustine arm) and therefore randomisation will be lost.

3. Cost-Effectiveness analysis

A Markov model (lifetime horizon) analysed the cost effectiveness of obinutuzumab (+ chlorambucil) for this indication. The analysis was conducted from the perspective of the Health Service Executive (hospital-only product). The model consists of three health states: 'Progression Free Survival ('with' or 'without therapy')', 'Progression' and 'Death'.

The treatment duration in CLL11 is limited to a maximum of six treatment cycles; no parametric function is fitted for treatment duration. A parametric function was fitted to the network progression free survival data. Transition from 'Progression Free Survival' was modelled using data from CLL11 and background mortality. The proportion of people in 'Progression' in each cycle was the difference between the proportion alive and the proportion in 'Progression Free Survival'. Overall survival was estimated by applying post-progression survival data from CLL5.

The model structure does not account for additional lines of treatment post-progression. This does not reflect standard practice in Ireland where it is expected that a patient with CLL will receive three to four lines of treatment for their disease.

The model only considered Grade 3-5 adverse events that occurred at an incidence of more than 2% in any treatment arm.

Instead of using the health related quality of life data that was collected in the CLL11 study, the Applicant undertook a utility elicitation study with a representative sample of the UK general public (n=100), using the time trade-off method. The resultant utility values will be uncertain as they were not elicited from patients and health state vignettes (rather than a generic questionnaire) were used. Utility values are applied to health states; disutilities are not explicitly applied to adverse events. The model will underestimate the impact of adverse events on health related quality of life.

Under the model assumptions, the ICER for obinutuzumab (+chlorambucil) vs. rituximab + bendamustine is €50,942/QALY (incremental cost = €11,728; incremental QALY = 0.23), vs. rituximab (+ chlorambucil) is €29,676/QALY (cost = €36,328; QALY = 0.995) and vs. chlorambucil is €36,521/QALY (cost = €17,355; QALY = 0.585).

The Applicant's basecase assumed there would be vial sharing when the first dose of obinutuzumab is given as a split dose. Whilst this appears to be a reasonable assumption, it cannot be assumed that it will occur in all cases. The ICERs increase to €67,409/QALY (vs. rituximab + bendamustine), €36,159/QALY (vs. rituximab + chlorambucil) and €38,722/QALY (vs. chlorambucil) when two vials are used for a split first dose.

The ICER versus the most commonly used comparator (rituximab + bendamustine) is sensitive to a number of model input changes including: the model time horizon, the parametric model used to extrapolate progression free survival data and the utility values. All these inputs are uncertain. This ICER is also sensitive to the estimated hazard ratio for progression free survival (obinutuzumab (+ chlorambucil) vs. rituximab + bendamustine). If the Applicant's original hazard ratio (0.41) is used, the ICER falls to €19,405/QALY. This analysis assumes vial sharing for a split first dose.

At a payer threshold of €45,000/QALY, the probabilities that obinutuzumab (+ chlorambucil) and rituximab + bendamustine are the most cost-effective regimens are about 39% and 61% respectively. The probabilities that either rituximab (+ chlorambucil) or chlorambucil are the most cost-effective regimens are negligible. Not all parameters were varied in this analysis. This analysis assumes vial sharing for a split first dose.

4. Budget Impact Analysis

The Applicant expects that 80 patients annually will be eligible for obinutuzumab and predicts uptake rates of 35% in year, rising to 50% in year 2 and 55% in subsequent years. The annual Gross Budget Impact is expected to be about €1.05 million in year 1, €1.51 million in year 2, increasing to about €1.7 million in year 5. The 5 year cumulative Gross Budget Impact is estimated to be about €7.6 million. The Net Budget Impact assumes displacement of the weighted cost (drug acquisition) of the comparator regimens according to market research. The annual Net Budget Impact is expected to be about €642,400 in year 1, €923,800 in year 2, increasing to about €1.04 million in year 5. The 5 year cumulative Gross Budget Impact is estimated to be about €4.66 million.

5. Conclusion

Following NCPE assessment, obinutuzumab (+ chlorambucil) is not considered cost effective compared to rituximab (+ bendamustine) for the treatment of adult patients with previously untreated CLL and with comorbidities making them unsuitable for full-dose fludarabine based therapy.

The model indicates that obinutuzumab (+ chlorambucil) might be considered cost effective compared to either rituximab (+ chlorambucil) or chlorambucil monotherapy. However, no survival benefit compared to rituximab (+ chlorambucil) has been demonstrated to date. The obinutuzumab arm of CLL11 had an inferior safety profile compared to the rituximab (+ chlorambucil) or chlorambucil arms and this model will underestimate the costs and outcomes associated with adverse events. The dose of chlorambucil used in the analysis is lower than that used in routine clinical practice in Ireland. The model structure does not account for additional lines of treatment post-progression and thus does not reflect the expected pathways of treatment for this disease in Ireland.

References

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