Cost effectiveness of ibrutinib (Imbruvica®) in the treatment of patients with chronic lymphocytic leukaemia who have received ≥1 prior therapy, or as a first-line treatment in the presence of del(17p) or TP53 mutation in patients not suitable for chemo-immunotherapy.

The NCPE has issued a recommendation regarding the cost-effectiveness of ibrutinib (Imbruvica®). Following NCPE assessment of the applicant's submission, ibrutinib is not considered cost effective for this indication and therefore is not recommended for reimbursement.

The HSE asked the National Centre for Pharmacoeconomics (NCPE) to carry out an assessment of the applicant's (Janssen) economic dossier. 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 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   **October 2015**

Background

In April 2015, Janssen submitted a dossier examining the cost effectiveness of ibrutinib for the treatment of patients with chronic lymphocytic leukaemia who have received ≥1 prior therapy, or as a first-line treatment in the presence of del(17p)/TP53 mutation in patients not suitable for chemo-immunotherapy. Final data submitted by the Applicant was received on 17th September 2015.

The recommended dose is 420 mg once daily. Treatment should continue until disease progression or no longer tolerated. The dose should be lowered to 140 mg once daily when used concomitantly with moderate CYP3A4 inhibitors. The dose should be reduced to 140 mg once daily or withheld for up to 7 days when used concomitantly with strong CYP3A4 inhibitors.

In the original submission, comparators investigated were bendamustine + rituximab (R-Benda) and ofatumumab. R-Benda is likely to be the main comparator in Ireland and alemtuzumab is likely to be used first line in those with del(17p)/TP53 mutation. On request from the NCPE, cost effectiveness versus alemtuzumab was also investigated.

1. **Comparative effectiveness of ibrutinib**

Efficacy outcomes for the comparison with ofatumumab were derived from RESONATE. RESONATE was a multicentre, open-label, phase III study in which 391 patients (with relapsed/refractory chronic lymphocytic leukaemia or small lymphocytic lymphoma) were randomly assigned to ibrutinib (n=195) 420mg once daily until disease progression or unacceptable toxic effects or to intravenous ofatumumab (n=196) (for up to 24 weeks at an initial dose of 300 mg at week 1, followed by 2,000 mg weekly for 7 weeks and then every 4 weeks for 16 weeks). All efficacy analyses were performed in the intent-to-treat population.

In January 2014, the study was stopped early due to progression free survival improvement with ibrutinib. At a median follow-up of 9.4 months, the median progression free survival duration was not reached with ibrutinib and was 8.1 months with ofatumumab; (HR for progression or death, 0.22; 95% CI: 0.15, 0.32; p<0.001). Ibrutinib prolonged overall survival (HR for death in the ibrutinib group, 0.43; 95% CI: 0.24, 0.79; p = 0.005). At 12 months, the overall survival rate was 90% and 81% in the ibrutinib and ofatumumab groups respectively.

At this time, 57 patients in the ofatumumab group had crossed over to ibrutinib after progression. This survival effect was based on data being censored at crossover. The survival effect was also observed in the uncensored sensitivity analysis (HR for death, 0.39; p = 0.001), overall survival rates were 90% and 79% respectively.

Overall response rate was 43% (ibrutinib) vs. 4% (ofatumumab); odds ratio 17.4; 95% CI: 8.1, 37.3; p<0.001. Median treatment duration was 8.6 months (ibrutinib) vs. 5.3 months (ofatumumab). Similar effects were observed regardless of del(17p) or resistance to purine analogues.

An updated efficacy and safety analysis of RESONATE describes 18-month overall survival rates of 85% and 78% for ibrutinib and ofatumumab respectively, despite 120 patients (61%) randomised to ofatumumab who crossed over to ibrutinib and were censored at that time.

For the cost-effectiveness analysis, the key effectiveness inputs in the model were progression free survival and overall survival. In addition, response rates were considered. Inputs for the model for the ibrutinib vs. obinutuzumab comparison were derived from RESONATE. Parametric survival extrapolations projected overall survival and progression free survival data for ibrutinib and ofatumumab from the RESONATE 16-month data cut. The 16-month data cut full trial overall survival data are not published and were not made available to the NCPE Review Group, despite this request being made.

Due to a lack of data, it was not possible to conduct a network meta-analysis for the other comparators. For the comparison with R-Benda, a Matching-Adjusted Indirect Comparison (MAIC) analysis adjusted for population differences between the trial published by Fischer *et al* (R-Benda in relapsed/refractory CLL) and RESONATE. Likewise, a MAIC analysis adjusted for population differences between RESONATE and the trial published by Stilgenbauer *et al* (alemtuzumab in fludarabine-refractory CLL). The derived efficacy outputs (ibrutinib vs. R-Benda and ibrutinib vs. alemtuzumab) will be uncertain. Further, the comparison with alemtuzumab is evaluated in the entire target population, not solely in the subgroup with del(17p)/TP53 mutation. To estimate efficacy inputs for R-Benda and alemtuzumab, the projected ibrutinib curves were adjusted using hazard ratios derived from the respective MAIC analyses.

2. Safety of ibrutinib

In RESONATE the most frequent non-haematologic adverse events that occurred in at least 20% of patients were diarrhoea, fatigue, pyrexia, and nausea in the ibrutinib group and fatigue, infusion-related reactions, and cough in the ofatumumab group. Grade ≥ 3 adverse events that occurred more frequently in the ibrutinib group included diarrhoea (4% vs. 2%) and atrial fibrillation (3% vs. 0%). Infections of any grade were more common in the ibrutinib group (70% vs. 54%); the frequency of Grade ≥ 3 infections was similar in both groups (24% vs. 22%). Fatal events occurred in 4% and 5% of the ibrutinib and ofatumumab groups respectively; these were most commonly due to infections. Adverse events resulting in dose reductions occurred in 4% of the ibrutinib group; only diarrhoea (which occurred in three patients) led to a dose reduction in more than one patient.

3. Cost effectiveness of ibrutinib

Cost effectiveness was investigated using a health state model with a 15 year time horizon. The perspective is that of the HSE under the High Tech Drug Scheme.

The model simulates patients through three main health states: 'progression free survival (PFS)', 'post-progression survival (PPS)', and 'death'. Within 'PFS' all patients begin in the 'stable disease/non-response' category. A proportion of patients will respond to treatment and move to the 'response' category. From 'PFS', patients move into 'PPS', where a proportion will enter the 'Subsequent Treatment' category and others enter the 'best supportive care (BSC)' category. Once patients on subsequent line of therapy progress, they will receive BSC. Patients in 'PFS' and 'PPS' can move directly into the 'death' state.

In the original cost-effectiveness model, the cost of ibrutinib is based on a dose intensity of 94.85% (from RESONATE). The dose intensity of the comparators was assumed to be 100%. The NCPE requested that all dose intensities be changed to 100%. The Applicant did not make this change. The Review Group undertook this analysis; we increased the dose intensity of ibrutinib to 100% and we present this as the basecase.

Due to concerns raised by the Review Group a number of other changes were made to the original basecase. In the revised basecase, the cost of R-Benda was reduced to reflect the dose given in Fischer *et al*. All concurrent medications were set at zero. The cost of G-CSF

was reduced to reflect market share of product. A new functionality was added to the model to allow different administration costs to be applied to different intravenous therapies.

The model only considered Grade ≥ 3 AEs that occurred in ≥5% of patients in at least one of the comparator treatments. The Review Group believe that the model may underestimate the true impact of adverse events on costs and outcomes. Information to characterise resource use and frequency associated with treatment of adverse events and terminal care was elicited from an Advisory Board. The methodologies and disaggregated results of this elicitation process were not provided.

The utility value for the 'PFS' health state was derived from EQ-5D data which was collected in the intent-to-treat population in RESONATE. Published studies were accessed for post-progression utility and adverse event related disutility values. It is assumed that the relative utility changes from baseline derived from these sources will apply to the RESONATE population. Further, the post-progression utility and AE related disutility values were not elicited from patients, and vignettes (rather than a generic questionnaire) were used. The different studies and methods used to determine baseline utility, post-progression utility and AE related disutility values will introduce uncertainty into the cost-effectiveness analysis.

At a 100% dose intensity, the ICER (ibrutinib vs. R-Benda) is €82,786/QALY (incremental cost €243,725; incremental QALY 2.94). The ICER (ibrutinib vs. ofatumumab) is €91,284/QALY (incremental cost €148,212; incremental QALY 1.62). There is a zero probability of cost effectiveness compared to R-Benda or ofatumumab at €45,000/QALY.

The primary comparator for the subgroup with del(17p)/TP53 mutation, in Ireland, is likely to be alemtuzumab, the NCPE requested that cost effectiveness vs. alemtuzumab be evaluated. However, this analysis was performed in the entire target population and not in the subgroup of interest. At 100% does intensity, ibrutinib dominates if the list price for Lemtrada® is assumed. The ICER is about €82,491/QALY when a zero cost is applied to alemtuzumab (although administration costs are included). The model for this analysis was not provided to the NCPE. Therefore it is difficult to access the robustness of this estimate.

The cost-effectiveness results are sensitive to approach taken to extrapolate efficacy data, comparator drug acquisition costs, utility values inputs, the model time horizon and the discount rate.

4. Budget impact of ibrutinib

The Budget Impact (BI) model estimates the impact of ibrutinib treatment for frontline CLL with del(17p)/ TP53 mutation and relapsed/refractory CLL. The original analysis included drug administration costs and concurrent medication. Similar to the cost-effectiveness analysis, the Review Group have set the concurrent medications to zero (as this adjustment was not made by the Applicant). The original Budget Impact assumes a dose intensity of 94.8% for ibrutinib and 100% for the comparators. Similar to the cost-effectiveness analysis, the Review Group have changed this to 100%.

The Budget Impact model estimates that the per-patient cost of treatment with ibrutinib is about €72,914. It is estimated that the Gross cumulative 5 year impact will be about €32 million.

The original Net BI included a range of comparators based on Advisory Board elicitation. It is estimated that cumulative 5 year Net impact will be ~ €22.69 million when administration costs are included and ~ €25.26 million when excluded. The Review Group have re-run the Net BI analysis with comparator data informed by Local Expert Opinion. We have assumed that R-Benda is the only comparator in the relapsed/refractory setting and alemtuzamab is used for those with del(17p)/ TP53 mutation. No cost is assigned to alemtuzumab, as is the current situation in Ireland. Under these assumptions, the cumulative 5 year Net impact is ~ €23.96 million when administration costs are included and ~ €26.44 million when excluded.

5. Conclusion

Following NCPE assessment of the applicant's submission, the cost effectiveness of ibrutinib (Imbruvica®) in the treatment of patients with CLL who have received ≥1 prior therapy, or as a first-line treatment in the presence of del(17p)/TP53 mutation in patients not suitable for chemo-immunotherapy has not been demonstrated, and therefore is not recommended for reimbursement at the submitted price.