Cost effectiveness of ibrutinib (Imbruvica®) in the treatment of patients with relapsed or refractory mantle cell lymphoma

The NCPE has issued a recommendation regarding the cost effectiveness of ibrutinib (Imbruvica®). Following NCPE assessment of the applicant's submission, ibrutinib (Imbruvica®) is not considered cost effective for the treatment of relapsed or refractory mantle cell lymphoma 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 on the cost effectiveness of ibrutinib (Imbruvica®). 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 **October 2015**

Summary

In April 2015, Janssen submitted a dossier examining the cost effectiveness of ibrutinib for the treatment of patients with relapsed or refractory mantle cell lymphoma (MCL). Final data, submitted by the Applicant, was received on the 28th September 2015.

The recommended dose is 560 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 140mg once daily or withheld for up to 7 days when used concomitantly with strong CYP3A4 inhibitors.

Due to a lack of available clinical data in the population of interest, the comparators considered, in the cost-effectiveness analysis, are bortezomib and temsirolimus only. The Review Group note that relevant comparators, particularly bendamustine + rituximab (R-Benda), are not considered. We also note that temsirolimus is rarely used in Ireland and although bortezomib is used, it is usually given as part of a regimen with other agents.

1. Comparative effectiveness of ibrutinib

PCYC-1104-CA was a phase II, single arm, multicentre, open-label trial that enrolled 115 patients without randomisation (65 bortezomib-naïve; 50 bortezomib-exposed) with relapsed/refractory MCL. The median time since diagnosis of MCL to study entry was 42.4 months. The median age of the population was 68 years. The median number of prior therapies was three with more than 55% receiving ≥3 prior regimens. Baseline ECOG performance status grade was 0 to 1 in 89.1% of the population.

Patients were treated with ibrutinib 560 mg daily for continuous 28-day cycles until disease progression. The primary endpoint was investigator-assessed objective response rate; secondary endpoints included duration of response, progression free survival, overall survival and safety/tolerability. Efficacy analyses were performed in the all-treated population (received ≥1 dose) (n=111). The median number of cycles administered was 9 (range, 1 to 24).

The estimated median follow-up was 15.3 months (range, 1.9 to 22.3). Investigator-assessed objective response rate was observed in 68% of patients; 21% and 47% had a complete response and partial response respectively. Response rates for patients in the bortezomib-exposed and bortezomib-naïve groups were consistent with those for all-treated patients. The estimated median duration of response in patients who had a response was 17.5 months (95% CI, 15.8 - not reached). The estimated median progression free survival was 13.9 months (95% CI: 7.0 - not reached). The median overall survival was not reached; the estimated overall survival rate was 58% at 18 months.

For the cost-effectiveness analysis, efficacy outcomes for ibrutinib were derived from an undated analysis of PCYC-1104-CA. Parametric survival extrapolations projected patient level data.

Due to a lack of data, it was not possible to conduct a network meta-analysis for the other comparators. For the comparison with temsirolimus, a Matching-Adjusted Indirect Comparison (MAIC) analysis adjusted for population differences between Hess *et al* (temsirolimus vs. investigator's choice in relapsed/refractory MCL) and PCYC-1104-CA. Also a MAIC analysis adjusted for population differences between the PINNACLE trial (bortezomib in relapsed/refractory MCL) and PCYC-1104-CA.

To estimate efficacy inputs for the comparators, the projected ibrutinib curves were adjusted using hazard ratios derived from the respective MAIC analyses. The Applicant used the MAIC progression free survival and response outputs for the bortezomib evaluation but not overall survival outcomes. The Applicant deemed the MAIC overall survival outputs to be clinically implausible; however it is unclear, to the Review Group, why this is the case. Instead, overall survival data was estimated by summing progression free survival (from PINNACLE) and post-progression survival data (post-progression survival data for all treatments was derived from the investigator choice arm of Hess *et al*). The Review Group note the uncertainties associated with this approach. Amongst these, numerous assumptions are made regarding transferability of data from one population to another and there is a lack of validation of the estimated outputs. On request from the Review Group, the Applicant performed a scenario analysis based on the MAIC analysis overall survival outputs.

2. Safety of ibrutinib

For the cost-effectiveness analysis the safety data for ibrutinib is derived from updated analysis from PCYC-1104-CA. The most common adverse events in >30% of patients included diarrhoea (54%), fatigue (50%), nausea (33%), and dyspnoea (32%). The most frequent Grade ≥3 infections included pneumonia (8%), urinary tract infection (4%), and cellulitis (3%). Grade ≥3 bleeding events in ≥2% of patients were haematuria (2%) and subdural haematoma (2%). The most common Grade ≥3 hematologic adverse events were neutropenia (17%), thrombocytopenia (13%), and anaemia (11%). Eighteen patients (16%) had Grade 5 adverse events (death) within 30 days of the last dose. Eight of these fatal adverse events were reported as MCL by investigators, and six were considered associated with disease progression.

3. Cost effectiveness of ibrutinib

The perspective is that of the HSE under the High Tech Drug Scheme. Cost effectiveness was investigated using a health state model. The original model had a 15 year time horizon; the Applicant used a 10 year horizon for the base case following request by the Review group.

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 model, the cost of ibrutinib was based on a 92.8% dose intensity (consistent with PCYC-1104), however 100% dose intensity for all comparators is assumed. The NCPE requested that all dose intensities be changed to 100%. The Applicant did not make this change. Instead, the Applicant provided us with an updated basecase in which the dose intensity of temsirolimus is reduced to reflect that in Hess *et al*. We note that the dose intensity of bortezomib is still assumed to be 100% (which is not reflective of PINNACLE).

Due to concerns raised by the Review Group a number of other changes were made to the basecase. Bortezomib costs were reduced to match trial treatment duration, the assumed mean Body Surface Area was reduced to 1.88m^2, the frequency of monitoring in the 'BSC' health state was reduced and the duration of utility decrement applied to adverse events was reduced.

The model only considered Grade ≥ 3 adverse events that occurred in ≥5% of patients in at least one of the comparator treatments. The model may underestimate the true impact of adverse events. 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 to the Review Group.

Utility inputs for the 'PFS' health state were collected in PCYC-1104-CA. Published studies were accessed for post-progression utility and AE related disutility values. The different studies and methods used to determine baseline utility, post-progression utility and AE related disutility values will introduce uncertainty.

The NCPE Review Group give preference to the ICERs calculated at 100% dose intensity for ibrutinib and comparators. When 100% dose intensity is assumed for ibrutinib and comparators, the ICER (ibrutinib vs. temsirolimus) is €63,628 /QALY (incremental cost €43,963; incremental QALY 0.69). The ICER (ibrutinib vs. bortezomib) is €89,931/QALY (incremental cost €33,010; incremental 0.37 QALY). There is a 26% probability of cost effectiveness vs. temirolimus. There is a 27% probability of cost effectiveness vs. bortezomib.

The Applicant also presents their analysis where the dose intensity of ibrutinib and temsirolimus are informed from trial data. Here, the ICER (ibrutinib vs. temsirolimus) is €49,464/QALY. The ICER (ibrutinib vs. bortezomib) is €63,269/QALY. There is a 73% probability that ibrutinib is cost effective vs. temsirolimus; the probability of cost effectiveness vs. bortezomib is 41%.

The cost-effectiveness results are most sensitive to the approach taken to extrapolate efficacy data, the assumed duration of ibrutinib, the percentage of patients who receive subsequent

therapy, cost of intravenous administration, vial sharing assumptions, cost of acyclovir given with bortezomib (the model assumes that all patients on bortezomib will receive prophylactic Zovirax® suspension daily until 1 month after therapy), utility values inputs, the model time horizon and the discount rate.

4. Budget impact of ibrutinib

Similar to the cost-effectiveness analysis, the original Budget Impact analysis assumes a 92.8% dose intensity for ibrutinib. The Review Group changed this to 100%. Similar to the cost-effectiveness analysis the Review Group also reduced the mean Body Surface Area, in the analysis, to 1.88m^2.

At 100% dose intensity, the per-patient cost of treatment with ibrutinib is estimated to be about €96,967. It is estimated that the cumulative 5 year gross budget impact will be ~ €7 million. It is estimated that the cumulative 5 year net budget impact will be ~ €3 million. When we remove administration costs and concomitant drug costs, the cumulative 5 year net budget impact is ~ €3.75 million.

5. Conclusion

Following NCPE assessment of the applicant's submission, the cost effectiveness of ibrutinib (Imbruvica®), in the treatment of patients with relapsed or refractory MCL, as compared to relevant comparators, has not been demonstrated. Therefore is not recommended for reimbursement at the submitted price.