Cost effectiveness of idelalisib (Zydelig®) (in combination with rituximab) for the treatment of adult patients with chronic lymphocytic leukaemia: who have received at least one prior therapy, or as first-line treatment in the presence of 17p deletion/TP53 mutation in patients unsuitable for chemo-immunotherapy

The NCPE has issued a recommendation regarding the cost effectiveness of idelalisib (Zydelig®) (in combination with rituximab). Following NCPE assessment of the applicant's submission, idelalisib (Zydelig®) 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 (Gilead Sciences Ltd) economic dossier on the cost effectiveness of idelalisib (Zydelig®) (in combination with rituximab). 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   **February   2016**

Summary

In June 2015, Gilead Sciences Ltd submitted a dossier examining the cost effectiveness of idelalisib (Zydelig®) (in combination with rituximab) for the treatment of adult patients with chronic lymphocytic leukaemia (CLL): who have received at least one prior therapy, or as first-line treatment in the presence of 17p deletion/TP53 mutation in patients unsuitable for chemo-immunotherapy. The clinical data available for idelalisib pertains to patients with high risk CLL (i.e. patients who relapse within 24 months after previous therapy) who are ineligible for chemo-immunotherapy. Also, limited data is available on treatment naïve patients with del(17p)/TP53 mutation. This submission cannot support decision-making for the entire licensed population.

The recommended dose of idelalisib is 150 mg, orally, twice daily. Treatment should be continued until disease progression or unacceptable toxicity. The SmPC does not state a dose for the concomitant rituximab.

For the submission, Expert Opinion indicated that a range of comparators for patients who are eligible for chemo-immunotherapy should be considered. However, the clinical data for idelalisib (+ rituximab) cannot be used to inform decision-making for patients who are eligible for chemo-immunotherapy. For patients ineligible for chemotherapy, rituximab + steroids, alemtuzumab ± steroids and best supportive care were deemed appropriate. For patients with untreated CLL with del(17p)/TP53 mutation, alemtuzumab, best supportive care and rituximab + steroids were considered.

The base case analysis evaluates the cost effectiveness of ibrutinib (+ rituximab) versus rituximab monotherapy (and not rituximab + steroids as recommended by Expert Opinion) and versus best supportive care for patients who are ineligible to chemo-immunotherapy. Further analyses compare ibrutinib (+ rituximab) to rituximab + steroids and to alemtuzumab. Cost effectiveness versus alemtuzumab, best supportive care and rituximab + steroids in untreated CLL with del(17p)/TP53 mutation was also evaluated.

1. **Comparative effectiveness of idelalisib**

Study 116 was a Phase III, multicentre, randomised, double-blind, placebo-controlled trial in which 220 patients were randomly assigned to receive intravenous rituximab and either oral

idelalisib (150 mg twice daily) or placebo (twice daily). Eligible patients had progressed within 24 months after their last treatment for CLL and were not able to receive cytotoxic agents. At 24 weeks, the rates of progression free survival were 93% and 46% in the idelalisib + rituximab and the rituximab + placebo groups respectively (adjusted hazard ratio for progression or death = 0.15; 95% CI, 0.08 to 0.28; unadjusted p<0.001, (crossed the prespecified stopping boundary for efficacy). Treatment effect was consistent regardless of del(17p)/TP53 mutation status. Patients receiving idelalisib + rituximab had improved rates of overall response (81% vs. 13%; odds ratio, 29.92; p<0.001). Idelalisib + rituximab was associated with improved overall survival at 12 months (92% vs. 80%; HR for death, 0.28; p = 0.02).

The trial was stopped early for benefit; this may lead to an overestimation of treatment effect.

A systematic literature review did not identify any evidence directly comparing idelalisib with the other comparators deemed relevant by Expert Opinion. The Applicant's search included evidence for cytotoxic chemotherapy regimens; these are not presented here since the clinical evidence available for idelalisib (+rituximab) pertains only to patients who are ineligible for chemo-immunotherapy.

For the cost-effectiveness model, key effectiveness data are derived from the intent to treat population in Study 116. For the submission, efficacy data was derived from the most recent data cut (median follow-up of 13 months; conference poster) and not from the published pivotal trial.

The Applicant used the Rank-Preserving Structural Failure Time methodology to adjust for patients in Study 116 who progressed on rituximab and crossed over to idelalisib (+ rituximab); the resultant HR was 0.20, 95%CI 0.10, 0.35. This Kaplan Meier data was extrapolated; best fit was investigated using AIC/BIC statistics. Mean overall survival estimates for idelalisib (+ rituximab) are 6.53 years (Exponential; best fit) and 4.59 years (Weibull; chosen as the base case as considered most clinically plausible). The mean estimates for rituximab are 2.11 years (log-normal; best fit) and 1.39 years (Weibull; chosen for the base case). The choice of Weibull for rituximab will be favourable for the cost effectiveness of idelalisib (+ rituximab).

Parametric curves were fitted to unadjusted progression free survival Kaplan Meier data. The Weibull extrapolation was the best fit (AIC/BIC) for both trial arms and was deemed clinically plausible. Mean progression free survival estimates were 1.71 years and 0.56 years for idelalisib (+ rituximab) and rituximab respectively.

For the other comparators, estimated Kaplan Meier curves from published studies were compared to parametric survival curves from Study 116 data; the evidence synthesis methodologies used will result in uncertain model input parameters.

Results from Study 116 showed an overall response rate of 84% with idelalisib (+ rituximab) and of 15% with rituximab. The cost-effectiveness model does not disaggregate overall response rate as complete response and partial response. In reality, costs and health related quality of life (HRQoL) associated with both are likely to be different. The model does not account for this. For the other comparators, overall response rate data were sourced from the literature.

Time on treatment data was not available from Study 116. A Cox proportional hazards model was used to calculate a hazard ratio for time on treatment compared with progression free survival. The resultant hazard ratio was applied to the progression free survival curve for idelalisib (+ rituximab) to derive a time on treatment curve. The same hazard ratio was used for the rituximab arm. This approach may underestimate true cost of treatment. For the other comparators, treatment costs were applied to the proportion of patients remaining in the progression-free health states in the model, up to maximum treatment durations.

For the comparison with best supportive care, it was assumed that the survival outcomes with best supportive care would be the same as those of rituximab. Best supportive care was assumed to have an overall response rate of zero.

The evidence for the treatment naïve del(17p)/TP53 mutation population is limited. **Study 101-08** was a Phase II, single-arm study of 64 previously untreated patients (≥ 65 years) with CLL or SLL enrolled to have idelalisib (150 mg twice daily) + rituximab. Older patients were targeted due to lack of tolerability of chemo-immunotherapy. In total, 9 patients had del(17p)/TP53 mutation. Patients were treated for 48 weeks, and those who completed 48 weeks without progression (n=43) could continue to receive idelalisib in an extension study.

Progression free survival for the overall population and for del(17p)/TP53 mutation group at 36 months were 83% and 100% respectively. The respective overall response rates were 96.9% and 100%.

Two further trials for this population were identified. One randomised controlled trial of alemtuzumab versus chlorambucil in untreated patients containing a small subgroup (n=11 vs. n=10) of patients with del (17p)/TP53 mutation and one single-arm study of alemtuzumab (with high-dose methylprednisolone) in patients with del (17p)/TP53 mutation; a subgroup of which 17 patients had not received any previous treatment. It was not possible to construct a network or to perform an indirect/mixed treatment comparison. Instead, the trial results (progression free survival and overall survival) are reported qualitatively in the submission without any attempt to adjust for population differences.

2. Safety of idelalisib

In the Study 116 safety set analysis, 98.2% and 98.1% of the idelalisib + rituximab and rituximab + placebo groups respectively had at least one adverse event. Grade $\geq$ 3 adverse events occurred in 73.6% (idelalisib + rituximab) and 53.7% (rituximab + placebo) of patients. The most commonly reported $\geq$ Grade 3 adverse events with idelalisib + rituximab were neutropenia (22.7%), pneumonia (10.0%) and diarrhoea (9.1%). In total, 17.3% and 12% of the idelalisib + rituximab and rituximab + placebo arms respectively discontinued the study drug due to an adverse event.

3. Cost effectiveness of idelalisib

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

The model has five health states. The 'pre-progression on treatment' state is determined by the area under parametric time-on-treatment curves. The 'pre-progression off treatment' and 'post-progression' states are informed by the parametric survival curve analysis of progression free survival and overall survival data. It is possible to transition to 'death' from any health state via the transitory 'terminal care' state.

HRQoL data was collected in Study 116 using the EQ-5D instrument. A treatment effect was found with patients receiving idelalisib (+ rituximab) having a better HRQoL than those on rituximab (absolute difference = 0.0652). The model was only marginally sensitive to this treatment effect. Utility estimates for post treatment discontinuation were derived from the literature.

Only Grade ≥ 3 adverse events that occurred in ≥3% of patients in either treatment arm of Study 116 were considered. In total, seven adverse events were incorporated. Disutility estimates for three adverse events were derived from the literature; assumptions were made for the remaining. For all other comparators, it is assumed that adverse events do not impact on costs or on HRQoL.

The cost of active treatment includes drug acquisition costs and administration. Health state monitoring costs are included; the model does not include monitoring costs specifically associated with active treatments.

Due to concerns raised by the Review Group a number of changes were made to the original base case. In the original submission, the cost of idelalisib was based on a dose intensity of 93.25% (from STUDY 116); on request, this was increased to 100%. The assumed mean body mass index was reduced from $1.92m^2$ to $1.82m^2$. The proportion of patients assumed to receive intravenous immunoglobulin was decreased. The hospitalisation rate for all adverse events was increased to 100%.

Results

For adult patients with chronic lymphocytic leukaemia who have received at least one prior therapy and who are ineligible for chemo-immunotherapy, the ICER for idelalisib (+ rituximab) versus rituximab is estimated to be €46,961/QALY (incremental cost = €83,900; incremental QALYs = 1.79). The dose (cost) of rituximab for this analysis was informed by study 116. In reality, the ICER of idelalisib (+ rituximab) vs. rituximab will be reliant on the dose of rituximab used.

The ICER versus best supportive care is estimated to be €57,440/QALY (incremental cost = €102,325; incremental QALY = 1.78). Probabilistic ICERS are comparable.

Cost effectiveness estimations versus the other comparators will be uncertain. The ICER versus rituximab (+ steroids) is about €45,772/QALY. The ICERs versus alemtuzumab are €8,218/QALY when the list price for alemtuzumab is assumed; this rises to €46,010/QALY when a zero cost (compassionate use) is assumed.

The ICERs for the treatment naïve del(17p)/TP53 mutation population will be uncertain due to the limited clinical data available. ICERs are €71,388/QALY versus rituximab (+ steroids) and €66,644/QALY versus best supportive care. The ICERs versus alemtuzumab are €10,358/QALY (at list price) and €57,002/QALY (at zero cost).

Sensitivity analysis

Sensitivity analyses have been explored only on the comparisons with rituximab and with best supportive care.

Deterministic analyses reveal that the cost-effectiveness results are most sensitive to approach taken to extrapolate efficacy data, the model time horizon and the discount rate.

Probabilistic analysis indicates that, at €45,000/QALY, there is a 43% probability that idelalisib (+ rituximab) is cost effective versus rituximab. There is a 22% probability that idelalisib (+ rituximab) is cost effective versus best supportive care.

4. Budget impact of idelalisib

The model estimates that the per-patient treatment course cost (acquisition) for idelalisib (+ rituximab) will be about €117,600.

According to the Applicants assumptions, the gross budget impact (across the treatment-naïve and previously treated CLL populations), is estimated to be €4.02 million (Year 1), €4.72 million (Year 2), €4.98 million (Year 3), €5.04 million (Year 4) and €5.06 million (Year 5). The 5 year cumulative impact is about €23.82 million.

The NCPE estimate that this may be higher, with a 5 year cumulative impact of about €27.51 million.

5. Conclusion

Following NCPE assessment of the Applicant's submission, cost effectiveness of idelalisib (Zydelig®) (in combination with rituximab) for the treatment of adult patients with chronic lymphocytic leukaemia: who have received at least one prior therapy, or as first-line treatment in the presence of 17p deletion/TP53 mutation in patients unsuitable for chemo-immunotherapy, has not been demonstrated. Therefore it is not recommended for reimbursement.