Cost-effectiveness of Venetoclax (Venclyxto®) in Combination with Rituximab for the Treatment of Adult Patients with Chronic Lymphocytic Leukaemia (CLL) who have Received at Least One Prior Therapy

The NCPE has issued a recommendation regarding the cost effectiveness of venetoclax (Venclyxto®). Following assessment of the Applicant's submission, the NCPE recommends that venetoclax (Venclyxto®) be considered for reimbursement if cost effectiveness can be improved relative to existing treatments*.

The HSE asked the National Centre for Pharmacoeconomics (NCPE) to carry out an assessment of the Applicant's (AbbVie Ltd) economic dossier on the cost effectiveness of venetoclax (Venclyxto®). 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.

*This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.

National Centre for Pharmacoeconomics **November 2019**

Summary

In October 2018, the European Commission granted marketing authorisation for venetoclax plus rituximab (VEN+R) for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior therapy. In January 2019, AbbVie Ltd. submitted a dossier examining the cost-effectiveness of VEN+R for the above licensed indication.

Venetoclax is first delivered according to a five-week dose titration schedule: 20 mg once daily during week one, 50 mg once daily during week two, 100 mg once daily during week three, 200 mg once daily during week four and 400 mg once daily during week five. Then from week six onwards, 400 mg of venetoclax is given once daily until disease progression or up to a maximum treatment duration of two years. Intravenous rituximab is delivered after completion of the 5-week dose titration period at 375 mg/m^2 on day one of a 28-day treatment cycle and 500 mg/m^2 on day one of cycles two to six, for a total of six treatment cycles (each cycle is 28 days). The Applicant is seeking reimbursement on the High-Tech Drug Arrangement. Venetoclax (ATC code: L01XX52) is a selective inhibitor of BCL-2.

Ibrutinib is considered the main comparator in the cost-effectiveness analysis. Due to the availability of direct head-to-head evidence, a cost-effectiveness analysis is also presented including bendamustine + rituximab (BR) as a comparator.

1. **Comparative effectiveness of VEN+R**

The only direct evidence available for the efficacy of VEN+R is from the international, randomised, open-label, phase III MURANO trial comparing VEN+R with BR in 389 patients with relapsed or refractory CLL (R/R CLL) who have received at least one prior therapy. BR was administered up to a maximum of six 28-day cycles. The dose of bendamustine was 70 mg/m^2 on days one and two of a 28-day cycle. The dose of rituximab was 375 mg/m^2 on day one of cycle one and 500 mg/m^2 on day one of cycles two to six. The primary endpoint was investigator-assessed progression-free survival (PFS-INV). Secondary endpoints included independent review committee assessed PFS (PFS-IRC), PFS in patients with del[17p], overall response rate (ORR), minimal residual disease (MRD), duration of response (DoR), overall

survival (OS), event-free survival (EFS), time to next treatment (TTNT), safety and tolerability. Health-related quality of life (HRQoL) was also measured using EORTC QLQ-C30, EORTC QLQ-CLL16 and EQ-5D-3L. The latest data-cut from the MURANO trial is from May 2018 with a median follow-up of 36-months.

At the May 2018 data-cut the median PFS-INV was not reached in the VEN+R arm and was 17.0 months (95% CI 15.7, 21.7) in the BR arm; HR = 0.16 (95% CI 0.12, 0.23). Median OS was not reached in either treatment arm; HR = 0.50 (95% CI 0.30, 0.85). The NCPE Review Group has identified the following key issues and uncertainties with the available clinical efficacy data from the MURANO trial. The main issue is the immaturity of the OS data which does not provide robust evidence of the effect of VEN+R over time. In addition, there are concerns that differences in post-progression treatments between the two treatment arms may have affected OS estimates. Furthermore, bias may have been introduced into HRQoL results due to the open label nature of the trial and lower completion rates in the VEN+R arm.

In the absence of direct comparative evidence between VEN+R and ibrutinib (at a dose of 420mg once daily until progression), an indirect treatment comparison was undertaken to estimate the relative effectiveness between venetoclax and ibrutinib. Both an unanchored and anchored matched adjusted indirect comparison (MAIC) were performed. The NCPE Review Group has concerns that both MAICs were at a high risk of unaccounted unobserved residual bias. The anchored MAIC was based on evidence from the literature suggesting that ibrutinib+BR has similar efficacy to ibrutinib. Therefore a comparison of VEN+R versus ibrutinib+BR (as a proxy for ibrutinib) was conducted using BR as a common comparator. Data from the MURANO and HELIOS (ibrutinib+BR versus BR) trials was used to inform this effect. Due to the uncertainty in the anchored MAIC analysis, we note that the NICE Evidence Review Group (ERG) constructed a network meta-analysis (NMA) using hazard ratios (HRs) for the ibrutinib versus BR comparison from Hillmen *et al* (2015) and HRs for VEN+R versus BR from the MURANO trial. Although there are several limitations to this NMA, the NCPE Review Group considers that it addresses some of the uncertainty in the anchored MAIC and provides a plausible estimate of the relative efficacy of VEN+R and

ibrutinib. The results indicate that HRs for VEN+R versus ibrutinib for PFS were 1.43 (95% CI 0.78,2.61) and for OS HR was 1.08 (95%CI 0.42,2.73).

2. Safety of VEN+R

In the MURANO trial, at the May 2018 data-cut the median duration of exposure to venetoclax was 24.8 months, with a median dose intensity of 97.4%. The median dose intensity of bendamustine was 100%. The safety population included all patients who had received at least one dose of study drug.

The proportion of patients experiencing adverse events (AEs) was similar in both treatment groups, regardless of the difference in the length of the AE reporting period. Overall, 100.0% of patients in the VEN+R treatment group and 98.4% in the BR treatment group experienced an AE. The most common AE of any grade in both treatment groups was neutropenia (VEN+R: 61.9%; BR: 45.2%).The most frequently reported (≥5%) AEs considered related to venetoclax treatment by the investigator were neutropenia (53.6%), diarrhoea (22.2%), nausea (14.9%), fatigue (7.7%), anaemia (6.7%), thrombocytopenia (6.7%), upper respiratory tract infection (5.7%), and hyperphosphatemia (5.2%). The most frequent AEs that resulted in venetoclax dose reduction or interruption were neutropenia and febrile neutropenia. Discontinuation rates due to AEs were significantly higher in the VEN+R arm compared to the BR arm (12.4% vs. 5.9%, p=0.03). AEs of grade 3 or 4 severity were reported in 83.0% and 70.7% of patients in the VEN+R and BR treatment groups respectively. Neutropenia was the most common grade 3 or 4 AE, with a higher incidence in the VEN+R group than in the BR group (58.8% vs. 39.9%). The incidence of serious AEs, was balanced between the treatment groups (VEN+R: 47.9%; BR: 43.1%).

3. Cost effectiveness of VEN+R

Methods

A three-state partitioned survival cost-utility model with a 28-day cycle length and a 30-year time horizon was presented. The key effectiveness inputs in the model were PFS and OS. All patients enter the model in the pre-progression health state and remain there until disease progression. Costs of disease management, utilities and risks of death all differ between the pre-progression and the post-progression health states. The partitioned survival approach

uses “area under the curve”, where the number of patients in each health state at a given time is taken directly from survival curves fitted to the clinical data from the MURANO trial. This approach allows the survival of the ibrutinib arm to be estimated using PFS and OS hazard ratios applied to the VEN+R survival curves. A half-cycle correction was applied in the base-case analysis.

The Applicant undertook a number of approaches to the extrapolation of OS and PFS. The NCPE Review Group had concerns in relation to some of these approaches. The NCPE Review Group consider the model which assumes individual modelling of OS and PFS for VEN+R and BR, despite its limitations, to be the most appropriate given the data available. Additionally, the NCPE Review Group has concerns regarding the application of the relative benefit of VEN+R for the duration of the model. Consequently, the NCPE Review Group explored methods to apply a waning effect of treatment benefit over time in the model, providing a compromise between the assumptions of continued treatment effect and assuming no benefit after cessation of treatment.

Utilities identified in the model included health state utilities, age related utility decrements and decrements for AEs. Due to unrealistic utility values obtained from the MURANO trial, health state utility values were derived from the literature.

Relevant costs are included in the model. Costs were included for active treatment, routine care and monitoring, terminal care, treatment specific monitoring and AEs. Irish cost data were used where possible.

Results

Applicant base case

- VEN+R has decreased costs compared to ibrutinib and a QALY gain of 0.988. Therefore **VEN+R dominates ibrutinib**.
- The incremental cost due to treatment with VEN+R versus BR was €133,847 for an incremental QALY gain of 2.118 resulting in an ICER of **€63,198/QALY.**

Due to uncertainty in the assumptions used in the economic model, the NCPE Review Group suggested several changes based on plausible alternative assumptions, including the use of HRs from the NICE ERG NMA, no assumption of proportionality and the application of a continued waning effect of VEN+R benefit, amongst other changes. This gave the following results:

NCPE adjusted base case

- VEN+R has decreased costs compared to ibrutinib and decreased QALYs of 1.247 i.e. less costly, less effective. In this case net monetary benefit (NMB) provides a better representation of results. The **NMB equates to €333,872** (a positive value indicates that VEN+R is cost-effective versus ibrutinib at a willingness-to-pay threshold of €45,000/QALY).
- The incremental cost due to treatment with VEN+R versus BR was €120,024 for an incremental QALY gain of 1.249 resulting in an ICER of **€96,130/QALY.**

Sensitivity analysis

The Applicant presented a probabilistic sensitivity analysis for each comparison, which gave the following ICERs and probabilities of being cost-effective at willingness-to-pay thresholds of €45,000 and €20,000 per QALY:

- VEN+R vs. ibrutinib = **VEN+R dominates,** probability of being cost effective at a threshold of €20,000/QALY = 100% and €45,000/QALY = 100%.
- VEN+R vs. BR = **€67,703 per QALY,** probability of being cost effective at a threshold of €20,000/QALY = 0% and €45,000 per QALY = 2.7%.

The Applicant presented comprehensive scenario and one-way sensitivity analyses (OWSA) using their base case. From the OWSA, variance in the VEN+R joint model hazard rates and MAIC HRs had the largest influence on model results for the VEN+R vs. ibrutinib comparison. The largest driver of incremental QALYs was the OS HR which led to VEN+R having a much longer post-progression period compared to ibrutinib. For the BR comparison, utility values and discounting had the greatest effect on the model outputs.

Two scenario analyses resulted in VEN+R no longer dominating ibrutinib, namely assuming a model time horizon of two or less years or including post-progression treatment costs in the base case. For the BR comparison, the effect of using alternative distributions for the joint survival model lead to modest changes in incremental results, with the inclusion of post-progression treatments costs resulting in a decreased ICER.

In summary, the uncertainty surrounding the estimated VEN+R survival data extrapolations and comparator HRs contribute substantially to variations in the modelled cost-effectiveness results.

4. Budget impact of VEN+R

The price to wholesaler (PTW) for venetoclax tablets is €75.42 for 14 x 10 mg, €189.10 for 7 x 50 mg, €378.57 for 7 x 100 mg, €757.50 for 14 x 100 mg and €5,814.26 for 112 x 100 mg. The average annual cost per patient of VEN+R, including all relevant fees, mark-ups, rebates and 23% VAT on rituximab is estimated at €86,077 (year 1), €68,785 (year 2) and €2,487 (year 3), considering treatment discontinuation and death. This results in an average treatment cost of €157,349.

The Applicant estimates that there will be 21 patients receiving VEN+R in year 1, increasing to 83 in year 5. The projected gross budget impact, including drug acquisition costs only for VEN+R, is €42 million over 5 years.

The Applicant also presented a net drug budget impact representing the gross budget impact if VEN+R is introduced minus the gross budget impact of continuing the current treatment pathway for R/R CLL assuming VEN+R is not introduced. This resulted in 5-year cost-savings of €12.5 million, due to the two-year fixed duration of treatment with VEN compared to treatment to progression with ibrutinib.

When costs associated with treatment administration, progression-free and post-progression health states, terminal care, treatment specific monitoring and AEs are considered, 5-year cost-savings are reduced to €11 million.

5. **No patient submissions were received in support of the application.**

6. **Conclusion**

The NCPE recommends that venetoclax (Venclyxto®) be considered for reimbursement if cost-effectiveness can be improved relative to existing treatments*.

*This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.