Cost-effectiveness of venetoclax (Venclyxto®), in combination with obinutuzumab, for adult patients with previously untreated chronic lymphocytic leukaemia.

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of venetoclax (Venclyxto®) in combination with obinutuzumab. Following assessment of the Applicant's submission, the NCPE recommends that venetoclax (Venclyxto®) be considered for reimbursement. This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.

The HSE asked the NCPE to carry out a review of the Applicant's (Abbvie) Health Technology Assessment 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.

National Centre for Pharmacoeconomics **August 2021**

Summary

In February 2021, Abbvie submitted a dossier investigating the clinical effectiveness, cost effectiveness and budget impact of venetoclax in combination with obinutuzumab (VenO), for adult patients with previously untreated chronic lymphocytic leukaemia (CLL). Reimbursement is sought under the High Tech Drug Arrangement.

Venetoclax is a selective, orally bioavailable, small molecule, B-cell lymphoma-2 (BCL-2) inhibitor that restores programmed cell death (apoptosis) in cancer cells. BCL-2 over expression is a major contributor to the pathogenesis of some types of lymphoid malignancies, including CLL. Obinutuzumab is a humanised anti-CD20 monoclonal antibody which is administered via intravenous infusion. Venetoclax is administered for a total of 12 cycles, each cycle consisting of 28 days: six cycles in combination with obinutuzumab, followed by six cycles of venetoclax as a single agent. In Ireland, standard of care includes fludarabine, cyclophosphamide in combination with rituximab (FCR) or bendamustine in combination with rituximab (BR) for fit patients with limited co-morbidities, and obinutuzumab in combination with chlorambucil (OClb) for patients with co-morbidities making them less fit for intensive treatment. For patients with a del(17p)/TP53 mutation (i.e. a subpopulation of the population for which VenO is licensed), ibrutinib is the current standard of care treatment. Ibrutinib is also licensed for first-line use in CLL in those without a del(17p)/TP53 mutation; cost-effectiveness of ibrutinib in this population has not been demonstrated, due to non-submission of a full HTA..

1. Comparative effectiveness of venetoclax in combination with obinutuzumab

The clinical effectiveness of VenO versus OClb was investigated in the CLL14 trial. This was an open-label randomised controlled trial, in adult patients with previously untreated CLL. A total of 432 patients were randomised; patient baseline characteristics were well balanced between treatment arms. Trial outcomes are provided in Table 1. VenO was associated with a greater progression free survival and time to next treatment compared with OClb, as well as a higher objective response rate and a higher rate of minimal residual disease (MRD) negativity. Overall survival data is immature; median OS has not yet been reached in either arm. Quality of life analyses did not show a difference in disease specific and generic quality

of life assessments between treatment arms. Additional academic-in-confidence data was provided and considered by the Review Group.

Table 1 Summary of CLL14 outcomes

	August 2018 data cut (28.1 months median follow-up)		**August 2019 data cut** (40 months median follow-up)	
	VenO (N=216)	**OClb (N=216)**	**VenO (N=216)**	**OClb (N=216)**
Investigator-assessed Progression Free Survival				
Median PFS, months (95% CI)	Not reached	Not reached	Not reached	35.6 (33.7, 40.7)
HR for PFS (95% CI)	0.35 (0.23, 0.53;p<0.0001)		0.31 (0.22, 0.44; p<0.001)§	
24 month PFS %, (95% CI)	88 (83.7, 92.6)	64 (57.4, 70.8)	NA	
36 month PFS %, (95% CI)	-	-	82 (76.5, 87.3)	50 (42.4, 56.6)
Overall Survival				
Median OS, months (95% CI)	Not reached	Not reached	Not reached	Not reached
Deaths, n (%)	20 (9.4)	17 (8.0)	27 (12.5)	27 (12.5)
HR for OS (95% CI)	1.24 (0.64, 2.40;p=0.5216)		1.03 (0.60, 1.75; p=0.9210)	
24 month OS % (95% CI)	92 (88.1, 95.5)	93 (89.9,96.7)	Not reported	
Response Rates measured at EOT assessment				
ORR*	84.7%	71.3%	NA	
MRD negativity rate-peripheral blood %*†	75.5%	35.2%	NA	
MRD negativity rate-bone marrow %*†	56.9%	17.1%	NA	

OS: Overall survival; **PFS:** progression free survival; **ORR:** objective response rate; **CI:** confidence intervals; **HR:** hazard ratio; **EOT**: end of treatment; **MRD:** minimal residual disease.
*Differences between treatment arms were statistically significant.
†MRD negativity defined as $<10^{-4}$
§Descriptive p-value

The immaturity of the PFS and OS data, with median survival times not reached for either endpoint, is a concern, as is the lack of data on second and subsequent lines of treatment in both arms. CLL14 recruited only a sub-population (those ineligible for FCR and BR) of the final licensed population (which includes those eligible for FCR and BR). The CHMP concluded that extrapolation of the treatment benefit seen in CLL14 to those eligible for FCR and BR was acceptable, as the safety profile in fitter patients (i.e. those eligible for FCR and BR) was not anticipated to be less favourable. Also, the PFS effect size (although not directly compared with FCR) was considered sufficient to make VenO a reasonable first-line alternative. No direct comparative evidence is available for FCR, BR and ibrutinib; clinical trials are ongoing.

In the absence of direct comparative evidence, the Applicant conducted indirect treatment comparisons. The Applicant presented outcomes from a network meta-analysis (NMA) to obtain estimates of relative efficacy versus ibrutinib, FCR and BR, in those without a del(17p)/TP53 mutation. A statistically significant improvement in PFS was observed for venetoclax versus BR, FCR and ibrutinib in patients without a del(17p)/TP53 mutation. No significant improvement in OS was observed for VenO. The Applicant's NMA results, particularly for the FCR and BR comparisons, should not be considered robust as they may be subject to bias of unknown direction and magnitude. The Review Group acknowledge that due to a lack of evidence for the efficacy of FCR and BR in unfit patient populations at the time of submission, a more robust NMA was not possible. The Applicant presented outcomes from a naïve indirect treatment comparison (ITC) versus ibrutinib in the population with a del(17p)/TP53 mutation. The estimates generated from the unadjusted ITC are not robust and the Review Group consider that they are not appropriate for decision-making purposes. The Review Group acknowledge that due to a lack of evidence a reliable ITC of VenO and ibrutinib was not possible for the population with a del17p/TP53 mutation at the time of submission.

2. **Safety of venetoclax in combination with obinutuzumab**

Similar proportions of patients in both arms of CLL14 experienced at least one adverse event (AE), with a higher number of AEs with fatal outcome (7.5% vs 3.7%), and serious AEs (49.1% vs 42.1%) in the VenO arm. Grade 3-4 AEs were reported in 73.3% of patients on OClb and 71.2% of patients on VenO. Grade 3-4 AEs that occurred with an incidence at least 2% higher with VenO included neutropenia (52.8% vs 48.1%), hyperglycaemia (3.8%v 1.4%), diarrhoea (4.2% vs 0.5%) and hypertension (2.8% vs 0.5%). Other grade 3-4 AEs with VenO included thrombocytopenia (13.7%) and infection (19.3%). All reported cases of tumour lysis syndrome in the VenO arm occurred prior to the first dose of venetoclax. The incidence of second primary malignancies was 10.3% in the OClb arm compared with 13.7% in the VenO arm. Based on available evidence the overall safety profile of VenO appears not less toxic than OClb.

3. Cost effectiveness of venetoclax in combination with obinutuzumab

The Applicant presented a partitioned survival model to estimate the cost-effectiveness of VenO versus OClb, FCR, BR and ibrutinib in the population without del(17p)/TP53 mutation , and versus ibrutinib in the population with a del(17p)/TP53 population. Population characteristics were based on the CLL14 trial. The Review Group note that the population of CLL14 excluded 'fit' patients who would be eligible for BR and for FCR, and thus the modelled population is not reflective of the full spectrum of patients who are eligible for treatment as per the product licence.

Efficacy inputs for the cost-effectiveness model were derived from CLL14 for VenO versus OClb, from the NMA for VenO versus ibrutinib, FCR and BR in those without a del(17p)/TP53 mutation, and from the naïve ITC for VenO versus ibrutinib in the population with a del(17p)/TP53 mutation. Resource use estimates were based on clinical opinion; Irish costs were sourced and applied where possible. Utility values were sourced from the literature. The extrapolation of time to next treatment, and the estimation of subsequent treatment costs were the main drivers of the cost-effectiveness estimates.

The Review Group made a number of necessary adjustments in the model, as well as changing a number of parameters to equally plausible albeit more conservative assumptions (compared with more optimistic assumptions applied in the Applicant base case). In the Applicant model base case, VenO was dominant of all comparators in the population without the del(17p)/TP53 mutation, and was less costly but less effective than ibrutinib in the population with a del(17p)/TP53 mutation, with a positive net monetary benefit of €408,276 (Table 2). In the Review Group's adjusted base case using probabilistic ICERs in the population without a del(17p)/TP53 mutation, VenO remained dominant of ibrutinib, and was associated with ICERs less than €45,000 per QALY for the remaining comparators (Table 3). The probability of cost-effectiveness at the €45,000 per QALY threshold was greater than 50% for all comparisons except that with FCR (46.7%). The Review Group did not present ICERs versus ibrutinib in the population with a del(17p)/TP53 mutation as the naive ITC was not considered sufficiently robust for decision making.

Table 2 Outcomes of the Applicant's base case cost-effectiveness model

Technologies	Total Costs (€)	Total QALYs	Incremental Costs (€)	Incremental QALYs	Pairwise ICERs (€/QALY)	Net monetary benefit @ WTP = €45,000 (€)
Population without a del(17p)/TP53 mutation						
VenO	142,873	7.170	-	-	-	-
OClb	320,100	6.376	-177,227	0.794	**Dominant**	**212,952**
Ibrutinib	776,485	6.300	-633,612	0.870	**Dominant**	**672,763**
BR	543,216	5.758	-400,343	1.412	**Dominant**	**463,884**
FCR	446,100	5.784	-303,227	1.386	**Dominant**	**365,604**
Population with a del(17p)/TP53 mutation						
VenO	127,322	4.729	-	-	-	-
Ibrutinib	550,446	5.059	-423,125	-0.330	**Less Costly, Less Effective**	**408,276**

QALY: Quality Adjusted Life Year; **ICER**: Incremental Cost-Effectiveness Ratio; **NMB**: Net Monetary Benefit; **VenO:** Venetoclax plus Obinutuzumab; **OClb**: Obinutuzumab plus Chlorambucil; **BR**: Bendamustine plus Rituximab; **FCR**: Fludarabine plus Cyclophosphamide.
Notes: Figures in the table are rounded, and so calculations may not be directly replicable. Errors in the Applicant's base case regarding the cost and dosing schedule of rituximab were corrected by the Review Group; presented Applicant base case results reflect these corrections.
Where a pairwise comparison demonstrates that VenO treatment is both more effective and less costly than the comparator the term "**Dominant**" is used. Where a pairwise comparison demonstrate that VenO treatment is less effective than the comparator but is less costly the term "**Less costly, Less effective**" is used. The Incremental Net Monetary Benefit is the value added by an intervention over a comparator, conditional on the willingness to pay threshold for an added QALY. A positive net monetary benefit indicates that value is added by the intervention, however it should be noted that value can be added in spite of poorer health outcomes if costs are sufficiently reduced.
A commercial in confidence patient access scheme is in place for ibrutinib and obinutuzumab, but not included for this analysis.

Table 3 Outcomes of the NCPE Review Group's adjusted base case cost-effectiveness model

Technologies	Total Costs (€)	Total QALYs	Incremental Costs (€)	Incremental QALYs	Pairwise ICERs (€/QALY)	Incremental NMB @ WTP = €45,000 (€)
Population without a del(17p)/TP53 mutation						
VenO	204,589	6.980	-	-	-	-
OClb	195,775	6.290	8,815	0.690	**12,782**	**22,217**
Ibrutinib	487,445	6.147	-282,856	0.832	**Dominant**	**320,317**
BR	176,454	5.755	28,135	1.224	**22,984**	**26,949**
FCR	156,842	5.823	47,747	1.156	**41,297**	**4,282**

QALY: Quality Adjusted Life Year; **ICER**: Incremental Cost-Effectiveness Ratio; **NMB**: Net Monetary Benefit; **VenO:** Venetoclax plus obinutuzumab; **OClb**: Obinutuzumab plus Chlorambucil; **BR**: Bendamustine plus Rituximab; **FCR**: Fludarabine plus Cyclophosphamide.
Notes: Results based on probabilistic analysis using 1,000 iterations and was run separately for the non-del(17p)/TP53 mutation and del(17p)/TP53 mutation subpopulations. Figures in the table are rounded, and so calculations may not be directly replicable.
Where a pairwise comparison demonstrates that VenO treatment is both more effective and less costly than the comparator the term "**Dominant**" is used. The Incremental Net Monetary Benefit is the value added by an intervention over a comparator, conditional on the willingness to pay threshold for an added QALY. A positive net monetary benefit indicates that value is added by the intervention.
No outcome is provided for the del(17p)/TP53 mutation population, as the Review Group had little confidence in efficacy inputs underpinning this comparison.
A commercial in confidence patient access scheme is in place for ibrutinib and obinutuzumab, but not included for this analysis.

4. **Budget impact of venetoclax in combination with obinutuzumab.**

All prices and calculations are based on the publicly available list prices. Confidential pricing arrangements are not included. The price of different venetoclax presentations are provided in Table 4. The costs of cycle 1 and 2 are variable due to up-titration of the dosing; the cost to the HSE per cycle of venetoclax from cycle 3 onwards is €5,761.28, including all fees and mark-ups, excluding VAT, and assuming 100% dose intensity. The cost for a treatment course of VenO, assuming 100% dose intensity is €85,310.17 excluding VAT. Per-cycle costs were variable due to the up titration and loading dose schedules for venetoclax and obinutuzumab, respectively.

Table 4 Prices of venetoclax presentations

	Venetoclax					
Tablet strength	10mg	50mg	100mg	100mg	100mg	100mg
Pack size	14	7	7	14	28	112
Price to wholesaler (€)	69.51	174.20	348.86	697.84	1,395.69	5,095.62

The budget impact analysis assumed that 270 patients would be treated with VenO over five years. The Review Group estimated that this would lead to a gross budget impact of €24.7 million including VAT over that timeframe (€23 million ex VAT). The net budget impact was estimated at €6.9 million including VAT over five years (€5.7 million ex VAT).

5. Patient Organisation Submissions

A Patient Organisation Submission was received from CLL Ireland. It will be provided to the HSE and form part of the data that the HSE considers.

6. Conclusion

The NCPE recommends that venetoclax in combination with obinutuzumab be considered for reimbursement.*

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