NCPE Assessment

Technical Summary

Venetoclax (Venclyxto ®)

22001

September 2023

Applicant: AbbVie

Venetoclax in combination with a hypomethylating agent for the treatment of adult patients with newly diagnosed acute myeloid leukaemia (AML) who are ineligible for intensive chemotherapy

NCPE
National Centre for Pharmacoeconomics, Ireland

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of venetoclax (Venclyxto ®) for this indication.

Following assessment of the Applicant's submission, the NCPE recommends that venetoclax (Venclyxto ®) not be considered for reimbursement unless cost-effectiveness can be improved relative to existing treatments*.

The Health Service Executive (HSE) asked the NCPE to carry out an evaluation 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 comparative 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.

Summary

In October 2022, AbbVie submitted a dossier which investigated the comparative clinical effectiveness, cost-effectiveness and budget impact of venetoclax (Venclyxto ®) in combination with a hypomethylating agent for the treatment of adult patients with newly diagnosed acute myeloid leukaemia (AML) who are ineligible for intensive chemotherapy. AbbVie is seeking reimbursement of venetoclax on the High Tech Drug Arrangement.

The licensed dose of venetoclax, for this indication, is 400mg orally once daily. Patients should receive a three-day dose ramp-up of venetoclax to reach this target dose (Day 1: 100mg once daily, Day 2: 200mg once daily, Day 3 onwards: 400mg once daily). Venetoclax is given in combination with a hypomethylating agent (either azacitidine 75mg/m^2 subcutaneously or intravenously on days 1 to 7 of each 28-day cycle or decitabine 20 mg/m^2 intravenously on days 1 to 5 of each 28-day cycle). Venetoclax in combination with a hypomethylating agent, should be continued until disease progression or unacceptable toxicity.

In Ireland, hypomethylating agents are currently the standard of care for this indication; azacitidine is more routinely used than decitabine. The primary comparator is azacitidine.

1. Comparative effectiveness of venetoclax

The efficacy and safety of venetoclax in combination with azacitidine (VenAZA) versus azacitidine in combination with placebo (AZA-placebo) is assessed in the VIALE-A trial, an on-going (not recruiting), international, randomised, double-blinded, phase III study. Patients were randomised 2:1 to the VenAZA arm or AZA-placebo arm. The co-primary efficacy endpoints are overall survival (OS) and composite complete remission (CR) rate (complete remission and complete remission with incomplete blood count recovery [CR+CRi]). Event free survival is a key secondary endpoint. Participants continued to receive treatment (28-day cycles) in both arms until disease progression, unacceptable toxicity, withdrawal of consent or other protocol criteria for discontinuation were met.

The Applicant submitted results from two interim efficacy analyses (IA1: 01 October 2018 and IA2: 04 January 2020). On request from the Review Group, updated results from a final

efficacy analysis (01 December 2021) were subsequently submitted. In the updated results (consistent with the earlier interim analyses), treatment with VenAZA resulted in statistically significant longer median OS compared with AZA-placebo (median OS was 14.7 months versus 9.6 months, HR 0.58, 95% CI 0.47 to 0.72). VenAZA was associated with a statistically significantly increased composite CR rate versus AZA-placebo (66.8% versus 29%). Median event free survival was statistically significantly longer in the VenAZA arm than in the AZA-placebo arm both at IA2 (9.8 months versus 7.0 months, HR 0.63, 95% CI 0.50 to 0.80) and at the final analysis (9.9 months versus 7.4 months, HR 0.58, 95% CI 0.47 to 0.73). Health-related quality of life (HRQoL), assessed using the cancer specific EORTC-QLQ-C30 and the EQ-5D-5L, was a secondary outcome. Overall, there were no differences in HRQoL outcomes between the treatment arms.

2. Safety of venetoclax

The VIALE-A trial includes 427 patients who received at least one study dose and were included in the safety analysis set (n=283 in the VenAZA arm, and n=144 in the AZA-placebo arm). All patients had at least one adverse event (AE); 83% and 73% in the VenAZA arm and AZA-placebo arm had a serious adverse event (SAE). Almost all patients experienced at least one grade 3 treatment emergent AE (TEAEs); 99% in the VenAZA arm and 97% in the AZA-placebo arm. The most frequently reported grade 3 or above TEAEs with an incidence 20% more in the VenAZA arm versus the AZA arm were: thrombocytopenia (45% versus 38%), neutropenia (42% versus 29%), febrile neutropenia (42% versus 19%), anaemia (26% versus 20%), leukopenia (21% versus 12%) and pneumonia (20% versus 25%). The incidence of tumour lysis syndrome (TLS) was 1.1% in the VenAZA arm (all occurred during ramp-up dosing and within 7 days of treatment initiation in Cycle 1) and 0% in the AZA-placebo arm. The licence for venetoclax highlights that concomitant use of venetoclax with strong or moderate CYP3A4 inhibitors increases venetoclax exposure and may increase the risk for TLS at initiation and during the dose-titration phase. The Review Group note that antifungal prophylaxis, with CYP3A4 inhibitors, are routinely prescribed in patients with AML; this would require dose reductions of venetoclax.

3. Cost effectiveness of venetoclax

Methods

The analysis was conducted from the perspective of the Health Service Executive in Ireland. A three health-state partitioned survival model was submitted. The modelled treatment effects were the delay of disease progression and death. Direct efficacy and safety data was derived from VIALE-A. The key efficacy inputs were event free survival and OS. The Review Group identified a number of limitations in the Applicant's cost-effectiveness model, which were addressed in the NCPE-adjusted base case. These included the use of an alternative parametric model for event free survival, the removal of a cure assumption and changes to a number of cost inputs.

Results

The results of the Applicant's base case deterministic cost-effectiveness analysis are presented in Table 1. Results of the NCPE-adjusted base case are presented in Table 2.

Table 1: Applicant base case incremental cost-effectiveness results [a]

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
AZA	257,669	0.73	-	-	-
VenAZA [b]	394,661	1.77	136,992	1.05	130,946

Abbreviations: AZA: azacitidine; VenAZA: Venetoclax plus azacitidine

[a] Corresponding probabilistic ICER using 1,000 iterations =€137,345/QALY. Figures in the table are rounded, and so calculations may not be directly replicable. Costs and QALY are discounted at 4%.

Table 2: NCPE adjusted base case incremental cost-effectiveness results [a]

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
AZA	291,104	0.73	-	-	-
VenAZA [b]	441,550	1.39	150,446	0.66	227,152[a]

Abbreviations: AZA: azacitidine; VenAZA: Venetoclax plus azacitidine

[a] Corresponding probabilistic ICER using 1,000 iterations =€235,153/QALY. Figures in the table are rounded, and so calculations may not be directly replicable. Costs and QALY are discounted at 4%.

The probability of cost-effectiveness for VenAZA versus AZA, in the Applicant's base case and the NCPE-adjusted base case analyses, were 1% and 0% respectively at a threshold of €20,000/QALY and 2% and 1% respectively at the €45,000/QALY threshold. Deterministic sensitivity analysis indicated that the most influential parameters related to the venetoclax drug-acquisition costs and medical costs associated with event free survival.

4. Budget impact of venetoclax

The price to wholesaler for venetoclax is €5,330.61 per pack (112 x 100mg tablets). When the mean treatment duration is informed by the VIALE-A trial, the total cost of VenAZA, per patient per treatment course, is estimated to be €106,230. The Applicant predicted that 59 patients will be treated in Year 1 rising to 62 patients in Year 5, resulting in a total of 302 patients expected to receive treatment over five years. The 5-year cumulative gross drug budget impact of VenAZA is an estimated €30.7 million (€29.3 million excluding VAT). The 5-year cumulative net drug budget impact of VenAZA is an estimated €26.2 million (€25.7 million excluding VAT). Venetoclax is an add on therapy to AZA. Gross and net budget impact estimates are not the same due to differences in mean treatment duration of VenAZA and AZA-placebo in VIALE-A. The Review Group consider that there is considerable uncertainty associated with the budget impact estimates including assumptions surrounding the incident patient population, eligible patient numbers, and the market share; these are likely to be underestimated.

5. Patient Organisation Submission

No patient organisation submissions were received during the course of the assessment.

6. Conclusion

Following the assessment of the Applicant's submission, the NCPE recommends that venetoclax not be considered for reimbursement unless 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.