The cost-effectiveness of vericiguat (Verquvo®) for the treatment of adults with symptomatic chronic heart failure with reduced ejection fraction who are stabilised after a recent decompensation event

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of vericiguat for the treatment of adults with symptomatic chronic heart failure with reduced ejection fraction. Following NCPE assessment of the Applicant's submission, vericiguat is not considered cost-effective for the treatment of symptomatic chronic heart failure in adult patients with reduced ejection fraction and reimbursement is not recommended*.

The HSE asked the NCPE to carry out an assessment of the Applicant's (Bayer Limited) Health Technology Assessment of vericiguat. 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 **July 2022**

Summary

On the 21 March 2022 Bayer Limited submitted an economic dossier on the cost-effectiveness of vericiguat (Verquvo®) for the treatment of adults with symptomatic chronic heart failure with reduced ejection fraction who are stabilised after a recent decompensation event. Heart failure may be divided into different phenotypes based on left ventricular ejection fraction (LVEF) where a normal ejection fraction is ≥ 50%. Therefore, in heart failure with preserved ejection fraction (HFpEF) the recognised symptoms and signs are accompanied with a LVEF of ≥ 50%, with evidence of structural and/or functional cardiac abnormalities and/or elevated levels of natriuretic peptides. Heart failure with reduced ejection fraction (HFrEF) is accompanied with the recognised symptoms and signs and a LVEF ≤ 40%. Patients with a LVEF between 41% and 49% have mildly reduced left ventricular function designated as heart failure with mid-range ejection fraction (HFmrEF).

The current HSE-Medicines Management Programme (HSE-MMP) managed access protocol indicates that the standard of care for the treatment of chronic heart failure is an angiotensin converting enzyme (ACE) inhibitor or an angiotensin II receptor blocker (ARB) where ACE inhibitors are not tolerated. The angiotensin receptor-neprilysin inhibitor (ARNi) sacubitril + valsartan (Entresto®) is only reimbursed for HFrEF patients who remain symptomatic despite a stable dose of ACE inhibitor or ARB. Patients with HFrEF should also be treated with beta blockers unless contraindicated. Loop diuretics such as furosemide or bumetanide will frequently be used. Mineralocorticoid inhibitors such as spironolactone may be added to therapy particularly in patients with an ejection fraction less than 35% and digoxin may be added for symptomatic control. Ivabradine may be used in chronic heart failure with systolic dysfunction where the patient is in sinus rhythm and a heart rate ≥ 70 beats per minute in combination with standard therapy.

Vericiguat is a soluble guanylate cyclase (sGC) stimulator which enhances the cyclic guanosine monophosphate (cGMP) pathway and is indicated for the treatment of symptomatic heart failure in adults with reduced ejection fraction (HFrEF) who are stabilised after a recent decompensation event requiring intravenous therapy. It is administered orally with a target maintenance dose of 10 mg once daily and will be prescribed as an add-on to appropriate standard of care for adult patients with symptomatic chronic HFrEF.

1. Comparative effectiveness

The submitted dossier indicates that two clinical trials provide the main evidence base for the clinical efficacy and safety of vericiguat in the population of heart failure patients with reduced left ventricular ejection fraction. The Soluble Guanylate Cyclase Stimulator in Heart Failure with Reduced Ejection Fraction Study (SOCRATES-REDUCED) was a phase II dose-finding trial designed to evaluate the effect on natriuretic peptide trajectory and tolerability of 12 weeks of treatment with four doses of vericiguat in patients with HFrEF. This study included 456 clinically stable patients (≥18 years) with an LVEF less than 45% within 4 weeks of a worsening heart failure event which was defined as worsening symptoms and signs of heart failure and elevated natriuretic peptide levels requiring hospitalisation or outpatient intravenous diuretic treatment. The mean time from stabilisation to randomisation was 14.4 days and patients were randomised to placebo (n=92) or one of four vericiguat doses i.e 1.25mg, 2.5mg, 5mg or 10mg (n=91 for all treatment groups) administered orally, once daily. The mean age at baseline was approximately 68 years and 20% were female. In terms of NYHA classification 52.7% had stage I/II heart failure and 47.3% had stage III or IV heart failure. The mean LVEF was approximately 29% and the median value for NT-proBNP was 3,076 pg/ml (< 125 pg/ml makes a diagnosis of HF unlikely). Just over 53% had ischaemic heart disease as the underlying cause of heart failure, 78% had a history of hypertension, over 33% had associated atrial fibrillation and 48% of participants had diabetes mellitus. Patients were receiving appropriate treatments for heart failure including, ACE inhibitors (61.4%) or ARBs (22.8%), beta-blockers (90.1%), mineralocorticoid receptor antagonists (62.3%) and diuretics (94.3%).

The primary outcome was change from baseline to week 12 in log-transformed level of N-terminal pro-B-type natriuretic peptide (NT-proBNP). The primary analysis specified pooled comparison of the 3 highest-dose vericiguat groups with placebo and secondary analysis evaluated a dose-response relationship with vericiguat and the primary end point. Some 351 patients (77%) completed treatment with the study drug with valid 12-week NT-proBNP levels. The difference in log-transformed NT-proBNP levels from baseline to week 12 was not statistically significant between the pooled vericiguat group and placebo. The exploratory secondary analysis suggested a dose-response relationship where higher vericiguat doses were associated with greater reductions in NT-proBNP ($p<0.15$).

The second clinical trial, the Vericiguat Global Study in Subjects with Heart Failure with Reduced Ejection Fraction (VICTORIA) was a phase III, randomised, double-blind, placebo-controlled trial

which assessed the efficacy and safety of vericiguat in patients with chronic heart failure and reduced ejection fraction following a recent decompensation event. Patients were categorised into three cohorts based on the timing of heart failure deterioration including (i) those hospitalised within 3 months before randomisation (66.9% of patients) (ii) those hospitalised 3 to 6 months before randomisation (17.2%) and (iii) those receiving intravenous diuretic therapy, without hospitalisation within the previous 3 months (15.9%). Exclusion criteria included a systolic blood pressure < 100 mmHg, concurrent or anticipated use of long-acting nitrates, sGC stimulators or phosphodiesterase type 5 inhibitors (e.g sildenafil & tadalafil) and the use of intravenous inotropes or implantable left ventricular assist devices. In the VICTORIA study 5050 patients (≥ 18 years) with chronic heart failure (NYHA class II, III or IV) and an ejection fraction less than 45% were randomised to receive vericiguat (target dose 10mg orally once daily) or placebo in addition to guideline-based medical therapy. The mean age at baseline was 67 years and 24% were female. In terms of NYHA classification 59% had stage I/II heart failure, 39.7% had stage III heart failure and 1.3% were classified as stage IV heart failure. The mean LVEF was 29% and the median NT-proBNP level was 2,816 pg/ml. Just over 58% had coronary artery disease, 79% had a history of hypertension, over 44% had associated atrial fibrillation and 47% of participants had diabetes mellitus. At baseline 91.4% of patients were receiving two or more guideline-directed medical therapies for heart failure. Just over 93% of participants were treated with beta-blockers, 73.4% received an ACE inhibitor or ARB, 70.3% received an MRA. The ARNi sacubitril + valsartan was used to treat 14.5% of patients and 2.7% were treated with a sodium-glucose co-transporter-2 inhibitor (SGLT2i) whilst 6% received ivabradine. Of the 5034 subjects treated, 83% reached the target dose of 10mg vericiguat or matching placebo during the course of the trial. Some 27.8% of participants had an implantable cardioverter-defibrillator and 14.7% had a biventricular pacemaker. The primary outcome was a composite of death from cardiovascular causes or first hospitalisation for heart failure.

Over a median of 10.8 months, a primary outcome event occurred in 897 of 2526 patients (35.5%) in the vericiguat group and in 972 of 2524 patients (38.5%) in the placebo group (hazard ratio (HR), 0.90; 95% confidence interval (CI), 0.82 to 0.98;p=0.02). Some 691 patients (27.4%) in the vericiguat group and 747 patients (29.6%) in the placebo group were hospitalised for heart failure (HR, 0.90; 95% CI, 0.81 to 1.00). Death from cardiovascular causes occurred in 414 patients (16.4%) in the vericiguat group and in 441 patients (17.5%) in the placebo group (HR, 0.93; 95% CI, 0.81 to 1.06). A secondary outcome included the composite of death from any cause or first hospitalisation for heart failure and occurred in 957 patients (37.9%) in the vericiguat group and in 1032 patients (40.9%) in the placebo group (HR, 0.90; 95% CI, 0.83 to 0.98; p=0.02). There was no significant difference in

death from any cause which occurred in 512 patients (20.3%) in the vericiguat group as compared with 534 patients (21.2%) in the placebo group (HR, 0.95; 95% CI, 0.84 to 1.07;p=0.38). Subgroup analysis indicated heterogeneity of effect in relation to NT-proBNP, LVEF, eGFR and age with NT-proBNP being the most influential predictor of treatment response particularly in patients with a baseline NT-proBNP > 5314 pg/ml where no treatment effect was found (HR, 1.16; 95% CI 0.99 to 1.34). There was no treatment effect seen in patients ≥ 75 years (HR, 1.04; 95% CI 0.88 to 1.21). There was no significant difference in quality of life between the vericiguat and placebo groups as measured using the Kansas City Cardiomyopathy Questionnaire (KCCQ) overall summary score or the EQ-5D-5L UK index score.

2. Safety

Adverse events (serious and non-serious) occurred in 80.5% of patients receiving vericiguat and in 81.0% of patients receiving placebo during the VICTORIA trial. Drug-related adverse events were more common in the vericiguat group (14.6%) as compared with placebo (11.7%). Symptomatic hypotension occurred in 9.1% of patients in the vericiguat group and 7.9% in the placebo group (p=0.12). Syncope occurred in 4% of patients in the vericiguat group and 3.5% of patients treated with placebo (p=0.30). Anaemia developed in more patients in the vericiguat group (7.6%) than in the placebo group (5.7%). The most frequently reported adverse event leading to discontinuation of study medication was hypotension in 1.9% of patients versus 1.3% in the placebo group.

3. Cost effectiveness

The population considered in this economic evaluation consisted of adult patients with symptomatic chronic heart failure with reduced ejection fraction who were stabilised after having had a heart failure hospitalisation within the past six months or the use of outpatient intravenous diuretics for heart failure within the past three months. The comparator included the current standard of care for heart failure with reduced ejection fraction. It is assumed that patients received appropriately titrated doses of agents such as ACE inhibitors or ARBs. Other treatments that may be used as add on therapy for HFrEF include ivabradine, dapagliflozin, empagliflozin and sacubitril + valsartan and these are also used as comparators in the economic model. The cost-effectiveness model was a cohort-based Markov state-transition model developed in Microsoft Excel® to undertake a cost-utility analysis. The model structure consisted of six health states, which included (i) alive, (ii) heart failure hospitalisation (HFH) event 1, (iii) post HFH event 1, (iv) HFH event ≥ 2, (v) post HFH event ≥2

and (vi) death. The starting point in the model was the 'alive' health state and patients could remain in this health state or transition to HFH event 1 or enter the dead state. Patients remained in hospital for one cycle (one month) and then transitioned to post HFH 1 or to the dead state. Patients who were alive following their first HFH event (i.e in the post HF hospitalization 1 state) could transition to one of three health states including: HFH event ≥ 2, death or the post HF hospitalization 1 health state. Patients who experienced a second HFH event entered HF hospitalization ≥ 2 and transitioned to post HFH ≥ 2 or the death state.

The application of treatment effect in the economic model was based on incidence data, baseline characteristics and a post-hoc analysis from the VICTORIA trial. Parametric risk equations using secondary endpoints and baseline characteristics were estimated for health state transitions and were extrapolated over time using parametric distributions. As there were no head-to-head clinical trials comparing vericiguat to comparator treatments for HFrEF, indirect treatment comparisons informed by up-to-date systematic literature reviews (SLRs) were conducted. These SLRs identified five relevant clinical trials including VICTORIA, PARADIGM-HF, DAPA-HF, EMPEROR Reduced and SHIFT. A matching-adjusted indirect comparison was used in the base-case economic analysis and NT-proBNP was considered the only relevant matching variable. As EQ-5D-5L data was collected during the VICTORIA trial it was used to obtain utility estimates. The United Kingdom (UK) EQ-5D-5L utility scores were transformed into EQ-5D-3L scores based on the crosswalk method. Resource usage and costs considered in the model included drug costs, routine care and monitoring costs, cost of hospitalisation, severe adverse events and urgent heart failure costs and terminal care costs. Results in the base case represent the perspective of the Health Service Executive (HSE). A discount rate of 4% was applied to costs and health outcomes.

A deterministic analysis of the cost-effectiveness of vericiguat as add-on therapy to the standard of care (SoC) versus SoC was associated with incremental costs of €6,938 and an incremental quality adjusted life-year (QALY) of 0.21 resulting in a base case incremental cost-effectiveness ratio (ICER) of €33,194/QALY. Vericiguat was dominated by the comparators dapagliflozin, empagliflozin and ivabradine. Vericiguat was less effective and less costly as compared with sacubitril + valsartan. Probabilistic analysis for vericiguat plus SoC versus SoC resulted in an ICER of 34,965/QALY and the probability of vericiguat being cost-effective at the €45,000/QALY threshold was 64.2%. The probabilistic ICERs for all matching-adjusted indirect comparisons involving dapagliflozin, empagliflozin, ivabradine and sacubitril + valsartan were consistent with the deterministic ICERs. A deterministic sensitivity analysis indicated that the parameters that impacted the cost-effectiveness

of vericiguat + SoC versus SoC to the greatest extent were NYHA group I/II, Eastern Europe cohort, log-transformed NT-proBNP, vericiguat + SoC case fatility rate and cost of a hospitalisation event. In relation to the comparators (except ivabradine) the most sensitive parameter was the matching-adjusted indirect comparison (MAIC) hazard ratios.

4. Budget impact

The price to wholesaler of vericiguat 2.5mg and 5mg for a pack size of 14 tablets is €49.42 and the price to wholesaler of vericiguat 10mg for a pack size of 28 tablets (target maintenance dose) is €98.84. The total cost per patient per annum is €1,369.52 inclusive of wholesale mark-up, rebates and pharmacy fees and taking into account the up-titration phase i.e 2.5mg x 14 days followed by 5mg x 14 days and vericiguat 10mg daily thereafter. It was estimated that the number of patients treated with vericiguat increased from 247 in year 1 to 1,351 in year 5 resulting in a 5 year gross budget impact of €5.65 million. The 5 year net budget impact was estimated at €3.04 million.

5. Patient submission

No patient organisation submission was received during the course of this assessment.

6. Conclusion

This assessment demonstrates that vericiguat is not a cost-effective treatment for HFrEF as compared with dapagliflozin, empagliflozin and ivabradine and is less effective than sacubitril + valsartan. Therefore, the NCPE recommends that vericiguat not 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.