

HEALTH TECHNOLOGY BRIEFING NOVEMBER 2019

Vericiguat for chronic heart failure with reduced ejection fraction

NIHRIO ID	9831	NICE ID	9832
Developer/Company	Bayer PLC	UKPS ID	643457

Licensing and market availability plans	Currently in phase III clinical trials.
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SUMMARY

Vericiguat is a medicinal product in clinical development for the treatment of heart failure (HF) with reduced ejection fraction. HF is a complex clinical syndrome of symptoms and signs that suggest the efficiency of the heart as a pump is impaired. Symptoms include breathlessness and fatigue, and signs of the condition include swollen ankles and crackling sounds in the lungs. More than half of people with HF have a reduced ejection fraction (HFrEF), also referred to as systolic heart failure, where the heart muscle does not contract effectively, and therefore less oxygen-rich blood is pumped out to the body. There remains a large unmet need for new therapies in the treatment of HFrEF.

Vericiguat is given by mouth (tablets) and works by stimulating a protein called soluble guanylate cyclase (sGC). In people without HF, sGC is naturally stimulated by a chemical called nitric oxide (NO) present within the blood vessels. The stimulation of sGC is required for normal heart function. Patients with HF produce less NO, meaning they are unable to naturally stimulate sGC which leads to symptoms of HF. Therefore, stimulation of sGC by vericiguat helps to relieve symptoms of HF. If licensed, vericiguat may provide a treatment option for people with HFrEF who currently have limited therapies available.

This briefing reflects the evidence available at the time of writing and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information. A version of the briefing was sent to the company for a factual accuracy check. The company was available to comment.

PROPOSED INDICATION

Vericiguat is indicated in adult patients with heart failure with reduced ejection fraction.¹

TECHNOLOGY

DESCRIPTION

Vericiguat (BAY 1021189, MK-1242) belongs to a novel class of oral stimulators of the soluble guanylate cyclase (sGC) enzyme which induces synthesis of a signaling molecule called cyclic guanosine monophosphate (cGMP).² cGMP plays an important role in regulating various cardiovascular processes in heart failure (HF). sGC is insufficiently stimulated in patients with HF due to a reduced nitric oxide (NO) availability. Vericiguat's dual mode of action sensitises sGC to the body's own NO and can increase sGC activity in the absence of NO. It works by widening the pulmonary arteries (the blood vessels that connect the heart to the lungs), making it easier for the heart to pump blood through the lungs.²

Vericiguat is currently in clinical development for the treatment of adults with symptomatic chronic heart failure with reduced ejection fraction (HFrEF) on top of standard of care. In the phase III clinical trial (NCT02861534; VICTORIA) patients will receive a starting dose of 2.5mg vericiguat tablet taken orally once a day with food, on a background of standard of care. Dose will be uptitrated to 5mg and then to 10mg.¹

INNOVATION AND/OR ADVANTAGES

HF remains one of the leading causes of mortality and morbidity in developed countries and contributes significantly to the economic burden of modern health care systems.³ There remains a large unmet need for new therapies in the treatment of HFrEF.⁴

Reduced sGC activity associated with coronary microvascular dysfunction, cardiomyocyte stiffness, interstitial fibrosis, and ultimately, myocardial dysfunction has been suggested as a driving factor behind the progression of myocardial dysfunction in HF. These mechanisms are not directly addressed by currently established therapies that modulate neurohumoral blockade and afterload reduction. Direct NO-independent sGC stimulation is hypothesised to offer a novel approach to address the relative cGMP deficit in HF, and the sGC stimulator, vericiguat, was developed for this purpose.⁵

The phase IIb dose-finding study of vericiguat (NCT01951625; SOCRATES-REDUCED) found a clinically significant reduction in the heart hormone N-terminal pro-B-type brain natriuretic peptide (BNP), which is elevated dramatically in patients with worsening chronic HF and an improvement in left ventricular EF.⁵

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Vericiguat does not currently have Marketing Authorisation in the EU/UK for any indication.

Vericiguat is currently in phase II development for heart failure with preserved ejection fraction (HFpEF).⁶

PATIENT GROUP

DISEASE BACKGROUND

Heart failure (HF) is a clinical syndrome of symptoms (e.g. breathlessness, fatigue) and signs (e.g. oedema, crepitations) resulting from structural and/or functional abnormalities of cardiac function which lead to reduced cardiac output or high filling pressures at rest or with stress. HF may arise as a consequence of a myocardial, valvular, endocardial or arrhythmic problem (or a combination of these). HF is defined on the basis of left ventricular ejection fraction (LVEF).⁷ This is calculated as the percentage of how much blood in the left ventricle (LV) is pumped out with each contraction; a normal LVEF may be between 50% and 70%.⁸

The European Society of Cardiology defines HFrEF as the presence of signs and symptoms of HF and LVEF <40%. Differentiation of patients with HF based on LVEF is important due to different underlying aetiologies, demographics, co-morbidities and response to therapies. It is only in patients with HFrEF that therapies have been shown to reduce both morbidity and mortality.⁹

For people with HF and their family members and carers, the condition can have adverse effects on their quality of life and be a financial burden. People with HF often experience poor quality of life because of breathlessness and fatigue, and over one-third of people experience severe and prolonged depressive illness.¹⁰

CLINICAL NEED AND BURDEN OF DISEASE

In England in 2017-18, 485,561 people were recorded by GPs as having HF (prevalence rate of 0.83%).¹¹ In 2017, it was reported that 66.8% of patients are reported to have HFrEF; if applied to the 2017-18 GP figures this equates to approximately 324,355 people in England.¹²

Both the incidence and prevalence of HF increases with age, with an average age at first diagnosis of 76 years. The prevalence is expected to rise in the future as a result of an ageing population, improved survival of people with ischaemic heart disease and more effective treatments for HF.¹⁰

HF has a poor prognosis: 30-40% of people diagnosed with HF die within one year, but thereafter the mortality is less than 10% per year. Patients on GP HF registers, representing prevalent cases of HF, have a 5-year survival rate of 58%, compared with 93% in the general population.¹⁰

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

The core specialist HF multidisciplinary team should work in collaboration with the primary care team, and should include a lead physician with subspecialty training in HF, a specialist HF nurse, and a healthcare professional with expertise in specialist prescribing for HF.¹³

Implantable cardioverter defibrillators (ICDs), cardiac resynchronisation therapy (CRT) with defibrillator (CRT-D) or CRT with pacing (CRT-P) are recommended as treatment options for people with heart failure who have left ventricular dysfunction with a left ventricular ejection fraction of 35% or less.¹⁴

CURRENT TREATMENT OPTIONS

NICE recommends the following treatment options for patients with HFrEF:¹⁴

First line:

- Offer an ACE inhibitor and a beta-blocker licensed for heart failure to people who have HFrEF. Use clinical judgement when deciding which drug to start first.
- Consider an angiotensin II receptor blocker (ARB) licensed for heart failure as an alternative to an ACE inhibitor for people who have HFrEF and intolerable side effects with ACE inhibitors.
- If neither ACE inhibitors nor ARBs are tolerated, seek specialist advice and consider hydralazine in combination with nitrate for people who have HFrEF.
- Offer a mineralocorticoid receptor antagonist (MRA) in addition to an ACE inhibitor (or ARB) and beta-blocker, to people who have HFrEF if they continue to have symptoms of heart failure.

Specialist treatment:

- Specialist treatment options include ivabradine, sacubitril valsartan, hydralazine with nitrate, and digoxin.

PLACE OF TECHNOLOGY

If licensed, vericiguat may offer an additional treatment option for patients with HFrEF who currently have few effective treatments available.

CLINICAL TRIAL INFORMATION

Trial	VICTORIA, MK-1242-001, NCT02861534 ; 2016-000671-25 ; ≥18 yrs; vericiguat vs placebo; phase III
Sponsor	Merck Sharp & Dohme Corp.
Status	Completed
Source of Information	Publication ⁵ , trial registry ^{1,15}
Location	EU (incl UK), Canada, United States and other countries
Design	Randomised, placebo-controlled, parallel assignment, double-blind
Participants	n=5050; ≥ 18 yrs; History of chronic HF (New York Heart Association [NYHA] Class II-IV) on standard therapy before qualifying HF decompensation; Left ventricular ejection fraction (LVEF) of <45%; Previous HF hospitalization within 6 months prior to randomization or intravenous (IV) diuretic treatment for HF (without hospitalization) within 3 months; Brain natriuretic peptide (BNP) levels: sinus rhythm-≥ 300 pg/mL; atrial fibrillation-≥ 500 pg/mL and N-terminal pro-Brain Natriuretic Peptide (NT-proBNP) levels: sinus rhythm-≥ 1000 pg/mL; atrial fibrillation -≥ 1600 pg/mL.
Schedule	Patients randomised 1:1 to 2.5mg vericiguat or matching placebo once daily and uptitrated over 4 wks to 5.0 then 10.0mg. Patients will be evaluated every 4 mths until study completion.
Follow-up	Up to approximately 3yrs

Primary Outcomes	<ul style="list-style-type: none"> Time to first occurrence of composite endpoint of cardiovascular (CV) death or heart failure hospitalisation [Time Frame: Up to approximately 3years]
Secondary Outcomes	<ul style="list-style-type: none"> Time to the first occurrence of CV death Time to the first occurrence of HF hospitalisation Time to total HF hospitalisations Time to first occurrence of composite endpoint of all-cause mortality or HF hospitalisation Time to all-cause mortality <p>[Time Frame for all five secondary outcomes: Up to approximately 3years]</p>
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Study completion date previously reported as Sep 2019.

ESTIMATED COST

The cost of vericiguat is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance. Sacubitril valsartan for treating symptomatic chronic heart failure with reduced ejection fraction (TA388). April 2016.
- NICE technology appraisal guidance. Implantable cardioverter defibrillators and cardiac resynchronisation therapy for arrhythmias and heart failure (TA314). June 2014.
- NICE technology appraisal guidance. Ivabradine for treating chronic heart failure (TA267). November 2012.
- NICE guideline. Chronic heart failure in adults: diagnosis and management (NG106). September 2018.
- NICE quality standard. Chronic heart failure in adults (QS9). September 2018.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- No guidance identified.

OTHER GUIDANCE

- NICE medical technologies guidance. ENDURALIFE powered CRT-D devices for treating heart failure (MTG33). 2017.¹⁶

- European Society of Cardiology (ESC). European Society of Cardiology Guidelines. 2016.⁹
- Scottish Intercollegiate Guidelines Network (SIGN). SIGN 147: Management of chronic heart failure. March 2016.⁷

ADDITIONAL INFORMATION

REFERENCES

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- 6 ClinicalTrials.gov. Vericiguat | Recruiting, Not yet recruiting, Active, not recruiting, Enrolling by invitation Studies | Phase 2, 3, Not Applicable. 2019. Available from: https://clinicaltrials.gov/ct2/results?term=Vericiguat&recrs=b&recrs=a&recrs=f&recrs=d&age_v=&gndr=&type=&rslt=&phase=1&phase=2&phase=5&Search=Apply [Accessed 01 October 2019].
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