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Verquvo® (vericiguat): One-A-Day Keeps the Hospital Away

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Heart failure (HF) is defined by the American College of Cardiology as a complex clinical syndrome that is a result from any structural or functional impairment of ventricular filling or ejection of blood.[1] As a result, the heart will struggle to compensate for the impairment, and the circulation of blood becomes inadequate to meet body requirements. Heart failure is the most prominent cause of hospitalization globally, with 3.6 million cases of newly diagnosed HF patients every year.[2] In the United States of America (USA) specifically, approximately 6.2 million adults (20 years of age and older) are diagnosed with HF.[3] The Framingham Heart Study found the mortality rate following diagnosis of HF to be approximately 10% at 30 days, 20-30% at 1 year and 45-60% over 5 years of follow-up, in the USA.[4] Above all, acute HF is the most frequent cause of unintended hospital visits in patients greater than 65 years old.[5]

Heart failure is categorized into two classifications: heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF). Systolic HF, also known as HFrEF, is defined by an ejection fraction (EF) of less than 40% due to cardiomyocyte loss. As a result, the cardiac muscle of the left ventricle is unable to contract sufficiently, resulting in a decrease of oxygen-rich blood circulating throughout the body. In contrast, diastolic HF, also known HFpEF, is characterized by structural alterations, including cardiomyocyte hypertrophy and inflammation, that ultimately leads to the inability of the left ventricle to relax properly. Despite the structural changes, HFpEF maintain an EF of greater than 50%. As a result, American Heart Association (AHA) states that cardiovascular mortality is much more frequent in HFrEF than in HFpEF, as previously shown in the Framingham Heart Study.[6]

Medical advances have developed efficient and specific treatments of HFrEF by acting on different parts of the neurohumoral axis.[7] The medication classes that represent the established therapies for treating HFrEF include angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), loop diuretics, beta blockers, aldosterone antagonists, vasodilators, angiotensin receptor-neprilysin inhibitor (ARNI) and ivabradine. According to The American College of Cardiology Foundation and American Heart Association (ACCF/AHA), the above medications have been shown in randomized controlled trials (RCTs) to improve symptoms, reduce burden of hospitalization, and/or provide survival benefit.[8] Although treatments are available to manage symptoms, HFrEF patients with a worsening condition, often marked by repeated hospital visits or the need for intravenous (IV) diuretics, have limited options for stemming the disease progression.[9]

Despite achievements made in treatment, the socioeconomic burden that HF places on the healthcare system remains high due to re-hospitalization. Clinical trials have shown that approximately 50% of the patients with chronic HF are re-hospitalized within 30 days of deterioration, and an estimated 1 out of 5 patients with chronic HF die within two years.[10] The frequent hospitalizations and extended emergency room visits to receive parenteral diuretics can result in a substantial decrease in quality of life. There is still an urgent need to identify new treatment approaches to help improve the survival rate outcomes and reduce the risk of re-hospitalization in patients across all stages of HF.

Verquvo® (vericiguat) was jointly developed by Merck® and Bayer® and recently approved by the Food and Drug Administration (FDA) in January 2021, to be the first oral soluble guanylate cyclase (sGC) stimulator to treat HFrEF. More specifically, approval was indicated for reducing the risk of cardiovascular death (CVD) and HF hospitalization following initial hospitalization for HF or the need for outpatient IV diuretics in adults with symptomatic chronic heart failure (CHF) and EF less than 45%.[5]

Pharmacology

Mechanism of Action

The pathophysiology of CVD and HF includes endothelial cell dysfunction, which impairs nitric oxide (NO) production, leading to decreased NO availability and reduced cyclic guanosine monophosphate (cGMP) tissue levels.[11] Vericiguat enhances sGC sensitivity in binding endogenous NO to increase the formation of cGMP from guanosine triphosphate (GTP)—thereby restoring the NO-sGC-cGMP pathway in HFrEF. Defects in this pathway are thought to contribute to the myocardial and vascular dysfunction associated with HF.[12] This pathway has often been an underrecognized component of the CHF syndrome and has not cur-

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rently been targeted by existing HF drugs.[13]

In patients with chronic HFrEF, endothelium-mediated vasodilation is an independent predictor of cardiac death and hospitalization, consistent with the thought that endothelium-derived NO may provide a protective role for CHF.[14] Vericiguat can bypass the need for NO-mediated activation and directly stimulate sGC activation by binding to a target site on the sGC beta-subunit.[14] By using vericiguat to target the NO-sGC-cGMP pathway, it can prevent the progression of heart failure and aggravation of disease symptoms after a secondary decompensation event.[15]

Additionally, a blunted response to natriuretic peptides (NPs), most notably atrial NP (ANP) or B-type NP (BNP), is commonly observed in HFrEF. This can lead to altered production or clearance of active NPs, their binding to membrane receptors, or their intracellular effects. Log-Transformed N-Terminal Pro-Brain NP (NTproBNP) is a circulating plasma biomarker of CV function and prognosis in HF.[16] Vericiguat acts downstream of the NO-sGC-cGMP pathway to circumvent NP resistance more effectively than medications such as nesiritide and ularitide that cause undesired worsening renal function.[17]

Pharmacokinetics

Vericiguat is a weakly basic medication with a low water solubility and high intestinal permeability (class II according to the Biopharmaceutics Classification System).[17] The half-life of vericiguat is 30 hours following daily oral administration with an average steady-state C_{max} and AUC in patients with heart failure of 350 µg/L and 6,680 µg•h/L, respectively.[18] The oral bioavailability of a crushed or whole tablet of vericiguat is 93%, but the effect of high-calorie meals can greatly increase the T_{max} from 1 hour (fasted) to 4 hours (non-fasting).[18] In healthy patients, the steady-state volume of distribution is around 44 liters with extensive (98%) protein-binding.[18] Vericiguat is primarily metabolized through phase II conjugation reactions to form the major inactive metabolite, vericiguat N-glucuronide (M1), mainly through glucuronidation via uridine glucuronosyl transferase (UGT) enzymes UGT1A9 and UGT1A1.[18] About 53% of the medication was recovered in the urine and contained mostly inactive metabolite, while the 45% eliminated in the feces contained unchanged vericiguat.[18] A summary of the pharmacokinetic parameters of vericiguat can be found in **Table 1**.

Pharmacodynamics

Under physiological conditions, the enzymatic activation of sGC by NO is a crucial step in initiating a signaling cascade to convert GTP to cGMP, a key second messenger regulating cardiac contractility and diastolic function.[10] This NO-sGC-cGMP pathway becomes defective in HFrEF patients since inflammation and oxidative stress causes decreased endothelial NO bioavailability and decreased activation of sGC. Vericiguat can selectively and specifically bind to the sGC resulting in concentration-dependent cGMP production.[11] The anti-inflammatory, antiproliferative and antifibrotic properties of sGC stimulators help to reduce myocardial hypertrophy and fibrosis and decrease platelet activation.[7]

Drug Interactions

Vericiguat has not been shown to effect pharmacokinetics of other medications metabolized via UGT enzymes.[11,12] Additionally, in vitro studies have shown no clinically significant differences on vericiguat pharmacokinetics when co-administered with cytochrome P450 (CYP) substrates since.[12]

Table 1 | Select Vericiguat Pharmacokinetics[18]

Absorption	
T_{max}[a]	1 hour (fasted) 4 hours (non-fasting)
Distribution	
V_{ss}[b]	44 L
Protein Binding	98%
Metabolism	
Primary	Phase II Conjugation (Glucuronidation)
Secondary	CYP Oxidative Metabolism
Elimination	
Plasma Clearance	1.6 L/h (healthy subjects) 1.3 L/h (HFrEF subjects)
Fecal	45%
Urine	53% (inactive)

[a]Time to maximum concentration; [b]Steady state volume of distribution; [c]Half-life

Clinical Trials

Vericiguat was approved by the FDA based on two clinical trials. A phase II trial (SOCRATES-REDUCED) and phase III (VICTORIA) trial, both of which focused on HFrEF patients at a high risk of decompensation, where the diuretic and natriuretic effects of sGC stimulation were expected to produce the greatest benefit.[17] The following sections will describe these two clinical trials in further detail.

SOCRATES-REDUCED Trial[19]

The phase II SOCRATES-REDUCED (Soluble Guanylate Cyclase Stimulator In Heart Failure Patients With Reduced EF) trial looked at 456 patients with LVEF <45% and a recent episode (<4 weeks) of HF decompensation. The design of the study was a prospective, randomized, placebo-controlled, double-blind, five parallel arm global multi-center dose finding phase II trial.[19] Eligible patients were randomized 1:1:1:1:1 to 1 of 5 equally sized study groups to either receive placebo (n=92) or one of four daily target maximal doses of oral vericiguat (1.25 mg [n=91], 2.5 mg [n=91], 5 mg [n=91], 10 mg [n=91]) for 12 weeks.[19] All active treatment groups except the 1.25 mg once daily group started with 2.5 mg once daily of vericiguat in the morning, followed by a doubling of the dose in 2 week increments to reach the target dose of 5 mg or 10 mg vericiguat.[11,19]

This phase II study had the following notable inclusion criteria: history of CHF New York Heart Association (NYHA) class II -IV with ≥30 days standard HF therapy before hospitalization or IV diuretic treatment for HF without hospitalization; left ventricular (LV) EF<45% by echocardiogram; NTproBNP ≥1000 (BNP ≥300 in sinus rhythm) or NTproBNP ≥1600 (BNP ≥500 pg/mL in AF) in local routine labs with congestion; and clinically stable [no IV vasodilator >24h or IV diuretic >12h before randomization, systolic blood pressure (SBP) ≥110 and <160 mmHg, and resting heart rate (HR) ≥50 and <100 beats per minute (bpm)].[16,20] Of the 632 patients screened, 456 patients were randomized, and only 77% of the randomized patients completed the 12-week follow-up. Majority of the patients were men with a mean age of 68 years old. 60% of the patients at randomization, patients were on therapy with β-blockers (23%), MRAs (62%), ACEi (61%), ARB (23%) or diuretics (94%).[17] Mean LVEF was

29.6%, median baseline NTproBNP level was 3076 pg/mL, and mean eGFR was 58mL/min/1.73m2.[17] At baseline, 240 patients had a NYHA class of I/II and the remaining 216 with NYHA class III/IV.[19]

The primary end point of the study was change from baseline to week 12 in log-transformed NT-proBNP level.[19] Patients (n = 351) were eligible for the primary endpoint analysis which was a pooled comparison between the three vericiguat dose arms (2.5 mg, 5 mg, and 10 mg) versus placebo and evaluated the change in log-transformed NTproBNP level from baseline to 12 weeks. The 1.25 mg dose arm was not included in the pool because it was assumed to have a very minimal to no effect.[19] The primary analysis data showed no significant difference in log-transformed NTproBNP from baseline to week 12 between the pooled vericiguat group and placebo arm (geometric means: baseline at 2890 pg/mL; 12 weeks at 1932 pg/mL) and placebo (geometric means: baseline at 3955 pg/mL; 12 weeks at 2988 pg/mL) [ratio of geometric means of 0.885; 90% CI (0.73-1.08); p=0.15].[19,21] The vericiguat dose-response relationship (p=0.017) displayed that the 10 mg vericiguat arm showed greater reductions in in log-transformed NTproBNP than placebo at 12 weeks (p=0.048), although not statistically significant.[21] The results of the primary analysis showed that the plasma biomarker [NTproBNP] did not indicate any difference in the prognosis of HF between the treatment groups. **Table 2** shows the specific log -transformed values that supported this conclusion.

The secondary analyses of the primary endpoints evaluated effects of the individual vericiguat dose arms. At week 12, the vericiguat 10 mg arm showed a greater increase in LVEF as compared to placebo (3.7% versus 1.5%; p=0.02).[17,23] The rate of HF hospitalization in the 10 mg vericiguat group was 9.9% compared with 17.4% in the placebo.[19,23] Although not statistically significant, the vericiguat 10 mg arm had lower composite of CV mortality or HF hospitalization rates by week 12 as compared to placebo (p=0.53).[19] **Table 3** explores the data on the specific endpoints in greater detail in regards to the different treatment groups.

VICTORIA Trial[20]

The phase III trial known as VICTORIA (Vericiguat Global Study In Subjects With Heart Failure With Reduced Ejection Fraction) evaluated patients with worsening CHF receiving optimal standard of care treatments for their condition. In this study, a total of 5,050 patients were enrolled with the following notable inclusion criteria: ≥18 years of age having CHF NYHA class II-IV, LVEF <45%, and guideline-directed HF therapy]; recent HF hospitalization or IV diuretic use; elevated NTproBNP ≥1000 pg/ml (≥1600 pg/ml if atrial fibrillation [AF]) or BNP ≥300 pg/ml (≥500 pg/ml if AF)]; and are clinically stable (SBP≥100 mm Hg and no IV diuretics for 24 hours).[22] The main exclusion criteria included having symptomatic hypotension or SBP<100 mmHg, use of long-acting nitrates or phosphodiesterase type 5 (PDE5) inhibitors, or having an eGFR <15 mL/min.[20]

The participants were randomized in a 1:1 ratio to receive either vericiguat 2.5 mg once daily, up-titrated to 5 mg and then 10 mg at 2-week intervals (n = 2,526) or placebo (n = 2,524).[17] The median medication dose was 9.2 mg in the vericiguat group and 9.2 mg in the placebo group. After a year, 90.3% of the patients received the 10 mg target dose (89.2% in the vericiguat group and 91.4% in the placebo group).[24] Most of the patients were men (76%) with a mean age of 67.3 years old. Sixty percent (60%) of the patients at randomization were on triple therapy with β-blockers, mineralocorticoid receptor antagonists (MRA), and either an angiotensin-converting enzyme inhibitor (ACEi), angiotensin II receptor blocker (ARB) or sacubitril-valsartan.[17] Majority of the patients had NYHA class II (59%) or NYHA class III (40%), median baseline NTproBNP level of 3377 pg/mL, and a mean EF of 28.9%.[25]

The primary outcome, CV death or HF hospitalization, occurred in 35.5% of the vericiguat group compared with 38.5% of the placebo group [HR 0.90; 95% CI (0.82–0.98); p= 0.019].[17] More specifically, at the median 10.8-month follow-up time frame, patients on vericiguat had a lower incidence of CV death or first HF hospitalization [HR 0.90; 95% CI (0.82–0.98); p=0.02].[17] However, there was no significant reduction in all-cause mortality with vericiguat compared to placebo (20.3% versus 21.2%; p=0.38).[24] Vericiguat appears less effective among the subgroups of patients in the highest quartile of NTproBNP levels with >5314 pg/L [HR 1.16; 95% CI (0.99-1.35)], patients ≥75 years old [HR 1.04; 95% CI (0.88-1.21)], patients with eGFR 15–30 mL/min/1.73 m2 [HR 1.06; 95% CI (0.83-1.34)], and/or patients with LVEF ≥40% [HR 1.05; 95% CI (0.81-1.36)].[17,24] On the other hand, vericiguat appears more effective in patients with lower NTproBNP levels >1556 to ≤2816 pg/L [HR 0.73; 95% CI (0.60-0.90)], patients <65 years of age [HR 0.81; 95% CI (0.70-0.95)], patients with eGFR >30 to ≤60 mL/min/1.73 m2 [HR 0.84; 95% CI (0.73-0.96)], and/or patients with LVEF <35% [HR 0.88; 95% CI (0.79-0.97)].[17,24] This data indicates that high-risk baseline characteristics, such as advanced age and lower renal function can negatively affect treatment responses. Further research is needed to confirm whether patients with higher LVEF percentages and NTproBNP levels correlate to having HF that is too advanced for a favorable effect of vericiguat. **Tables 2 and 3** summarize the primary and secondary endpoints of the trial respectively. The authors concluded that results of the VICTORIA trial showed that vericiguat was superior to placebo at effectively reducing the risk of CV death or hospitalization due to HF.

Table 2 | Summary of Primary Outcomes[16,26]

Trial	Treatment Arms	Endpoint	Results	Confidence Interval	P-Value
SOCRATES-REDUCED	Vericiguat[a] (n=364) Placebo (n=92)	Change in log-transformed NTproBNP level from baseline to 12 weeks	Baseline: 2890 pg/mL 12 Weeks: 1932 pg/mL Baseline: 3955 pg/mL 12 Weeks: 2988 pg/mL	90% CI (0.73-1.08)	0.15
VICTORIA	Vericiguat[b] (n=2526) Placebo (n=2524)	First occurrence of HF hospitalization or CV death	897 (35.5%) 972 (38.5%)	95% CI (0.82-0.98)	0.019

[a]Vericiguat pooled treatment groups (1.25mg, 2.5mg, 5mg, 10mg daily); [b]Target dose 10mg daily

Table 3 | Summary of Secondary Outcomes[16,26]

Trial	Outcome	Vericiguat 1.25mg (n=91)	Vericiguat 2.5mg (n=91)	Vericiguat 5mg (n=91)	Vericiguat 10mg (n=91)	Vericiguat[a] (n=364)	Placebo (n=92)	95% CI	P Value
SOCRATES-REDUCED	CV Death*	5 (5.5%)	4 (4.4%)	2 (2.2%)	4 (4.4%)	10 (2.75%)	3 (3.3%)	0.30—1.34	—
	First event of HF Hospitalization*	18 (19.8%)	20 (22%)	10 (11%)	9 (9.9%)	50 (13.7%)	16 (17.4%)	0.25—1.16	—
	All-cause mortality**	6 (6.5%)	5 (5.5%)	3 (3.3%)	4 (4.4%)	12 (3.2%)	3 (3.3%)	0.3—1.16	—

Trial	Outcome	Vericiguat (target dose 10mg daily) (n=2526)	Placebo (n=2524)	95% CI	P Value
VICTORIA	CV Death	414 (16.4%)	441 (17.5%)	0.81—1.06	0.269
	First event of HF hospitalization	691 (27.4%)	747 (29.6%)	0.81—1.00	0.048
	Total HF hospitalization events[b]	1223 (38.3%)	1336 (42.4%)	0.84—0.99	0.023
	All-cause mortality	512 (20.3%)	534 (21.2%)	0.84—1.07	0.377
	First event all-cause mortality or HF hospitalization	957 (37.9%)	1032 (40.9%)	0.83—0.98	0.021

[a]Vericiguat pooled treatment groups (1.25mg, 2.5mg, 5mg, 10mg daily); [b]Sum of first and recurrent events per 100 patient-years; *Up to 12 weeks; **Up to 16 weeks

Adverse Effects

Vericiguat was well tolerated in all studies, since most adverse effects were of mild-moderate severity.[27] In the VICTORIA trial, a slightly lower percentage of patients in the vericiguat group experienced a SAE as compared to the placebo group (32.8% versus 34.8%). This holds true for the SOCRATES-REDUCED trial as well, where the pooled treatment groups of vericiguat overall experienced a lower percent of SAE compared with placebo (32.7% versus 39.1%). Both the VICTORIA and SOCRATES -REDUCED trials defined a SAE as a medical occurrence, at any dose, that results in any of the following outcomes: death or significant disability; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); congenital defect; and/or another medically important SAE as determined by the investigator.[16] Vericiguat drug tolerability was further confirmed by an 89% rate of target dose achievement.[17]

In VICTORIA, the most commonly observed AE occurring at a frequency ≥ 5% as compared to placebo were gastrointestinal (GI) disorders (25.3%), hypotension (15.4%) and anemia (7.6%).[16,26] The SOCRATES-REDUCED trial observed an AE≥ 5% with hypotension in the pooled vericiguat treatment groups versus placebo (8% versus 6.5%).[16,26] A comparison of the top AEs between the VICTORIA trial and SOCRATES-REDUCED trial can be seen in Table 4.

Hypotension was more frequently reported in the vericiguat group than the placebo group in both trials. Comparable results were seen between orthostatic hypotension (1.3% versus 1.0%) and symptomatic hypotension (9.1% versus 7.9%).[11] Although the reports of treatment-related hypotension were higher in the vericiguat 10 mg group, hypotension in general occurred for most of the members while still on the 2.5 mg dose before titrating up to 10 mg.[23]

Contraindications and Toxicity

Based solely on animal reproduction study data, vericiguat is contraindicated in pregnant patients.[12] Vericiguat is also contraindicated in patients who use other sGC stimulators.[3] Treatment should not be initiated in HF patients with current symptomatic hypotension or SBP <100 mmHg since this was not studied in clinical trials.[11] Similarly, concomitant use of PDE5 inhibitors with vericiguat has not been studied in patients with HF and is not recommended due to the potential increased risk for symptomatic hypotension.[11] The potential for symptomatic hypotension should be considered in patients with hypovolemia, severe obstruction in LV outflow, history of hypotension, hypotension at rest, autonomic dysfunction, or concomitant treatment with antihypertensives and/or organic nitrates.[11] The FDA label for vericiguat contains a black box warning indicating its potential to cause embryo-fetal toxicity. Studies in animals have shown reproductive toxicity in presence of maternal toxicity, but no effect on human fertility.[11] The animal reproduction studies with vericiguat showed an increased incident of fetal malformations of the major vessels and heart (cardiac ventricular septal defect along with truncus arteriosus communis), as well as increased miscarriages, abortions and resorptions.[12] Postnatal toxicity studies involving oral administration of vericiguat during gestation and lactation caused maternal toxicity (decreased food consumption and body weight loss), resulting in increased fetal mortality.[12]

Dosage and Administration

Vericiguat is available as an oral, once-daily, film-coated tablet in the strengths 2.5 mg, 5 mg, and 10 mg. The recommended starting dose of vericiguat is one tablet of 2.5 mg by mouth once daily with food.[12] It is recommended to take vericiguat at the same time each day with food to help both with absorption and the GI AEs commonly experienced. The SOCRATES-REDUCED trial suggests that there is a benefit towards titration to vericiguat 5 mg or 10 mg once daily dose, while maintaining safety, due to the observed NP trajectory, HF clinical events, HF hospitalization rates, and LVEF at 12 weeks of treatment.[19] Therefore, patients should double the dose of vericiguat every 2 weeks, as tolerated,

Table 4 | Top Adverse Effects[16,19,26]

Trial	Adverse Effect	Vericiguat 1.25mg (n=91)	Vericiguat 2.5mg (n=91)	Vericiguat 5mg (n=91)	Vericiguat 10mg (n=91)	Vericiguat[a] (n=364)	Placebo (n=92)
SOCRATES-REDUCED	Hypotension	5 (5.5%)	6 (6.7%)	4 (4.4%)	14 (15.4%)	29 (8.0%)	6 (6.5%)
	Anemia	1 (1.1%)	0	0	1 (1.1%)	2 (0.6%)	1 (1.1%)
	GI Disorder[b]	0	2 (2.2%)	2 (2.2%)	2 (2.2%)	6 (1.7%)	4 (4.4%)
	SAE[c]	31 (34.1%)	35 (38.9%)	24 (26.4%)	29 (31.9%)	119 (32.7%)	36 (39.1%)

Trial	Outcome	Vericiguat (target dose 10mg daily) (n=2526)	Placebo (n=2524)
VICTORIA	Hypotension	389 (15.4%)	355 (14.1%)
	Anemia	192 (7.6%)	143 (5.7%)
	GI Disorder[d]	639 (25.3%)	547 (21.7%)
	SAE[c]	826 (32.8%)	876 (34.8%)

[a]Vericiguat pooled treatment groups (1.25mg, 2.5mg, 5mg, 10mg daily); [b]Includes abdominal pain, diarrhea, GI hemorrhage, hernia, obstruction, or mechanical ileus; [c]Serious adverse effects including death, significant disability, inpatient hospitalization, immediate risk of dying, or congenital defect; [d]Includes nausea, dyspepsia, vomiting, or gastroesophageal reflux disease

to reach the maximum target maintenance dose of vericiguat 10 mg once daily.[11] If the patient starts to experience tolerability issues, such as symptomatic hypotension or SBP <90 mmHg, temporarily down-titrating or discontinuing vericiguat is recommended.[11] More specifically, decreasing the dose is recommended if the patient is on vericiguat 5 mg or 10 mg, and discontinuation is recommended if the patient is on vericiguat 2.5 mg and has symptomatic hypotension.[11] If the patient is unable to swallow the tablet whole, vericiguat may be crushed and mixed with water immediately before oral administration.[12]

Special Populations

Pediatrics & Geriatrics

The safety and efficacy of vericiguat has yet to be established in the pediatric population, including children and adolescence less than 18 years of age. There should remain caution of use in this population. Meanwhile, elderly patients do not require any dose adjustments of vericiguat.[11,12]

Pregnancy & Breastfeeding

There is no data available regarding the use of vericiguat in pregnant women. However based on animal reproduction studies, there is a risk for fetal harm when vericiguat is administered to a pregnant woman and is contraindicated during pregnancy.[12] Similarly, there is no data regarding the effect of vericiguat on milk production, the effect on the breastfed infant, or the presence of vericiguat in human milk.[12] However, animal studies have shown the presence of the metabolite in milk at concentrations approximately 12% maternal plasma concentrations when administered to lactating rats at a dose of 1 mg/kg.[12] Due to the high potential for SAEs in breastfed infants, women should be advised not to breastfeed during treatment with vericiguat.[12] Pregnancy tests should be performed to verify the pregnancy status in women prior to vericiguat initiation. Additionally, females of reproductive potential should be advised to use effective contraception during treatment and for one month after the final dose.[12]

Renal & Hepatic Impairment

Vericiguat has no effects on renal function or troponin release and requires no dose adjustment if the eGFR is greater than 15 mL/min/1.73m2.[11,23] Vericiguat is not recommended for dialysis patients and should not be initiation in patients with an eGFR less than 15 mL/min/1.73 m2.[11] Additionally, while there is no dose adjustment is needed in patients with mild to moderate hepatic impairment, vericiguat is not recommended in patients with severe hepatic impairment.[11] Vericiguat is generally well tolerated and does not require any monitoring of electrolytes or renal function.[22] Hemodialysis is unlikely to be beneficial in vericiguat overdose given its high degree of protein binding.[12]

Cost and Availability

Currently, vericiguat is available as a brand name prescription drug only. Sold under the brand name Verquvo™ by Merck & Co., vericiguat costs $20.96 per tablet or $628.80 for a month (30 days) supply.[28] An increase or decrease in vericiguat strength does not provide any monetary benefit or deficit. All three strengths are available by the carton in a blister pack format with 10 tablets per card.[12] This novel medication can only be bought with cash since no insurance companies have added this medication as part of their covered formulary at the time of completing this review. Merck & Co. does offer a Patient Assistance Program (PAP) for Verquvo™, known as the Merck Access Program, where eligibility is determined on a case-by-case situation.

Clinical Implications

Regardless of vericiguat's pharmaceutical benefit, the cost of the drug will be an important factor in determining its use in patient care. According to the Centers for Disease Control and Prevention (CDC), the reduction in health plan copays for prescription drugs could result in significant cost savings in the prevention of acute events, such as hospitalizations, and reduce the progression of major chronic [HF] conditions.[29] There is also a need in determining the use of vericiguat in patients at different risks of HF hospitalization. Further clinical trials of vericiguat are needed to determine its role in lower-risk HF populations and how it differs in comparison. No pharmacologic therapy has been approved to reduce morbidity/mortality in HFpEF patients, and previous attempts to increase cGMP with nitrates have yielded

suboptimal results. There is still an ongoing need to conduct more studies in the future to determine if vericiguat also has a role in the treatment of HFpEF.

Conclusion

There continues to be a medical need to find additional HF treatments using different mechanisms of actions to target HFrEF. Insurance claims in the US reveal that up to 33% of HFrEF patients experience a worsening event (defined as HF hospitalization or IV diuretic use) within a year of the initial claim.[11] Further observation is warranted to determine how Verquvo™ (vericiguat) could challenge or compliment these current standard HF treatments in reducing hospitalizations and IV diuretic needs. Moving forward, if vericiguat is well-tolerated and cost-effective, it could become an asset in reducing the socioeconomic burden that HF hospitalization imposes on the healthcare system worldwide.

References

1. "Heart Failure." American College of Cardiology, www.acc.org/education-and-meetings/products-and-resources/guideline-education/heart-failure.
2. Simmonds, Steven J et al. "Cellular and Molecular Differences between HFpEF and HFrEF: A Step Ahead in an Improved Pathological Understanding." Cells vol. 9,1 242. 18 Jan. 2020, doi:10.3390/cells9010242
3. Merck & Co., Inc., et al. "Merck Announces U.S. Fda Approval of Verquvo® (Vericiguat)." Merck.com, 5 Aug. 2021, www.merck.com/news/merck-announces-u-s-fda-approval-of-verquvo-vericiguat/.
4. Levy D, Kenchaiah S, Larson MG, Benjamin EJ, Kupka MJ, Ho KK, et al. Long-term trends in the incidence of and survival with heart failure. N Engl J Med. 2002;347:1397–402.
5. Mattia, Arrigo. "Vericiguat in Heart Failure – Who Benefits the Most?" Cardiovascular Medicine, EMH Media, 10 Mar. 2021, cardiovascmed.ch/article/doi/CVM.2021.w10049.
6. Vergaro, Giuseppe, et al. "Noncardiac versus Cardiac Mortality in Heart Failure With PRESERVED, Midrange, and Reduced Ejection Fraction." Journal of the American Heart Association, 5 Oct. 2019, www.ahajournals.org/doi/full/10.1161/JAHA.119.013441.
7. Bytyçi, Ibadete, and Gani Bajraktari. "Mortality in heart failure patients." Anatolian journal of cardiology vol. 15,1 (2015): 63-8. doi:10.5152/akd.2014.5731
8. Yancy CW, Januzzi JL Jr, Allen LA, Butler J, Davis LL, Fonarow GC, Ibrahim NE, Jessup M, Lindenfeld J, Maddox TM, Masoudi FA, Motiwala SR, Patterson JH, Walsh MN, Wasserman A. 2017 ACC expert consensus decision pathway for optimization of heart failure treatment: answers to 10 pivotal issues about heart failure with reduced ejection fraction: a report of the American College of Cardiology Task Force on Clinical Expert Consensus Decision Pathways. J Am Coll Cardiol 2018;71:201-30.
9. "Vericiguat Improves Outcomes in Patients with Worsening Heart Failure." Edited by Dave Fornell, DAIC, 29 Mar. 2020, www.dicardiology.com/content/vericiguat-improves-outcomes-patients-worsening-heart-failure.
10. "VERQUVO (Vericiguat) for the Treatment of Heart Failure with Reduced Ejection Fraction." Clinical Trials Arena, 4 Aug. 2021, www.clinicaltrialsarena.com/projects/verquvo-vericiguat/
11. BUCKINGHAM, Liina. "Verquvo." European Medicines Agency, 27 July 2021, www.ema.europa.eu/en/medicines/human/EPAR/verquvo.
12. HIGHLIGHTS of Prescribing INFORMATION VERQUVO Safely and ... www.accessdata.fda.gov/drugsatfda_docs/label/2021/214377s000lbl.pdf.
13. "The Role of VERICIGUAT in the Expanding Realm of Heart FAILURE PHARMACOTHERAPY: An Overview of the VICTORIA Trial." American College of Cardiology, www.acc.org/latest-in-cardiology/articles/2020/07/08/08/49/the-role-of-vericiguat-in-the-expanding-realm-of-hf-pharmacotherapy.
14. Simmonds, Steven J, et al. "Cellular and Molecular Differences between Hfpef and Hfref: A Step Ahead in an Improved Pathological Understanding." Cells, MDPI, 18 Jan. 2020, www.ncbi.nlm.nih.gov/pmc/articles/PMC7016826/.
15. Verquvo, a New Drug for Heart Failure, Is Approved in the EU, and China Is Under Review https://inf.news/en/health/43f506875d3bcb22f1565011569671dc.html
16. "Phase IIb Safety and Efficacy Study of Four Dose Regimens of bay1021189 in Patients with Heart Failure with Reduced Ejection Fraction Suffering from Worsening Chronic Heart Failure (Socrates-Reduced) - Study Results." Study Results - ClinicalTrials.gov, clinicaltrials.gov/ct2/show/results/NCT01951625.
17. Aimo, A., Castiglione, V., Vergaro, G. et al. The place of vericiguat in the landscape of treatment for heart failure with reduced ejection fraction. Heart Fail Rev (2021). https://doi.org/10.1007/s10741-021-10146-1
18. "Vericiguat." Uses, Interactions, Mechanism of Action | DrugBank Online, go.drugbank.com/drugs/DB15456.
19. Gheorghiade, Mihai et al. "Effect of Vericiguat, a Soluble Guanylate Cyclase Stimulator, on Natriuretic Peptide Levels in Patients With Worsening Chronic Heart Failure and Reduced Ejection Fraction: The SOCRATES-REDUCED Randomized Trial." JAMA vol. 314,21 (2015): 2251-62. doi:10.1001/jama.2015.15734
20. Armstrong, Paul W., et al. "A MULTICENTER, Randomized, Double-Blind, Placebo-Controlled Trial of the Efficacy and Safety of the Oral SOLUBLE Guanylate CYCLASE Stimulator: THE VICTORIA Trial." JACC: Heart Failure, Elsevier, 11 Oct. 2017, www.sciencedirect.com/science/article/pii/S2213177917305620.
21. Team, PracticeUpdate Editorial. "Vericiguat Fails to Meet Primary Endpoint, but Meets Secondary Endpoints in Worsening Chronic Heart Failure with Reduced Ejection Fraction." PracticeUpdate, www.practiceupdate.com/content/vericiguat-fails-to-meet-primary-endpoint-but-meets-secondary-endpoints-in-worsening-chronic-heart-failure-with-reduced-ejection-fraction/32074.
22. "Vericiguat Global Study in Subjects with Heart Failure with Reduced Ejection Fraction." American College of Cardiology, 15 May 2020, www.acc.org/latest-in-cardiology/clinical-trials/2020/03/26/19/43/victoria.
23. Brauser, Deborah. "Vericiguat Misses End Point of Lowering Nt-Probnp in Chronic Hf." Medscape, Medscape, 17 Nov. 2016, www.medscape.com/viewarticle/854130.
24. Armstrong, P. W., Al., E., Group*, for the V. I. C. T. O. R. I. A. S., Author AffiliationsFrom the Canadian VIGOUR Centre, Burnett, J. C., Others, P. J. B. and, ATTACC, T., REMAP-CAP, T., Others, N. B. and, J. Lopez Bernal and Others, & Lange, B. (2020, May 14). Vericiguat in patients with heart failure and Reduced Ejection Fraction: NEJM. New England Journal of Medicine. https://www.nejm.org/doi/full/10.1056/NEJMoa1915928.
25. Pieske, B., Patel, M. J., Westerhout, C. M., Anstrom, K. J., Butler, J., Ezekowitz, J., Hernandez, A. F., Koglin, J., Lam, C. S. P., Ponikowski, P., Roessig, L., Voors, A. A., O'Connor, C. M., & Armstrong, P. W. (2019, December 9). Baseline features of the VICTORIA (Vericiguat global study in subjects with heart failure with Reduced ejection FRACTION) trial. Wiley Online Library. https://onlinelibrary.wiley.com/doi/pdf/10.1002/ejhf.1664.
26. Mihai Gheorghiade, MD. "Vericiguat and Worsening Chronic Heart Failure." JAMA, JAMA Network, 1 Dec. 2015, jamanetwork.com/journals/jama/fullarticle/2469195.
27. Boettcher, M., Gerisch, M., Lobmeyer, M. et al. Metabolism and Pharmacokinetic Drug –Drug Interaction Profile of Vericiguat, A Soluble Guanylate Cyclase Stimulator: Results From Preclinical and Phase I Healthy Volunteer Studies. Clin Pharmacokinet 59, 1407–1418 (2020). https://doi.org/10.1007/s40262-020-00895-x
28. "Verquvo Prices, Coupons & Patient Assistance Programs." Drugs.com, www.drugs.com/price-guide/verquvo.
29. Neiman AB, Ruppar T, Ho M, et al. CDC Grand Rounds: Improving Medication Adherence for Chronic Disease Management — Innovations and Opportunities. MMWR Morb Mortal Wkly Rep 2017;66. DOI: http://dx.doi.org/10.15585/mmwr.mm6645a2external icon.

Personalized Medicine Corner

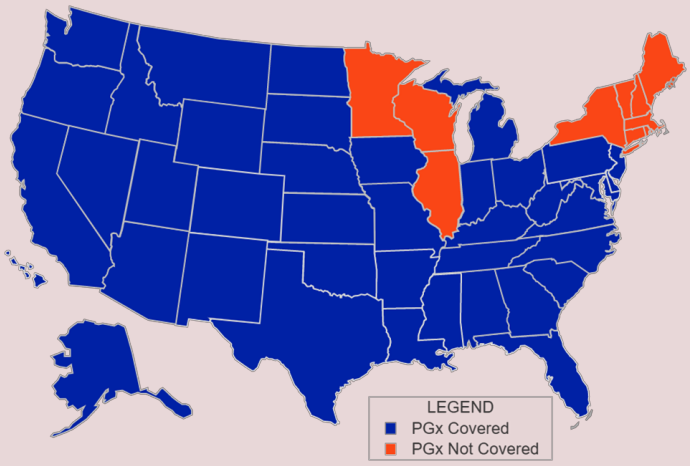
Update to Medicare Coverage for Pharmacogenomic Testing

Lauren Lemke, PharmD, BCPS

Cost is often cited as a major barrier to ordering pharmacogenomic (PGx) testing.[1] Over the years, the cost of PGx testing has fallen from thousands of dollars to a few hundred dollars for a commercial panel of pharmacogenes.[2] Even so, this is still cost prohibitive for many patients. Coverage of PGx testing by third party payers would ease the financial burden for patients and make PGx testing more widely accessible.

The first sign of reimbursement for testing came in 2009, when Medicare announced a National Coverage Determination (NCD) for CYP2C9 and VKORC1 testing to guide warfarin therapy.[3] The next major milestone occurred a decade later in 2019 when UnitedHealthcare (UHC) became one of the first major commercial insurers to cover PGx testing for anxiety and depression.[4] In 2020 several Medicare Administrative Contractors (MACs), who manage Medicare A/B claims for smaller geographical regions, approved Local Coverage Determinations (LCDs) to comprehensively cover PGx testing. Florida's MAC, First Coast Service Options (FCSO), joined with a proposed LCD in June of 2021. The PGx team at UF Health ceased the opportunity to provide constructive feedback to FCSO on how to optimize their coverage policy. After reviewing comments and incorporating our feedback, FCSO approved the LCD; it went into effect in December 2021.[5] With the approval of FCSO's LCD, only 2 of the 12 MACs have not added coverage for PGx testing (**Figure 1**).

Figure 1| Medicare Local Coverge of Pharmacogenomic Testing



FCSO's LCD succinctly includes the covered indications, limitations, and provider qualifications for PGx testing. The text for covered indications reads:

"Pharmacogenetics testing will be considered medically reasonable and necessary if:

1. The patient has a condition where clinical evaluation has determined the need for a medication that has a known gene-drug interaction(s) for which the test results would directly impact the drug management of the patient's condition; **AND**
2. The test meets evidence standards for genetic testing as evaluated by a scientific, transparent, peer-reviewed process and determined to demonstrate actionability in clinical decision making by CPIC guideline level A or B; or is listed in the FDA table of known gene-drug interactions where data support therapeutic recommendations or a potential impact on safety or response or the FDA label."

Briefly, FCSO will cover testing for medications subject to CPIC guidelines, listed in the FDA's Table of Pharmacogenetic Associations, or with PGx information in their FDA label—over 150 medications in total. Among these include common medication classes such as proton pump inhibitors, nonsteroidal anti-inflammatory drugs, opioids, selective serotonin reuptake inhibitors, and antipsychotics. Testing will be covered for patients already on one of these medications and for those whom one of the medications is being considered.

Approval of this policy expands access to PGx testing to 4.68 million Floridians—over 20% of the state's population—who are Medicare beneficiaries.[6,7] This will hopefully eliminate a previously significant barrier to the adoption of PGx into routine clinical care for many patients of UF Health and other systems throughout Florida.

References

1. Jameson A, Fylan B, Bristow GC, et al. What Are the Barriers and Enablers to the Implementation of Pharmacogenetic Testing in Mental Health Care Settings? Frontiers Genetics. 2021;12:740216.
2. Patient Information. OneOme. Accessed 1/10/22.
3. NCD 90.1: Pharmacogenomic Testing for Warfarin Response. Medicare Coverage Database. CMS.gov. Accessed 1/10/22.
4. Policy Number 2019T0587E: Pharmacogenomic Testing. United Healthcare Commercial Plans. https://www.uhcprovider.com/content/dam/provider/docs/public/policies/index/commercial/pharmacogenetic-testing-10012019.pdf#nameddest=soc
5. LCD L39073: Pharmacogenomics Testing. Medicare Coverage Database. CMS.gov. Accessed 1/10/22.
6. Medicare Monthly Enrollment. From Data.CMS.gov. Accessed 1/10/22.
7. Florida. United States Census Bureau. Accessed 1/10/22.

Drug Update:
New Indications and Dosage Forms
January 2022

Cibinqo® (abrocitinib) Tablet

New Molecular Entity: Janus kinase (JAK) inhibitor indicated for the treatment of adults with refractory, moderate-to-severe atopic dermatitis whose disease is not controlled with other systemic drug products, including biologics

Quviviq® (daridorexant) Tablet

New Molecular Entity: Orexin receptor antagonist indicated for the treatment of insomnia in adults characterized by difficulties with sleep onset and/or sleep maintenance; controlled substance schedule pending review

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