PDL DRUG REVIEW

Proprietary Name: Verquvo®
Common Name: vericiguat
PDL Category: Heart Failure Agents

Summary

Pharmacology/Usage: Vericiguat, the active ingredient of Verquvo®, is a soluble guanylate cyclase stimulator. Soluble guanylate cyclase (sGC) is an important enzyme in the nitric oxide (NO) signaling pathway. When NO binds to sGC, the enzyme catalyzes the synthesis of intracellular cyclic guanosine monophosphate (cGMP), a second messenger that plays a role in the regulation of vascular tone, cardiac contractility, and cardiac remodeling. Heart failure is associated with impaired synthesis of NO and decreased activity of sGC, which may contribute to myocardial and vascular dysfunction. By directly stimulating sGC, independently of and synergistically with NO, vericiguat augments levels of intracellular cGMP, leading to smooth muscle relaxation and vasodilation.

Indication: To reduce the risk of cardiovascular death and heart failure (HF) hospitalization following a hospitalization for heart failure or need for outpatient IV diuretics, in adults with symptomatic chronic HF and ejection fraction less than 45%.

There is no pregnancy category for this medication; however, the risk summary indicates that based on data from animal studies, Verquvo® may cause fetal harm when administered to a pregnant woman and is contraindicated during pregnancy. There are no available data with use in pregnant women. If a patient becomes pregnant while receiving Verquvo®, healthcare providers should report exposure by calling 1-877-888-4231. Verify the pregnancy status in females of reproductive potential prior to starting Verquvo®. Advise females of reproductive potential to use effective contraception during treatment and for one month after the final dose. The safety and efficacy of use in the pediatric population have not been established.

Dosage Form: Film-Coated Tablets: 2.5mg, 5mg, 10mg

Recommended Dosage: In females of reproductive potential, obtain a pregnancy test prior to starting treatment.

Start at 2.5mg PO QD with food. Double the dose about every 2 weeks to reach the target maintenance dose of 10mg QD, as tolerated by the patient. If not able to swallow tablets whole, Verquvo® may be crushed and mixed with water immediately before administration.

Dose adjustments are not required with mild or moderate hepatic impairment, but use has not been studied in patients with severe hepatic impairment. Dose adjustments are not required in patients with an estimated glomerular filtration rate (eGFR) ≥15ml/min/1.73m^2 who are not on dialysis. Use has not been studied in patients with eGFR <15ml/min/1.73m^2 at treatment initiation or on dialysis.

Drug Interactions: Use is contraindicated in patients with concomitant use of other soluble guanylate cyclase stimulators.

Concomitant use of Verquvo® with PDE-5 inhibitors is not recommended because of the potential for hypotension.

Box Warning: Verquvo® has a box warning regarding embryo-fetal toxicity. In females of reproductive potential, pregnancy must be excluded before the start of treatment. The warning adds that to prevent pregnancy, females of reproductive potential must use effective forms of contraception during treatment and for one month after stopping treatment. Do not administer Verquvo® to a pregnant female because it may cause fetal harm.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Verquvo®) minus reported % incidence for placebo. Please note that an incidence of 0% means the incidence was the same as or less than placebo.* The most frequently reported adverse events included hypotension (1%) and anemia (3%).

Contraindications: In patients with concomitant use of other soluble guanylate cyclase stimulators; In pregnancy

Manufacturer: Merck

Analysis: The efficacy of Verquvo® was assessed in a randomized, double-blind, placebo-controlled, parallel-group, event-driven, multicenter study (VICTORIA) that included adult patients (N=5,050) with symptomatic chronic heart failure (New York Heart Association [NYHA] class II-IV) and left ventricular ejection fraction (LVEF) less than 45% following a worsening heart failure event. A worsening heart failure event was defined as heart failure hospitalization within 6 months before randomization or use of outpatient IV diuretics for heart failure within 3 months before randomization.

Adults included in the study had a mean age of 67 years, while most were male (76%) and Caucasian (64%). At randomization, 59% of patients were NYHA Class II, 40% were NYHA Class III, and 1% were NYHA Class IV. The mean left ventricular ejection fraction (LVEF) was 29%; about 50% of all patients had an ejection fraction <30% and 14% had an ejection fraction between 40% and 45%. The most frequently reported medical history conditions other than heart failure included hypertension (79%), coronary artery disease (58%), hyperlipidemia (57%), diabetes mellitus (47%), atrial fibrillation (45%), and myocardial infarction (42%). At randomization, the mean eGFR was 62ml/min/1.73m^2.

At baseline, 93% of patients were on a beta-blocker, 73% were on an ACE inhibitor or ARB, 70% were on a mineralocorticoid receptor antagonist (MRA), 15% were on a combination of an angiotensin receptor and neprilysin inhibitor (ARNI), 28% had an implantable cardiac defibrillator, and 15% had a biventricular pacemaker. In addition, 91% were treated with 2 or more heart failure medications (beta-blocker, any renin-angiotensin system [RAS] inhibitor, or mineralocorticoid receptor antagonist) and 60% were treated with all 3. At baseline, 6% of patients were on ivabradine and 3% were on a sodium glucose co-transporter 2 (SGLT2) inhibitor.

The primary endpoint of this study was a composite of time to first event of cardiovascular (CV) death or hospitalization for heart failure. The median follow-up for the primary endpoint was 11 months. Results suggested that Verquvo® was superior to placebo in reducing the risk of CV death or heart failure hospitalization based on a time-to-event analysis (HR 0.90, p=0.019). Over the course of the study, there was a 4.2% annualized absolute risk reduction (ARR) with Verquvo® compared with placebo. The treatment effect reflected a reduction in both cardiovascular death and heart failure hospitalization. Results can be seen in the table below, which was adapted from the prescribing information.

Outcome	Verquvo® (N=2526)		Placebo (n=2524)		Treatment Comparison		
	n (%)	Event Rate: % of patients/year	n (%)	Event Rate: % of patients/year	HR	p-value	ARR
Composite of CV death or HF hospitalization*	897 (35.5%)	33.6	972 (38.5%)	37.8	0.90	0.019	4.2
Secondary Endpoints							
Cardiovascular Death	414 (16.4%)	12.9	441 (17.5%)	13.9	0.93		

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	n (%)	Event Rate: % of patients/year	n (%)	Event Rate: % of patients/year	HR	p-value	ARR
Heart Failure hospitalization	691 (27.4%)	25.9	747 (29.6%)	29.1	0.90		

HR- Hazard Ratio; ARR- Absolute Risk Reduction

*For patients with multiple events, only the first event contributing to the composite endpoint is counted.

Secondary endpoints other than the components of the primary endpoint were tested according to a hierarchical testing procedure to control the family wise type 1 error rate. Verquvo® was superior to placebo in reducing the risk of total (first and recurrent) events of HF hospitalization and the first occurrence of either all-cause mortality or HF hospitalization. Results can be seen in the table below, which was adapted from the prescribing information.

Outcome	Verquvo® (N=2526)		Placebo (N=2524)		Hazard Ratio
	n (%)	Rate	n (%)	Rate	
Total events of heart failure hospitalization	1,223	38.3*	1,336	42.4*	0.91 #
Composite of all-cause mortality or HF hospitalization	957 (37.9%)	35.9^	1,032 (40.9%)	40.1^	0.90 ~
All-cause mortality	266 (10.5%)		285 (11.3%)		
Heart Failure hospitalization	691 (27.4%)		747 (29.6%)		

*Event rate (total events, including recurrent events in the same patient, per 100 patient years at risk)

^ Incidence rate (total patients with ≥1 event per 100 patient years at risk)

HR based on an Andersen-Gill Model ~ HR based on a Cox proportional hazards model

Place in Therapy: Verquvo®, an oral soluble guanylate cyclase stimulator, is indicated to reduce the risk of cardiovascular death and heart failure hospitalization following a hospitalization for heart failure or need for outpatient IV diuretics, in adults with symptomatic chronic heart failure and ejection fraction less than 45%. In a clinical study assessing the safety and efficacy vericiguat, the primary endpoint of death from cardiovascular causes or hospitalization for heart failure was significantly reduced in the Verquvo® group as compared with placebo.

A 2020 systematic review and network meta-analysis (NMA) by Aimo et al[2] included 6 randomized controlled trials (4 were phase 3 studies) or subgroup analyses from randomized controlled trials to assess the effects of sacubitril/valsartan, vericiguat, and SGLT2 inhibitors (dapagliflozin and empagliflozin) with the respective control arms (standard-of-care, SOC) on heart failure with reduced ejection fraction (HFrEF). The primary outcome was cardiovascular death or first HF hospitalization. Annualized event rates for cardiovascular death and/or HF hospitalization were also assessed. Results suggested that all of the available treatments conferred a survival benefit in patients with HFrEF. SGLT2 inhibitors demonstrated the greatest relative reduction in the occurrence of the primary outcome as compared to SOC (HR 0.74).

In this analysis, SGLT2i were found to be more effective than sacubitril/valsartan and vericiguat, although statistical significance was not reached for the most clinically relevant outcomes of CV death or HF hospitalization and CV death alone. SGLT2i proved significantly more effective than vericiguat, but not than sacubitril/valsartan for the endpoint “first HF hospitalization.” Accordingly, SGLT2i had a higher SUCRA score (a synthetic measure of efficacy) than sacubitril/valsartan, which in turn ranked higher than vericiguat. It is important to stress that these results are preliminary and hypothesis generating, given the indirect nature of the comparison, and dedicated head-to-head comparisons between different therapeutic options should be designed.

The authors concluded that based on indirect comparisons, SGLT2 inhibitor therapy is not associated with a significantly lower risk of cardiovascular death or HF hospitalization or cardiovascular death alone compared to sacubitril/valsartan or vericiguat. The risk of HF hospitalization did not differ significantly between patients on SGLT2 inhibitors or sacubitril/valsartan, while dapagliflozin was superior to vericiguat.

It is recommended that Verquvo® should be non-preferred in order to confirm the appropriate diagnosis and clinical parameters for use.

PDL Placement: ☐ **Preferred**
☒ **Non-Preferred**

References

[1] Verquvo [package insert]. Whitehouse Station, NJ: Merck Sharp & Dohme Corp; 2021.
[2] Aimo A, Pateras K, Stamatelopoulos K, et al. Relative efficacy of sacubitril-valsartan, vericiguat, and SGLT2 inhibitors in heart failure with reduced ejection fraction: A systematic review and network meta-analysis. *Cardiovasc Drugs Ther*. 2020. [Online ahead of print].