Brand Name: Verquvo

Generic Name: Vericiguat

Manufacturer[1]: Merck & Co, Inc.

Drug Class[1,2,3]: Soluble Guanylate Cyclase (sGC) Stimulator

Uses:

Labeled Uses[1,2,3]: As adjunctive treatment to reduce the risk of cardiovascular death and hospitalization in adults with symptomatic chronic heart failure and ejection fraction <45%, following a recent hospitalization or need for outpatient IV diuretics.
Unlabeled Uses: None

Mechanism of Action[1,2,3]: Directly stimulates soluble guanylate cyclase (sGC) independent of nitric oxide (NO) and enhances sGC sensitivity to endogenous NO, to increase cGMP production, which leads to smooth muscle relaxation and vasodilation.

Pharmacokinetics

Absorption[1,2,3]:

T_{max}	4 hours (with food); 1 hour (fasting state)
V_d	~44 L
$t_{1/2}$	30 hours
Clearance	1.6 L/hour
Protein Binding	~98%
Bioavailability	93% when taken with food

Metabolism[1,2,3]: Undergoes glucuronidation primarily by UGT1A9 and, to a lesser extent, by UGT1A1, to form an inactive N-glucuronide metabolite

Elimination[1,2,3]: ~53% is excreted in urine and 45% excreted in feces, primarily as unchanged drug

Efficacy:

Kramer F, Voss S, Roessig L, Igl B, Butler J, Lam CSP, et al. Evaluation of high-sensitivity C-reactive protein and uric acid in vericiguat-treated patients with heart failure with reduced ejection fraction. Eur J Heart Fail. 2020;22(9):1675-1683.

Study Design: randomized, placebo-controlled, double-blind, dose-finding, Phase 2 study

Description of Study: *Methods:* 456 patients, who were post-hospitalization for HF or had

received outpatient treatment with IV diuretics for HF and a left ventricular ejection fraction of <45% within 4 weeks of a symptomatic HF event, were randomized to either receive vericiguat (1.25mg, 2.5mg, 5mg and 10mg once daily) or placebo for 12 weeks after clinical stabilization or within 4 weeks after discharge. Dose titration occurred at weeks 2 and 4 after randomization based on safety assessments and systolic blood pressure criteria. Blood samples were collected at all visits and high-sensitivity CRP and assays for SUA were measured. Associations of hsCRP and SUA changes from baseline to end of treatment with clinical outcomes, including CV death, CV hospitalization, and emergency presentation caused by worsening chronic HF, were assessed. *Outcome Results:* Baseline-adjusted mean percentage changes from baseline in SUA were 5.0% (95% CI=-0.1 to 10.4), -1.3% (95% CI=-6.1 to 3.7), -1.1% (95% CI=-5.8 to 3.8), -3.5% (95% CI=-8.3 to 1.6) and -5.3% (95% CI=-9.8 to -0.6) in the placebo group and vericiguat 1.25mg, 2.5mg, 5.0mg, and 10mg groups, respectively. In the vericiguat 5.0mg and 10.0mg groups, significant reductions in SUA relative to placebo were observed (-3.5% vs 5.0% [p=0.02] and -5.3% vs 5.0% [p=0.004], respectively). In all vericiguat dosage groups, a significant linear trend in the reduction of SUA from baseline to end of treatment from placebo was noted, indicating a dose-dependent effect.

Limitations: It is unknown whether hsCRP is a true biomarker for the prognosis of HF patients, so it cannot be concluded that vericiguat improves clinical outcomes. In addition, correlations between changes in hsCRP and SUA and the relative odds of clinical outcome were not statistically significant in the study. Additional research needs to be completed to evaluate the associations between inflammatory biomarkers and clinical outcomes, as the prognostic value of reducing SUA as a treatment goal in HFrEF is unknown. The study population was relatively small, and the drug was tested for a short duration (12 weeks), warranting the need for additional clinical studies. Further studies should evaluate the effectiveness of vericiguat in terms of symptom control and clinical outcomes, such as hospitalizations and death.

Conclusion: Vericiguat treatment for 12 weeks was associated with a decrease in hsCRP and SUA concentrations from baseline in patients with HFrEF. When data was adjusted for baseline levels and covariates, significant dose-dependent reductions in hsCRP and SUA were observed in vericiguat-treated subjects. Phase 3 clinical trials will evaluate the association of decreases in hsCRP and SUA with clinical outcomes, and if the results demonstrated in this study can be observed after 12-weeks.

Armstrong PW, Roessig L, Patel MJ, Anstrom KJ, Butler J, Voors AA, 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. J Am Coll Cardiol Heart Fail. 2018 Feb;6(2)96-104.

Study Design: a multicenter, randomized, double-blind, placebo-controlled, parallel-group study

Description of Study: *Methods:* 5,050 subjects age 18 and over with chronic HF (NYHA functional classes II to IV) and left ventricular ejection fraction (LVEF) less than 45% following a worsening heart failure event (hospitalization for HF within 6 months or use of outpatient IV diuretics for HF within 3 months before randomization) were randomized in a 1:1 ratio to receive either 5mg vericiguat, subsequently titrated to target dose of 10mg, or matching placebo in addition to standard of care. A screening period of 30 days was conducted prior to randomization, followed by a 4-week titration phase. Titration was based on mean systolic blood pressure measurement and safety considerations. Subjects were then evaluated every 4 months until study completion, or until the required number of cardiovascular deaths was observed. Safety and tolerability were assessed by clinical review of relevant parameters, including adverse events,

laboratory tests, and vital signs. The primary endpoint was a composite of time to first event of CV death or hospitalization for HF, with a mean-follow up of 11 months. *Outcome Results:* Vericiguat 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, 95% CI=0.82-0.98, p=0.019). Subgroup analyses produced results consistent with the results of this endpoint, except for patients in the highest baseline NT-proBNP quartile, with estimated hazard ratios for both CV death (HR: 1.16; 95% CI: [0.95, 1.43]) and first HF hospitalization (HR: 1.19; 95% CI: [0.9, 1.44]) being unfavorable but not statistically significant. There was a 4.2% absolute risk reduction (ARR) with vericiguat compared to placebo. The secondary endpoints of cardiovascular death and heart failure hospitalization had hazard ratios of 0.93 (0.81-1.06) and 0.90 (0.81-1.0), respectively.

Limitations: Multiple investigators were employees of Merck & Co, Inc. (manufacturer of vericiguat) and the manufacturer was involved in many aspects of the study design and collection of data. The study population was 76% male and did not evaluate the safety and efficacy of vericiguat in patients with severe hepatic or renal impairment. This makes results difficult to extrapolate to women and also raises the question of effective doses in patients with renal and hepatic impairment.

Conclusion: Vericiguat was superior to placebo in reducing the risk of CV death or heart failure hospitalization based on time-to-event analysis (HR: 0.90, 95% CI, 0.82-0.98, p=0.019). Vericiguat provides a safe and effective add-on treatment to standard of care for patients with NYHA class II-IV heart failure with left ventricular ejection fraction less than 45%. More studies need to be completed to evaluate the safety and efficacy of vericiguat in additional patient populations, including severe hepatic and renal impairment.

Contraindications[1,2,3]:

Concomitant use of other soluble guanylate cyclase stimulators (eg, riociguat);

Pregnancy (BBW): May cause fetal harm. Exclude pregnancy before starting treatment. Females of reproductive age must use effective forms of contraception during treatment and for 1 month after stopping treatment.

Precautions[1,2,3]:

Nitrates: Patients who were concurrently using, or anticipated using, long-acting nitrates were excluded from clinical trials. Co-administration of short-acting nitrates was allowed.

PDE-5 Inhibitors: Patients who were concurrently using, or anticipated using, a PDE-5 inhibitor were excluded from clinical trials. May cause hypotension when used concomitantly.

Lactose Intolerance: Formulation may contain lactose.

Adverse Effects[1,2,3]:

Occurring in >10% of patients:

Cardiovascular: Hypotension (16%)

Occurring in >1% to <10% of patients

Hematologic & oncologic: Anemia (10%)

Drug Interactions[1,2,3]:

Phosphodiesterase-5 (PDE-5) Inhibitors: Vericiguat may enhance the hypotensive effect of PDE-5 inhibitors

Soluble Guanylate Cyclase (sGC) Stimulators: may enhance the adverse/toxic effect of vericiguat

Dosing/Administration[1,2,3]:

Adult Dosing

Initial dose: 2.5mg once daily with food

Dosage titration: increase in ~2 week intervals to 5mg and then 10mg once daily, as tolerated based on blood pressure and clinical symptoms

Maintenance dose: 10mg once daily

Dose adjustment based on systolic blood pressure:

Systolic BP ≥100mmHg: Consider up-titrating dose if not already on 10mg target dose; maintain if already on 10mg target dose

Systolic BP ≥90 and <100mmHg: Maintain current dose

Systolic BP <90: Decrease dose (if on 5 or 10mg) or interrupt therapy (if on 2.5mg and patient has symptomatic hypotension)

Pediatrics

Safety and effectiveness have not been established

Elderly

Refer to adult dosing

Renal Impairment

eGFR ≥15 mL/minute/1.73m^2: No dose adjustment necessary

eGFR <15 mL/minute/1.73m^2: No dose adjustments provided in manufacturer's labeling (has not been studied)

Dialysis: No dose adjustments provided in manufacturer's labeling (has not been studied)

Hepatic Impairment

Mild-moderate hepatic impairment (Child-Pugh class A and B): No dose adjustment necessary

Severe hepatic impairment (Child-Pugh class C): No dose adjustments provided in manufacturer's labeling (has not been studied)

Use in special circumstances:

Overdosage[1]: In event of an overdose, hypotension may result. Symptomatic treatment should be provided. Vericiguat is unlikely to be removed through hemodialysis due to high protein binding.

Conclusion:

Vericiguat has moderate efficacy as adjunct therapy for patients with heart failure with reduced ejection fraction. More studies need to be completed to evaluate the effectiveness of vericiguat as add-on therapy to various medications that are used to treat heart failure. More research needs to be completed to assess the safety and dosing of vericiguat in patients with severe renal or hepatic disease. The side effects and adverse effects of vericiguat appear to be minimal, with hypotension being the most common. With its benefit in reducing the occurrence of adverse outcomes in patients with HFrEF, minimal drug interactions and side effects, and oral dosing, vericiguat appears to be a clinically useful medication in the treatment of heart failure.

References:

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3. Vericiguat Oral. Facts & Comparisons 4.0 Online [database online]. Wolters Kluwer. Available at: http://online.factsandcomparisons.com. Accessed March 4, 2021.
4. Kramer F, Voss S, Roessig L, Igl B, Butler J, Lam CSP, et al. Evaluation of high-sensitivity C-reactive protein and uric acid in vericiguat-treated patients with heart failure with reduced ejection fraction. Eur J Heart Fail. 2020;22(9):1675-1683. Accessed March 4, 2021.
5. Armstrong PW, Roessig L, Patel MJ, Anstrom KJ, Butler J, Voors AA, 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. J Am Coll Cardiol Heart Fail. 2018 Feb;6(2)96-104. Accessed March 4, 2021.
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