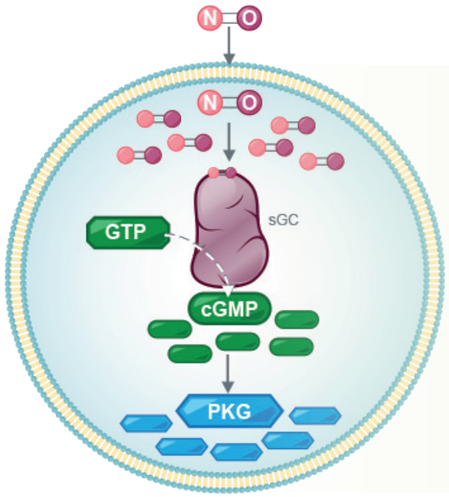
NO-sGC-cGMP Pathway and the Heart

Overview of the NO-sGC-cGMP Pathway

- The production of cGMP via NP signaling has effects on the SNS and RAAS to help maintain homeostasis.[1,2]
- cGMP can also be produced via the nitric oxide-soluble guanylate cyclase-cyclic guanosine monophosphate, or NO-sGC-cGMP, pathway.[3,4]
- cGMP plays a role in the regulation of vascular tone, cardiac contractility, and cardiac remodeling.[3-5]

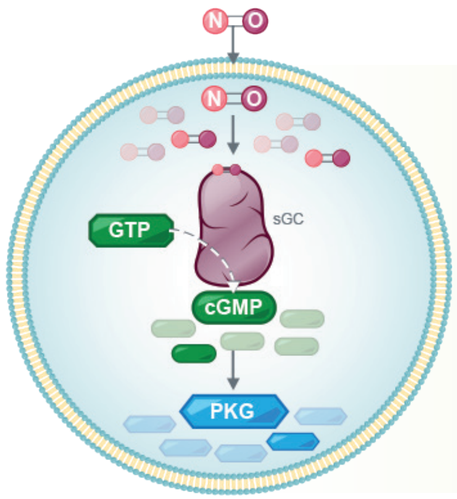


NO-sGC-cGMP Pathway

Nitric oxide, or **NO**, is generated by endothelial cells, which are cells that line blood vessels.[4,6]

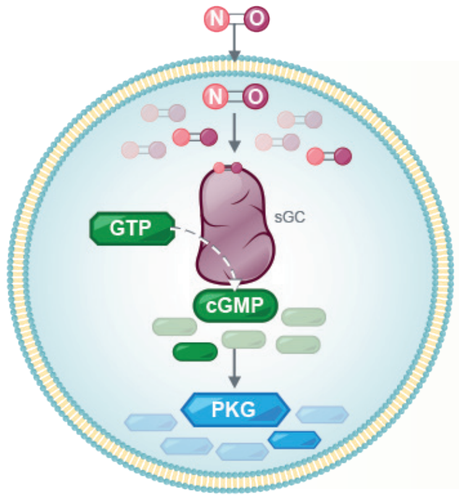
NO then diffuses into **smooth muscle** cells, where it binds to soluble guanylate cyclase, or sGC. sGC is an intracellular receptor for NO. Binding of NO and sGC catalyzes the conversion of guanosine triphosphate, or GTP, to cGMP.[3,4,7]

cGMP stimulates protein kinase G, or PKG, that can induce smooth muscle relaxation.[4,8]



Decreased cGMP in Heart Failure

Signaling via the NO-sGC-cGMP pathway has been shown to be attenuated in a variety of cardiovascular disease states.[7] In heart failure, oxidative stress is associated with decreased NO production and may increase NO inactivation contributing to heart failure progression.[3,9]



Decreased NO bioavailability due to oxidative stress associated with heart failure

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Decreased sGC stimulation

↓

Decreased cGMP production

↓

Decreased PKG activation

↓

May contribute to heart failure progression

Associated Effects of Decreased cGMP Production in Heart Failure

- Decreased coronary blood flow[4,10]
- Cardiac remodeling[5,10]
- Increased myocardial stiffness[11]
- Decreased peripheral blood flow[3,5]
- Increased vascular stiffening[4,8]

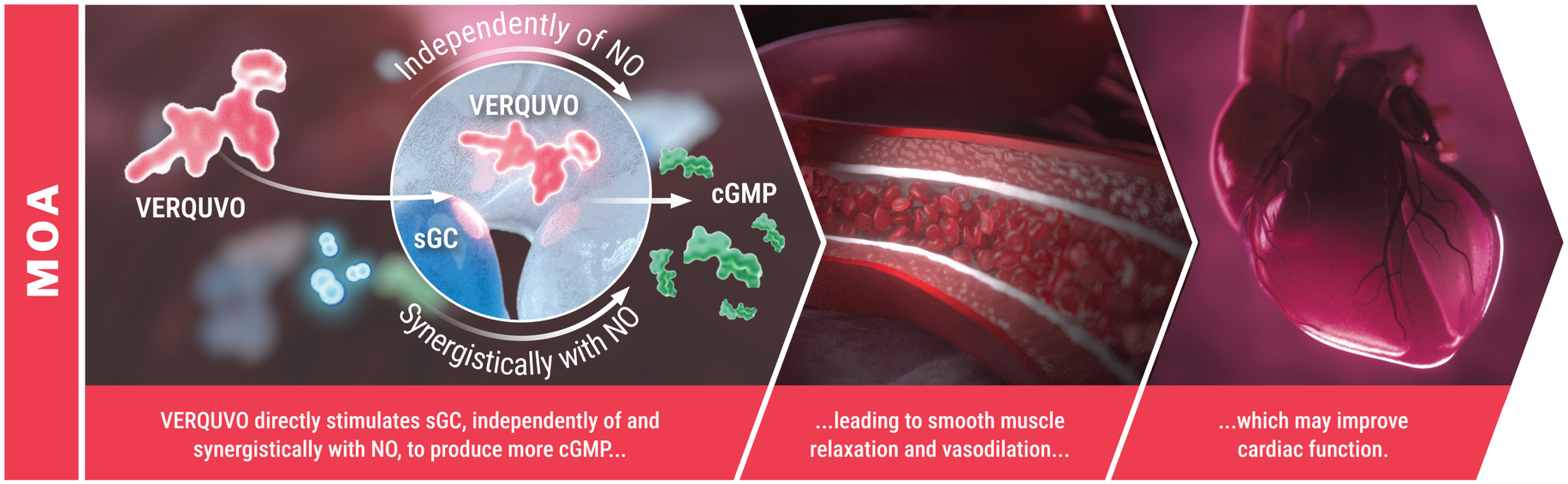
GTP, guanosine triphosphate; NO, nitric oxide; NP, natriuretic peptide; PKG, protein kinase G; RAAS, renin-angiotensin-aldosterone system; sGC-cGMP, soluble guanylate cyclase-cyclic guanosine monophosphate; SNS, sympathetic nervous system.

Verquvo® (vericiguat) tablets
2.5 mg, 5 mg, 10 mg

Discover a Different Treatment Option for Your Appropriate HFrEF Patients[12]

VERQUVO employs a novel MOA for the treatment of HF, resulting in smooth muscle relaxation and vasodilation[12]

VERQUVO augments cGMP levels by addressing impaired NO-sGC-cGMP pathway, which is important in the pathophysiology of HF



HF, heart failure; HFrEF, heart failure with reduced ejection fraction; MOA, mechanism of action; NO, nitric oxide; sGC-cGMP, soluble guanylate cyclase-cyclic guanosine monophosphate.

INDICATION

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

SELECTED SAFETY INFORMATION

WARNING: EMBRYO-FETAL TOXICITY

Females of reproductive potential: Exclude pregnancy before the start of treatment. 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.

SELECTED SAFETY INFORMATION (*continued*)

- VERQUVO is contraindicated in patients with concomitant use of other soluble guanylate cyclase (sGC) stimulators.
- VERQUVO is contraindicated in pregnancy.
- **Embryo-Fetal Toxicity:** Based on data from animal reproduction studies, VERQUVO may cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential of the potential risk to a fetus. Obtain a pregnancy test before the start of treatment. Advise females of reproductive potential to use effective contraception during treatment with VERQUVO and for at least one month after the final dose.
- There is a Pregnancy Surveillance Program that monitors pregnancy outcomes in women exposed to VERQUVO during pregnancy. Health care providers should report any prenatal exposure by calling 1-877-888-4231 or at https://pregnancyreporting.verquvo-us.com.

Selected Safety Information continued on next page.

Verquvo® (vericiguat) tablets 2.5 mg, 5 mg, 10 mg

Once-daily VERQUVO provided a powerful annualized absolute risk reduction of CV death or HF hospitalization compared to placebo

Primary composite endpoint of CV death or HF hospitalization in the VICTORIA study[a]

4.2% **annualized ARR[b]**
HR=0.90 (95% CI: 0.82-0.98)
P=0.019[c,d]

NNT of 24
For **1 year** to prevent 1 event

Based on an event rate of 33.6% of patients per year for VERQUVO (N=2,526) vs 37.8% of patients per year for placebo (N=2,524)[e,f]

The effect of VERQUVO reflects a reduction in CV death and HFH

Study Design

VICTORIA was a Phase 3, randomized, parallel-group, placebo-controlled, double-blind, event-driven, multicenter trial comparing VERQUVO to placebo when added to background HF therapy[e] in 5,050 adult patients with NYHA class II-IV chronic HF and LVEF <45% following a worsening HF event (defined as HF hospitalization within 6 months before randomization or use of outpatient IV diuretics for HF within 3 months before randomization). Patients were treated up to the target maintenance dose of VERQUVO 10 mg once daily or matching placebo. The primary endpoint was a composite of time to first event of CV death or HF hospitalization.[12]

[a]For patients with multiple events, only the first event contributing to the composite endpoint is counted.
[b]ARR, calculated as difference (placebo - VERQUVO) in event rate per 100 patient years.
[c]HR (VERQUVO over placebo) and CI from a Cox proportional hazards model.
[d]From the log-rank test.
[e]Background therapy included beta blocker, ACE inhibitor, ARB, MRA, ARNI, or SGLT2 inhibitor.
[f]Total patients with an event per 100 patient years at risk.

ACE, angiotensin-converting enzyme; ARB, angiotensin (II) receptor blocker; ARNI, angiotensin receptor and neprilysin inhibitor; ARR, absolute risk reduction; CI, confidence interval; CV, cardiovascular; HF, heart failure; HFH, heart failure hospitalization; HR, hazard ratio; IV, intravenous; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; N, number of patients in intent-to-treat (ITT) population for efficacy outcomes[12]; NNT, number needed to treat; NYHA, New York Heart Association; SGLT2, sodium-glucose co-transporter 2; VICTORIA, Vericiguat in Patients with Heart Failure and Reduced Ejection Fraction.

Scan here for more information or visit verquvohcp.com

SELECTED SAFETY INFORMATION (*continued*)

- In a clinical trial, the most commonly observed adverse events with VERQUVO vs placebo, occurring at a frequency ≥5%, were hypotension (16% vs 15%) and anemia (10% vs 7%).
- Concomitant use of VERQUVO with PDE-5 inhibitors is not recommended due to the potential for hypotension.
- There are no data on the presence of vericiguat in human milk, the effects on the breastfed infant, or effects on milk production. Because of the potential for serious adverse reactions in breastfed infants from VERQUVO, advise women not to breastfeed during treatment with VERQUVO.

Before prescribing VERQUVO, please read the accompanying Prescribing Information, including the Boxed Warning about embryo-fetal toxicity. The Medication Guide also is available.

References: 1. Liu RC. Focused treatment of heart failure with reduced ejection fraction using sacubitril/valsartan. *Am J Cardiovas Drugs*. 2018;18:478-482. **2.** Levin ER, Gardner DG, Samson WK. Natriuretic peptides. *N Engl J Med*. 1998;339(5):321-328. **3.** Hasenfuss G, Mann DL. Pathophysiology of heart failure. In: Mann DL, Zipes DP, Libby DP, Bonow RO, Braunwald E, eds. *Braunwald's Heart Disease A Textbook of Cardiovascular Medicine*. 10th ed. Elsevier Saunders; 2015:454-472. **4.** Gheorghiade M, Marti CN, Sabbah HN, et al. Soluble guanylate cyclase: a potential therapeutic target for heart failure. *Heart Fail Rev*. 2013;18:123-134. **5.** Brutsaert DL. Cardiac endothelial-myocardial signaling: its role in cardiac growth, contractile performance, and rhythmicity. *Physiol Rev*. 2003;83:59-115. **6.** Taber's Medical Dictionary Online. Accessed May 20, 2024. https://www.tabers.com/tabersonline **7.** Boerrigter G, Lapp H, Burnett JC. Modulation of cGMP in heart failure: a new therapeutic paradigm. *Handb Exp Pharmacol*. 2009;191;485-506. **8.** Fulton DJR, Li X, Bordan Z, et al. Reactive oxygen and nitrogen species in the development of pulmonary hypertension. *Antioxidants*. 2016;6(3):1-22. **9.** Higashi Y, Noma K, Yoshizumi M, Kihara Y. Endothelial function and oxidative stress in cardiovascular disease. *Circ J*. 2009;73:411-418. **10.** Breitenstein S, Roessig L, Sandner P, Lewis KS. Novel sGC stimulators and sGC activators for the treatment of heart failure. *Handb Exp Pharmacol*. 2016;243:225-247. **11.** Greene SJ, Gheorghiade M, Borlaug BA, et al. The cGMP signaling pathway as a therapeutic target in heart failure with preserved ejection fraction. *J Am Heart Assoc*. 2013;2(6):e00536. **12.** Armstrong PW, Pieske B, Anstrom KJ, et al. Vericiguat in patients with heart failure and reduced ejection fraction. *N Engl J Med*. 2020;382(20):1883-1893.

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