NEW DRUG APPROVAL

Brand Name	Verquvo™
Generic Name	vericiguat
Drug Manufacturer	Merck Sharp & Dohme Corp.

New Drug Approval

FDA Approval Date: January 19, 2021

Review Designation: Priority

Type of Review: Type 1 – New Molecular Entity

Dispensing Restrictions: N/A

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Heart failure (HF) is classified into three subtypes: HF with reduced ejection fraction (HFrEF); HF with preserved ejection fraction (HFpEF), and HF with mid-range ejection fraction (HFmrEF). Approximately 50% of people with HF have HFrEF, and those with HFrEF have a high prevalence of coronary artery disease, particularly in males and older patients. HFrEF occurs when the left ventricular ejection fraction (LVEF) is 40% or less and is accompanied by progressive left ventricular dilatation and adverse cardiac remodeling.

Heart failure (HF), which is characterized by the reduced ability of the heart to pump and/or fill with blood, is widely considered a global pandemic. Despite significant advances in therapies and prevention, mortality and morbidity rates are still high. HF affects at least 26 million people worldwide. In the United States, about 5.7 million people have HF, and this number is expected to increase to 8 million by 2030 (a 46% increase in prevalence). Recent data indicate that although the incidence of HF is stable, the prevalence is rising because of an aging population and improvements in treatment. This will result in further increases in hospitalization rates.

NEW DRUG APPROVAL

Efficacy

VICTORIA (NCT02861534): Study Design Summary	

Study Population	• 5050 male and female participants 18 years of age or older with worsening chronic HF (New York Heart Association class II–IV), LVEF <45% within 12 months prior to randomization, and elevated natriuretic peptide levels (determined by sites) within 30 days prior to randomization.
	• For patients in sinus rhythm, required criteria included plasma B-type natriuretic peptide (BNP) levels ≥300 pg/mL or N-terminal (NT)-proBNP levels ≥1000 pg/mL.
	• For those in atrial fibrillation, BNP levels ≥500 pg/mL and NT-proBNP levels ≥1600 pg/mL were required.
	• A worsening HF event was defined as:
	  ○ HF hospitalization within 6 months before randomization
	  ○ Use of outpatient IV diuretics for HF within 3 months before randomization

Interventions	Patients were randomized to receive either: • Vericiguat once daily, titrated up to 10 mg (n = 2526), or • Placebo (n = 2524)
Endpoints	• **Primary endpoint:** Composite of time to first occurrence of HF hospitalization or CV death • **Secondary endpoints:** Time to occurrence of CV death, time to first occurrence of HF hospitalization, time to total HF hospitalizations (including first and recurrent events), time to the composite of all-cause mortality or HF hospitalization, and time to all-cause mortality

Efficacy and Safety Results	• Over a median of 10.8 months, the incidence of CV death or HF-related hospitalization occurred in 897 (35.5%) patients receiving vericiguat and 972 (38.5%) receiving placebo (HR, 0.90; 95% CI, 0.82–0.98; *P* = 0.02) for a 10% relative risk reduction in composite CV-related death and HF hospitalization.
	• This effect was consistent across the majority of prespecified subgroups, including patients receiving or not receiving sacubitril/valsartan. Levels of NT-proBNP at baseline and by age were shown to correlate with the treatment effect. The data suggest that the majority of patients in the study with NT-proBNP in the lower quartile ranges and those under 75 years of age may have achieved a greater benefit.
	• The safety profile of Verquvo was consistent with that reported in previous studies. The overall incidences of serious adverse events were similar for the vericiguat (32.8%) and placebo (34.8%) groups:
	  ○ Symptomatic hypotension (9.1% vs. 7.9%) and syncope (4.0% vs. 3.5%) tended to be more common with vericiguat than placebo, but the differences were not statistically significant.
	  ○ Throughout the VICTORIA study, there were no significant between-group differences for renal adverse events such as hyperkalemia or decreases in estimated glomerular filtration rate (eGFR).
	  ○ The Verquvo safety profile was also similar when Verquvo was given in combination with other therapies used in patients with HF.

Safety

ADVERSE EVENTS

Most common adverse reactions reported in ≥5% are hypotension and anemia.

WARNINGS & PRECAUTIONS

- Do not administer Verquvo™ to a pregnant female because it may cause fetal harm.
- 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.

CONTRAINDICATIONS

- Patients with concomitant use of other soluble guanylate cyclase (sGC) stimulators.
- Pregnancy.

NEW DRUG APPROVAL

Clinical Pharmacology

MECHANISMS OF ACTION

Verquvo™ is a stimulator of soluble guanylate cyclase (sGC), 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.

Dose & Administration

ADULTS

Initial, 2.5 mg orally once daily with food; titration, double the daily dose approximately every 2 weeks as tolerated to a target maintenance dose of 10 mg/day.

PEDIATRICS

Safety and efficacy have not been established.

GERIATRICS

Refer to adult dosing.

RENAL IMPAIRMENT

eGFR 15 mL/minute/1.73 m2 or more and not on dialysis: No dosage adjustment necessary.

eGFR less than 15 mL/minute/1.73 m2 at treatment initiation or on dialysis: Vericiguat has not been studied in this patient population.

HEPATIC IMPAIRMENT

Mild or moderate hepatic impairment (Child-Pugh A or B): No dosage adjustment is necessary.

Severe hepatic impairment (Child-Pugh C): Vericiguat has not been studied.

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Tablets: 2.5 mg, 5 mg and 10 mg