

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

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**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Reviewer Name(s)	Theresa Ng, PharmD, BCPS, CDE
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Review Completion Date	January 20, 2021
Subject	Evaluation of Need for a REMS
Established Name	Vericiguat
Trade Name	Verquvo
Name of Applicant	Merck Sharp and Dohme Corp
Therapeutic Class	Soluble guanylate cyclase (sGC) stimulator
Formulation(s)	2.5, 5, 10 mg oral tablets
Dosing Regimen	Starting dose at 2.5 mg once daily, take with food, double dose every two weeks to reach the targeted maintenance dose of 10 mg once daily, as tolerated by the patient

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EXECUTIVE SUMMARY

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Verquvo (vericiguat) is necessary to ensure the benefits outweigh its risks. Merck Sharpe and Dohme Corp (Merck) submitted a New Drug Application (NDA) 214377 for Vericiguat with the proposed indication to reduce the risk of CV 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%. The potential risks associated with vericiguat include: embryo-fetal toxicity and effects of vericiguat on bone formation. The Applicant did not submit a proposed REMS or risk management plan with this application.

Although vericiguat is in the same drug class as Adempas (riociguat), NDA 204819, which has a REMS to mitigate the risk of embryo-fetal toxicity, the intended patient population and prescribing practices differ significantly. The HF population, the intended population for vericiguat, tends to be older and of male gender compared to pulmonary arterial hypertension (PAH) which occurs more frequently in younger females. Many of the well-established guideline directed management therapies for HF have the risk of embryo-fetal toxicity without additional risk mitigation strategies such as a REMS. Findings from the Division of Epidemiology (DEPI) analyses in Sentinel System evaluated the frequency of pregnancies in patients with HF and heart failure with reduced ejection fraction (HFrEF) and the use of HF pharmacotherapies with embryo-fetal toxicity risk to better understand the extent of the at-risk population. This evaluation provided reassuring data of very low pregnancy rates in females with HFrEF. DEPI conducted further analyses to examine utilization of HF drugs commonly used in HF including those with embryo-fetal toxicity risk during pregnancy and maternal and fetal outcomes. The analysis showed low rates of HF medications with embryo-fetal risk during pregnancy. For example, ACE-inhibitor use during pregnancy reduced to 5.3% in the first trimester, less than 1% in the second or third trimester, but resumed to 8.0% in the post-pregnancy period. This data appears to suggest that prescribers who treat HF are knowledgeable of the risk of embryo-fetal toxicity and patients with HFrEF who become pregnant are discontinued off of HF medications with embryo-fetal toxicity risk.

Short-term rat studies showed reversible effects of vericiguat on bone formation consisting of hypertrophy of growth plate and hyperostosis and remodeling of metaphyseal and diaphyseal bone at doses that exceed a maximally tolerated dose. This observation was also seen in riociguat and appears to be common to all soluble guanylate cyclase (sGC) stimulators.

Per the medical review, pre-specified analysis of trial efficacy outcomes accounting to baseline NT-pro-BNP quartile demonstrated an adverse trend in subjects in the highest quartile. However, comprehensive cardiac safety findings from the TQT study, ECG data from VICTORIA, and comprehensive CiPA-compliant ion channel studies did not corroborate a proarrhythmic mechanism for vericiguat.

The other AEs for the vericiguat treatment group were similar or lower than the placebo treatment group. Prespecified adverse events such as symptomatic hypotension, syncope, anemia, hepatic AEs, and elevated liver function test occurred more frequently in vericiguat treatment group compared to

placebo. However, in most cases, the events were manageable, did not require specific therapy, and did not result in an increase in study treatment discontinuation.

The totality of evidence support the benefits of vericiguat in reducing CV death and hospitalization in HFrEF population. Like other HF pharmacotherapies that have embryo-fetal toxicity, this risk will be communicated through labeling. Bone formation abnormalities were observed in nonclinical studies and may be associated with the sCG class. As vericiguat is intended for the adult population, a non-clinical postmarket requirement (PMR) along with Pediatric Research Equality Act (PREA)^a study will be issued to evaluate the developmental toxicity in order to support dosing in any potential studies of a pediatric population. Prescribers will be informed on the CV deaths observed in patients with elevated NT-proBNP via labeling.

Division of Risk Management (DRM) and the Division of Cardiology and Nephrology (DCN) determined that a REMS is not needed to ensure the benefits of vericiguat outweigh its risks.

1 Introduction

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Verquvo (vericiguat) is necessary to ensure the benefits outweigh its risks. Merck Sharpe and Dohme Corp. (Merck) submitted a New Drug Application (NDA) 214377 for vericiguat with the proposed indication to reduce the risk of CV 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%. Vericiguat is to be used in combination with other HF therapies. This application is under review in the Division of Cardiology and Nephrology (DCN). The applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION

Verquvo (vericiguat) is a new molecular entity^b. It 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 stimulating sGC directly, independently of NO, vericiguat augments levels of intracellular cGMP, leading to smooth muscle relaxation and vasodilation. The proposed indication for this product is to reduce the risk of CV death and heart failure (HF) hospitalization following a hospitalization for HF or need for outpatient IV diuretics, in adults with

^a PREA gives FDA the authority to require pediatric studies in certain drugs and biological products. Studies must use appropriate formulations for each age group. The goal of the studies is to obtain pediatric labeling for the product.

^b Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

symptomatic chronic HF and ejection fraction less than 45%. The recommended starting dose of vericiguat is 2.5 mg orally once daily. The dose is doubled approximately every two weeks to reach the target maintenance dose of 10 mg once daily, as tolerated by the patient and is intended for long-term treatment^c.

Vericiguat belongs to the same drug class as Adempas (riociguat), NDA 204819, approved in 2013, for Pulmonary Arterial Hypertension (PAH) with a REMS and a boxed warning in labeling for the risk of embryo-fetal toxicity. Vericiguat received fast track designation in 2014 under its IND 116743 for the treatment of HFrEF and this NDA application received priority review status on July 14, 2020. Vericiguat is currently not approved in any jurisdictions.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 214377 relevant to this review:

- 06/23/2014: Fast track designation granted for IND 116743 for the treatment of HFrEF.
- 05/20/2020: NDA 214377 application received for the proposed indication to reduce the risk of CV death and HF hospitalization following a worsening HF event, in adults with symptomatic chronic HF and ejection fraction less than 45% (HFrEF), in combination with other HF therapies.
- 07/14/2020: The Agency granted priority review for NDA 214377 in its filing communication to the Applicant.
- 09/01/2020: The Agency communicated to the Applicant via teleconference during the Mid-Cycle meeting (MCM) that a REMS is not needed to mitigate the risk of embryo-fetal toxicity given the differences in patient population and prescribing practices. The Agency asked the Applicant to submit appropriate postmarketing pharmacovigilance plan and proposal to communicate this risk in labeling. Additionally, the Agency conveyed concern for imbalances for CV mortality finding, including sudden cardiac death (SCD) to the Applicant: compared to placebo, vericiguat-treated subjects with an ICD at baseline tended to have lower CV mortality than those without an ICD; this was true in the high NT-proBNP quartile as well as in the study, overall. The Agency asked the Applicant to conduct further ion channel study.¹ The Applicant agreed to conduct an evaluation of vericiguat and the M1 metabolite individually for interactions with human cardiac ion channels to help understand their potential clinical effects.
- 9/17/2020: The Agency issued a Mid-Cycle Communication with the meeting minutes and information request as discussed in the MCM teleconference, dated September 1, 2020.
- 11/18/2020: Merck submitted cardiac ion channel study results with vericiguat and the M1 metabolite in response to the MCM information request, dated September 17, 2020.

^c Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

- 11/20/2020: Merck discussed preliminary findings of the ion channel studies requested by the Agency and conveyed no clinical evidence for proarrhythmia with vericiguat treatment or its metabolite in the Late Cycle Meeting (LCM) via teleconference.
- 11/25/2020: Merck submitted a revised proposed labeling to include the risk for embryo-fetal toxicity in a Box Warning, included a pregnancy testing prior to initiating vericiguat (section 2), a contraindication to pregnancy (section 4), a “Warnings and Precautions” for embryo-fetal toxicity (section 5), and included pregnancy in Use in Special Populations (section 8) in response to the MCM communication.²
- 12/1/2020: Further amendment for the cardiac ion channel studies received from Merck in response to the MCM communication.³

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Heart failure (HF) is a clinical syndrome typically manifested as dyspnea, edema, fatigue or weakness, and exertional limitations due to a structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood. The HF syndrome is typically categorized by its associated left ventricular ejection fraction (LVEF) measurements: preserved LVEF $\geq 50\%$ (HFpEF), reduced LVEF $< 40\%$ (HFrEF); and, midrange LVEF of 40–49% (HFmEF). The clinical severity of HF is described using the New York Heart Association (NYHA) functional classification with increasing disabilities as it progresses from NYHA class I to IV.⁴ HF affects approximately 1-2% of adults in developed countries and the prevalence of HF increases with age, rising to $> 10\%$ among those over 70 years of age.⁵ In the United States (US) over 6 million adults are affected by HF and it is projected to increase by 46% from 2012 to 2030, resulting in greater than 8 million people or 2.97% of the population greater than 18 years of age.⁶ The mortality and morbidity associated with HF is significant with a 1-year mortality rate of 7.2% and a 1-year hospitalization rate of 31.9% in patients with chronic heart failure. In patients hospitalized for acute HF, these rates increase to 17.4% and 43.9% respectively.⁷ The direct costs of physician visits in 2013 for HF were equal to \$32 billion; this cost is projected to increase by about three-fold by 2030.⁸ The estimated lifetime cost of HF per individual patient was \$110,000/year, with more than three-fourths of this cost consumed by in-hospital care.⁹ HFrEF accounts for 40-60% of HF patients and affects males more than females with greater occurrence in the older population. The mortality rate associated with HFrEF is high: the 5-year survival after hospitalization for HFrEF is 24.7%.^{10,d,e}

^d Section 505-1 (a) of the FD&C Act: FDAAA factor (A): *The estimated size of the population likely to use the drug involved.*

^e Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

Despite multiple classes of medical and device therapies, HF can severely affect the patient's quality of life. The prognosis of HF continues to be poor and new therapies are continuously sought. The Applicant proposes vericiguat as an additional therapeutic option in the management of patients with HFrEF.

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

The goals of therapy of HFrEF are to reduce morbidity (i.e., reduce symptoms, improve health-related quality of life and functional status, and decrease the rate of hospitalization), and to reduce mortality.

Guideline-directed management and therapy (GDMT) from the American College of Cardiology Foundation/ American Heart Association (ACCF/AHA) and the European Cardiovascular Society (ESC) heart failure guidelines include combinations of diuretics as needed for symptomatic and volume overload relieve, along with therapies targeted specifically for HF that are titrated to maximum tolerated doses.^{5,11,12} Both guidelines recommend initiating treatment with an angiotensin system blocker (angiotensin-converting enzyme [ACE] inhibitors, angiotensin II receptor blockers [ARB], or angiotensin receptor-neprilysin inhibitor [ARNI]) in conjunction with beta-blocker therapy. Additional therapies that reduce mortality in randomized controlled trials (RCTs) include mineralocorticoid receptor antagonists (MRAs), a sodium-glucose cotransporter 2 (SGLT2) inhibitor, and the combination of isosorbide and hydralazine in African Americans. Ivabradine, a selective sinus node f-channel inhibitor (I_f), can reduce hospitalization for symptomatic patients with high resting heart rates (HRs) at or greater than 70 beats per min (bpm) who are on standard heart failure therapies (including maximally tolerated doses of a beta blocker). None of the pharmacological therapies for HFrEF are approved with a REMS. See Appendix 1 for summary of pharmacological therapies for HFrEF from the ACCF/AHA Heart Failure Management Guidelines and the ACC 2020 Expert Consensus Decision Pathway for CV risk reduction in patients with type 2 diabetes.

Device therapies that decrease morbidity and/or mortality in patients with heart failure include biventricular pacemakers for cardiac resynchronization therapy (CRT), implantable cardioverter-defibrillators (ICD), or devices with both of these capabilities (CRT-D).

4 Benefit Assessment

The efficacy and safety data for the Vericiguat HFrEF program rely predominantly on the large Phase 3 VICTORIA study.¹³ The Vericiguat HFrEF development program categorized patients with EF <45% as HFrEF. Of note, the sponsor categorized those with an LVEF \geq 45% as HFpEF and studied them in a separate development program in order to investigate the full EF range of HF patients.

VICTORIA (NCT 02861535) is a randomized, parallel-group, placebo-controlled, double-blind, event-driven, multicenter, superiority study that compared the addition of vericiguat or placebo to GDMT for adult subjects with symptomatic HFrEF following a worsening HF event. The Applicant defined a worsening HF event as a HF hospitalization within 6 months before randomization or use of outpatient IV diuretics for HF within 3 months before randomization. The study used a titration regimen starting with 2.5 mg daily of vericiguat or matching placebo, followed by 2 dose doublings in 2-week intervals to

reach the 10-mg daily target dose, dependent on the subject's tolerance determined by sitting systolic blood pressure (SBP) and symptoms of hypotension. The study protocol allowed for dose decreases as determined by SBP, symptoms of hypotension, or at the discretion of the investigator.

The primary endpoint was the time to the first occurrence of the composite endpoint of CV death or HF hospitalization. Key secondary endpoints included the components of the primary endpoints: CV death and HF hospitalization. Other secondary endpoints included total events of HF hospitalization, all-cause mortality or HF hospitalization, and all-cause mortality.

Efficacy analyses were performed in the Intention-to-Treat (ITT) population, which included all randomized subjects analyzed according to the planned treatment. Analysis of the primary endpoint was based on a stratified log-rank test using a 2-sided type I error rate of 0.05. An independent Clinical Events Committee (CEC) performed a blinded adjudication of all hospitalizations and deaths to assess the cause of the events as CV or non-CV, and all serious adverse events; only clinical events confirmed by the CEC were analyzed for efficacy.

The 5050 subjects in VICOTRIA were randomized to treatment with vericiguat (2526 subjects) or placebo (2524 subjects) across 42 countries in 5 regions including Eastern Europe, Western Europe, North America, Latin and South America, and Asia Pacific between September 25, 2016 and September 2, 2019. The US accounted for 8% of the study population. The median length of follow-up for the primary endpoint in the ITT population was 10.8 months. The study population that completed follow-up for the primary endpoint consisted of 2515 (99.6%) subjects in the vericiguat group and 2511 (99.5%) subjects in the placebo group. The treatment groups were similar in all baseline demographics and disease characteristics and were consistent with an adult population with HFrEF. Use of concomitant GDMT was well balanced among the treatment groups: 93% of subjects were taking a beta-blocker, 73% were taking an ACE inhibitor or ARB, 70% were taking an MRA and 15% were taking sacubitril/valsartan at baseline. However, GDMT varied by region due to differences in treatment guidelines, prescriber practices, and access to therapies. A higher proportion of subjects in regions outside of North America received MRAs compared to subjects in North America. A higher number of subjects were treated with ICDs and CRT devices (biventricular pacemakers) in North America and Western Europe than other regions. The use of an ARNI was higher in North America and Western Europe compared to Asia Pacific. Overall, the mean age was 67.3 years (range 23 to 98 years) with 76.1% male and 23.9% female subjects. Most subjects were white (64%), Asian (22%), and Black (5%). Most subjects were of NYHA Class II or III (Class II at 59% and Class III at 40%). Forty nine percent of subjects had LVEF < 30% (mean LVEF 29%), and the median NT-proBNP level was 2816.0 pg/mL (Range 0 to >175000 pg/mL). The median time from index event to randomization was 32.0 days. The mean time from initial HFrEF diagnosis to randomization was 4.8 years.

The Applicant concluded that the VICTORIA study results showed beneficial effects of vericiguat compared to placebo in increasing the time to CV death or HF hospitalization (primary endpoint) with a 10% relative hazard reduction (HR 0.90 [95% CI 0.82,0.98]; p=0.019) which translated to an annualized absolute risk reduction of 4.2% and an estimated number needed (NNT) to treat of 24 (i.e., 24 patients

would need to be treated over an average of 1 year to prevent 1 primary endpoint event).^f Sensitivity analysis support durability of treatment effect. The clinical reviewer agreed that the Applicant demonstrated a statistically significant effect on its primary endpoint. The following table summarizes the primary endpoint results.

Table 1. Primary Endpoint: Composite of CV Death or HF Hospitalization (ITT population)^g

		Vericiguat (N=2526)		Placebo (N=2524)		HR (95% CI)	p- Value
		n (%)	KM% at 2 years	n (%)	KM% at 2 years		
Adjudicated	Composite of HF hospitalization and CV death	897 (35.5)	43.9 %	972 (38.5)	46.9%	0.90 (0.82, 0.98)	0.019
	HF hospitalization	691 (27.4)		747 (29.6)			
	CV death	206 (8.2)		225 (8.9)			
Investigator -reported	Composite of HF hospitalization and CV death	1016 (40.2)	49.6%	1077 (42.7)	50.9%	0.92 (0.84, 1.00)	0.04

Analysis of the primary efficacy endpoint of vericiguat relative to placebo for pre-specified subgroups characteristics (i.e., sex, race, geographic regions, and other relevant clinical characteristics) were consistent except for age and NT-proBNP. Significant interactions for adverse trends for vericiguat treatment relative to placebo were noted in older subjects (age \geq 75 years, HR 1.04 [95% CI, 0.88-1.21], p = 0.03), and subjects with the highest baseline NT-proBNP quartile (NT-proBNP > 5314 pg/ml, HR 1.16 [95% CI, 0.99-1.35], p = 0.001), per table 2 below:

^f Section 505-1 (a) of the FD&C Act: *FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

^g Table from the clinical reviewer's Midcycle meeting presentation, dated 8/21/2020.

Table 2. Subgroup Analysis of the Primary Composite Endpoint (prespecified subgroups)^h

	Vericiguat (N=2526)	Placebo (N=2524)	Hazard Ratio 95% CI	p-value ¹
Age				
<75	579/1741 (33.3%)	669/1741 (38.4%)	0.84 (0.75, 0.94)	0.03
≥ 75	318/785 (40.5%)	303/783 (38.7%)	1.04 (0.88, 1.21)	
NT-proBNP at baseline (pg/mL)				
Q1 (≤1556)	128/599 (21.4%)	161/604 (26.7%)	0.78 (0.62, 0.99)	0.001
Q2 (1556-2816)	165/613 (26.9%)	201/589 (34.1%)	0.73 (0.60, 0.90)	
Q3 (2816-5314)	213/586 (36.3%)	257/613 (41.9%)	0.82 (0.69, 0.99)	
Q4 (>5314)	355/616 (57.6%)	302/585 (51.6%)	1.16 (0.99, 1.35)	

¹ p value for treatment by subgroup interaction from Cox proportional hazard model.

However, when adjusted for other factors in a multivariate model, treatment effect was similar across age subgroups and no longer significant. For key secondary endpoints, vericiguat-treated subjects experienced fewer first HF hospitalizations and CV deaths, with only HF hospitalization (p 0.048) achieving statistical significance. The Clinical reviewer noted that both components of the primary efficacy endpoint trended towards favoring vericiguat.

5 Risk Assessment & Safe-Use Conditions

The safety data for the Vericiguat HFrEF program relied predominantly on the large Phase 3 VICTORIA study.¹³ Known safety concerns for riociguat were also reviewed for vericiguat. These included embryo-fetal toxicity, hypotension, and anemia or bleeding.

Most randomized subjects completed the VICTORIA study with 2519 subjects receiving at least one dose of vericiguat. The mean duration of exposure was 375.5 days and was similar between the treatment groups (vericiguat and placebo). The incidences of adverse events (AEs), serious AEs (SAEs), and SAEs with fatal outcome were similar across treatment groups, with placebo-treated patients having a higher proportion. SAEs are events that the CEC determined not to meet the endpoint criteria. Specific SAEs imbalances of preferred terms or groupings of preferred terms occurring more frequently in the vericiguat-treatment arm included: anemia at 1.6% versus 0.9% (risk difference 0.7 (95% CI: 0.1, 1.3)), liver injury at 1% and 0.5%, respective (risk difference 0.5 (95% CI: 0.0, 1.0)), and syncope at 2.1% and 1.4%, respectively (risk difference 0.7 (95% CI: 0.0, 1.4)). Adverse events leading to dose modification, interruption, or reduction occurred in a marginally higher proportion of the vericiguat-treated patients. The most common Treatment-Emergent AEs (TEAEs) occurring more frequently in the vericiguat arm than in the placebo arm were anemia, GI events (nausea, dyspepsia), headache, hypotension, and syncope. Dyspepsia, nausea, and headache are associated with vericiguat's mechanism of action (MoA) and have previously been reported with other sGC stimulators.

^h Table from the clinical reviewer's Midcycle meeting presentation, dated 8/21/2020.

The Applicant provided comparisons of vericiguat to placebo (PBO) on several prespecified adverse events of special interests (AESIs). In most cases, the events were manageable, did not require specific therapy, and did not result in an increase in study treatment discontinuation.

Symptomatic hypotension and syncope were evaluated due to the vasodilatory effects of vericiguat. Symptomatic hypotension events were mostly mild and balanced between treatment arms (AEs: 9.1% (vericiguat) versus 7.9% (PBO) and SAEs 1.2% versus 1.5%, respectively). Fall and fracture rates related to symptomatic hypotension events were balanced and low between treatment groups (0.2% versus 0.3%, respectively). Syncope event rates were also similar between treatment groups (AEs: 4.0% vs 3.5%; SAE: 1.7% vs 1.3%, respectively) and falls and fractures rates were balanced and low between treatment groups (0.5% vs 0.6%, respectively). No deaths resulted from symptomatic hypotension in either treatment group.

Hepatic AESIs (AST or ALT $\geq 3 \times$ ULN and bilirubin $\geq 2 \times$ ULN and ALP $< 2 \times$ ULN) were low, but slightly higher in vericiguat group compared to PBO group (AEs: 0.9% vs 0.5%; SAEs 0.6%, 0.3%, respectively). There was no evidence of an exposure-response relationship and none of the cases were determined to be drug related.

Anemia incidence rate was higher in the vericiguat group compared to placebo group (9.7% and 7.4%, respectively). There was no evidence of a dose-response relationship. There were no reports of clinically meaningful differences in mean or median values of changes from baseline over time for hemoglobin or hematocrit parameters. There was no imbalance observed for serious bleeding events among treatment groups. Anemia and bleeding were previously reported with riociguat and this risk is reflected in its labeling (Warnings and Precautions for Bleeding (5.4) and section 6 Adverse Reactions).

5.1 DEATHS

All deaths (CV and non-CV deaths) were submitted for adjudication. Per study protocol, CV and non-CV death were not reported as SAEs. The incidence of death (treatment-emergent and AE with fatal outcome) was lower in the vericiguat group compared with the placebo group; however, there was an adverse imbalance in cardiovascular deaths favoring placebo noted in the subgroup of subjects in the highest baseline quartile of NT-proBNP (See section 5.4 below). Non-CV deaths were similar for both treatment groups.

5.2 EMBRYO-FETAL TOXICITY

There are no human data on vericiguat exposure and pregnancy. Teratogenicity was observed in embryo-fetal development studies in rabbits in six different litters in which pups had cardiac defects. Developmental toxicity studies in rats and rabbits with vericiguat administered orally during organogenesis showed maternal toxicity at ≥ 10 and ≥ 6 times the human exposure at the Maximum Recommended Human Dose (MRHD) which resulted in late spontaneous abortions and resorptions in rabbits. In pre- and postnatal studies, vericiguat administered orally to rats from gestation through lactation displayed pharmacodynamic-mediated maternal toxicity at approximately ≥ 9 times the MRHD. At higher doses, ≥ 21 times the MHRD, decreased pup body weight gain occurred and at 49 times the MHRD, pup mortality occurred. The Applicant concluded the events were within the range of historical

controls. The Applicant stated that the malformations were spontaneous rather than treatment-related and concluded no teratogenicity with high doses of vericiguat administration. However, the reviewer from the Division of Pharmacology and Toxicology for Cardiology, Hematology, Endocrinology, and Nephrology (DPT-CHEN) found the historical control data was inappropriate and did not meet criteria to support the Applicant's conclusion. The DPT reviewer along with members from the Pharmacology Toxicology Coordinating Committee Reproductive Toxicology Subcommittee (RTS) found that there was a demonstrated treatment-related malformation due to reproductive toxicity.¹⁴ The DPT reviewer also noted that the risk for embryo-fetal toxicity appears to be a class effect of sGC stimulators.ⁱ The clinical reviewer concurs with the DPT reviewer. Mitigation strategies for this risk will be discussed in Section 8.

5.3 EFFECTS ON BONE DEVELOPMENT

Abnormal bone growth such as hypertrophy of growth plate, hyperostosis, and remodeling of metaphyseal and diaphyseal bone were observed in preclinical toxicology studies in juvenile rats administered high doses of vericiguat exceeding maximally tolerated dose.¹⁵ Mechanistically, it is known that NO/intracellular cGMP signaling is important for bone growth and remodeling in response to mechanical and hormonal stimuli. Preclinical evidence suggests a concentration-dependent effect of cGMP on long bone growth and remodeling, most relevant to bone growth in children and adolescents. The skeletal risk for children is unclear and an effect on growing bone is possible. Similar findings of bone abnormalities were identified in riociguat.

5.4 NT-PROBNP AND INCREASED CARDIOVASCULAR DEATH

An adverse trend for CV deaths were observed among vericiguat-treated subjects within the highest quartile of baseline NT-proBNP (NT-proBNP > 5314 pg/ml). Both components of the primary efficacy showed unfavorable trends in this subgroup: CV death (HR 1.16, 95% Confidence Interval (CI): (0.95, 1.43)) and first HF hospitalization (HR 1.19, 95% CI (0.9, 1.44)).

Of interest, an imbalance of SCD was also seen in the phase 3 HFpEF study, VITALITY (NCT 03547583), a randomized, paralleled-group, placebo-controlled, double-blind, multicenter study to further evaluate the efficacy and safety of vericiguat (5 mg and 10 mg) compared to placebo on improving physical functioning over 24 weeks in subjects with an LVEF >45%. A total of 789 subjects enrolled in VITALITY. CV death occurred in 3.8% of vericiguat-treated patients compared to 1.5% of the placebo treated patients, including sudden cardiac death (SCD) in 2% of VERQUVO-treated patients compared to none of the placebo-treated patients.^j

The incidences of CV death and SCD from the highest baseline NT-proBNP quartile of HFpEF subjects from VICTORIA and the HFpEF population from VITALITY raised concerns for a potential drug-related proarrhythmic effect with vericiguat (as competing negative effect to its overall beneficial vasodilatory effect). The review team conducted an extensive evaluation for possible pro-arrhythmic mechanism.

ⁱ Vericiguat safety scoping meeting, June 23, 2020

^j MCM clinical presentation, dated October 24, 2020

The Thorough QT (TQT) study, electrocardiogram (ECG) and the adverse event data from VICTORIA, and comprehensive in vitro Proarrhythmia Assay (CiPA)-compliant cardiac channel studies found no evidence for vericiguat-induced life-threatening ventricular arrhythmia.^{3,16,17,18} As the efficacy outcomes by NT-proBNP subgroup was a prespecified analysis in the Vericiguat HFrEF clinical development program, this information will be described in labeling, as will the results of the cardiac channel studies.

6 Expected Postmarket Use

6.1 HEALTHCARE SETTING

Vericiguat is intended for chronic oral administration by the patient in an outpatient setting but may also be utilized prior to hospital discharge. The dosing regimen is like other oral medications for HF requiring dose titration to the targeted maximum dose as tolerated. The prescriber population for vericiguat included primary care providers and cardiologists who will likely be familiar with treating patients with HFrEF and associated GDMT. These prescribers should be familiar with the risk for embryo-fetal toxicity in this patient population as several of the GDMT for HF, such as ACE inhibitors, ARBs, and ARNIs, are known to have this risk and per the proposed indication, Vericiguat is intended as an additional therapy in combination to the existing HF regimens in patients who experienced a worsening of HF event (see section 8). Although vericiguat is intended for the adult population, bone formation abnormalities are likely a class effect with the sGC and will be studied in PMRs.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for vericiguat beyond routine pharmacovigilance and labeling.

8 Discussion of Need for a REMS

The Clinical Reviewer recommends approval of Vericiguat based on the efficacy and safety information currently available.

The phase 3 VICTORIA study demonstrated a statistically significant effect on its primary endpoint, the time to first occurrence of CV death or HF hospitalization (HR: 0.90, 95%CI: 0.82, 0.98; p = 0.019), resulting in a 10% relative hazard reduction and a 4.2% annualized absolute risk reduction of compared to placebo or an NNT of 24. Key secondary endpoints trend in favor of vericiguat, although only the primary component of HF hospitalization achieved statistical significance. Overall, the clinical reviewer determined that the totality of evidence and overall results from the Phase 3 study support the beneficial effect of vericiguat for the treatment of HFrEF.

The incidences of AEs were comparable in the vericiguat and placebo groups. SAEs were observed more frequently in the placebo-treated subjects. Several AESIs such as anemia, syncope, symptomatic hypotension, and changes in liver functions occurred more frequently in the vericiguat study group

compared to the placebo group. Overall, the AEs were manageable and did not require specific therapy.

Three safety concerns were discussed during the review of the vericiguat's application: (1) Embryo-fetal toxicity, (2) effects on bone development, and (3) increased CV death with elevated NT-proBNP. These safety concerns are described separately below.

Embryo-fetal toxicity

Although there were no human data on vericiguat exposure and pregnancy, nonclinical studies in Vericiguat's clinical development program showed embryo-fetal toxicities in rats and rabbits resulting in cardiovascular malformation and maternal toxicity such as spontaneous abortions and resorptions. Embryo-fetal toxicity is considered a class effect of sGC.

Adempas (riociguat), NDA 204819, a sGC stimulator, is approved for PAH with a REMS to mitigate the risk of embryo-fetal toxicity. The Adempas REMS consists of elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments of the REMS. The ETASU includes prescriber certification (A), pharmacy certification (B), documentation of safe use conditions (D), and monitoring (E).

The Agency considers several factors when deciding whether to require a REMS for a product. These factors include:

- Estimated size of the population likely to use the drug
- Seriousness of the disease being treated
- Expected benefit of the drug
- Duration of treatment
- Seriousness of known or potential adverse effects
- Whether the drug is a new molecular entity

Vericiguat is an NME intended for chronic use as an addition to the patient's existing HF therapies after a worsening of HF event. As discussed in section 2 (Background), HF is a serious condition affecting a significant size of the population. HF affects approximately 6 million people in the US and about 50% have HFrEF, with higher incidence in older population and male gender.

The review team discussed the risk of embryo-fetal toxicity with vericiguat at the safety scoping meeting on June 23, 2020. The review team brought this application to the REMS Oversight Committee (ROC)^k to seek advice on whether vericiguat would require a REMS similar to riociguat for the risk of embryo-fetal toxicity. Discussion at the meeting included differences in patient population and prescriber practices for vericiguat compared to riociguat. In general, HF occurs more frequently in an older age

^k As per the 21st Century review process, all REMS with elements to assure safe use (ETASU) are discussed at the REMS Oversight Committee (ROC) which consists of senior level management from the Offices of New Drugs, Surveillance and Epidemiology, and Regulatory Policy.

group and in males, whereas, PAH occurs more frequently in younger females.^{19,20} The ROC was concerned that a REMS similar to riociguat (elements that restrict distribution) may cause access burden for females of non-reproductive potential with HFREF. As noted by several of the ROC members, none of the GDMT for HF such as ACE-inhibitors, ARBs, and ARNIs have a REMS and they stated that these drugs are well-known by prescribers to have embryo-fetal toxicity risk.²¹ The ROC recommended maximizing labeling to address this risk. DRM and DCN reviewers concurred with ROC that a REMS will not be required to mitigate the risk for embryo-fetal toxicity.

During the Midcycle meeting, held on September 1, 2020, the Agency informed the Applicant that the need for a REMS is unlikely, however, this risk is still an important major safety concern and asked the Applicant to provide adequate postmarketing pharmacovigilance activities to monitor for pregnancy exposure and appropriate labeling.¹ In response, the Applicant submitted a feasibility report using two large claims databases (from 2016 to 2019) with a combined total of more than 42 million patients and identified a total of 94 pregnancies in 5,772 females of childbearing age (CBA), females 10 to 55 years of age, who had HFREF and experienced a worsening heart failure event (WHFE).²² In the report, the Applicant projected that there would have been 11 pregnancies of interest in the year following a WHFE, assuming 12% as the peak targeted forecast uptake of vericiguat. Further, the Applicant estimated the number of potentially qualified patients for inclusion in a postmarketing safety epidemiology study would be very small, suggesting low feasibility and would not yield meaningful results from a pregnancy registry. Although the Applicant did not agree that vericiguat had significant embryo-fetal toxicity, they agreed to revise labeling to include a boxed warning, a contraindication, a Warnings statement, and instructions for Specific population which were not in the original labeling submission.

DCN consulted the Division of Pediatric and Maternal Health (DPMH) on labeling and postmarketing data to provide information on exposure during pregnancy. DPMH recommends labeling similar to other HF pharmacotherapies with this risk consisting of a BW, Pregnancy testing in FRP (Section 2), Contraindication (Section 4), Warning (Section 5), Use in Specific Populations (Section 8), and Patient Counseling (Section 17). DPMH concurred with the Applicant that a pregnancy registry would not be feasible in this population, however, DPMH recommended a Postmarketing Requirement (PMR) for a Single-Arm Pregnancy Safety Study to provide clinically relevant human safety data that can inform healthcare providers treating or counseling patients who are pregnant or anticipating pregnancy about the safety of drugs and biological products through inclusion of information in a product's labeling.²³ Labeling discussions are on-going, however, the Applicant agreed to the Agency's PMR in the LCM teleconference.

DRM consulted the Division of Epidemiology (DEPI) to assist in evaluating the frequency of pregnancies in patients with HF and HFREF and the usage of HF pharmacotherapies with embryo-fetal toxicity risk to better understand the extent of the at-risk population. DEPI conducted an analysis in six large data partners (covering more than 90% of the eligible population) to examine the prevalence of HF in females of childbearing age (defined as between the ages of 15 to 54 years old) and the frequency of pregnancies ending in live births or stillbirth deliveries between January 1, 2010 and February 29, 2020.²⁴⁻²⁶ DEPI also compared characteristics of and outcomes among pregnant females with HF, non-

pregnant females with HF, and pregnant females without HF. The results showed that the prevalence of HF and HFrEF increased with age and reached 1.2% in the 50-54 years group for HF and 0.3% for HFrEF. The overall prevalence of HF in females of childbearing age was low at 0.5% for HF and 0.1% for HFrEF. Pregnancy was rare in patients with HF and HFrEF. The majority of live birth or stillbirth deliveries occurred among younger patients, with the 25-29 age group having the highest proportions (34.9 per 1,000 females with HF and 33.6 per 1,000 females with HFrEF). Across different calendar years, the rate of live birth or stillbirth deliveries ranged from 2.6 to 3.6 per 1,000 females with HF and from 1.9 to 3.5 per 1,000 females with HFrEF. Using the prevalence of HF or HFrEF from this analysis and the 2019 US Census estimates, DEPI projected, among females of childbearing age in the US in 2019, there were 310,613 females with HF and 85,254 females with HFrEF. Among these females, projected numbers of pregnancies ending in live birth deliveries were 808 for females with HF and 247 for females with HFrEF, respectively. DEPI conducted further analyses to examine utilization of drugs commonly used in HF including those with embryo-fetal toxicity risk during pregnancy and maternal and fetal outcomes. There were 489 pregnancies (mean age, 32.4) in the pregnant HF cohort, 489 matched episodes (mean age, 32.4) in the non-pregnant HF cohort, and 1,245,931 pregnancies (mean age, 31.6) in the non-HF pregnant cohort. Results indicated beta-blockers (21.5%), diuretics (15.3%) and ACE-inhibitors (10.2%) were the most commonly used medications in females with HF during the pre-pregnancy period. ACE-inhibitor use during pregnancy reduced to 5.3% in the first trimester, less than 1% in the second or third trimester, but resumed to 8.0% in the post-pregnancy period. Other embryo-fetal toxic HF medications such as ARBs, ARNI, and Ivabradine were less common, especially during the second and third trimesters. Beta-blocker use remained unchanged during pregnancy. As expected, for pregnant females without HF, use of HF medications was low throughout the study period. A sensitivity analysis among women with HFrEF indicated that there were 91 pregnancies in females with HFrEF cases identified in the Sentinel¹ search for pregnant HFrEF cohort and the findings were consistent with the trends for pregnant females with HF. Based on the low use of HF medications generally, and the specific population (subtype of HF patients (symptomatic chronic HFrEF) vericiguat is indicated for, we expect vericiguat exposure to be limited. Thus, the possibility of inadvertent fetal exposure to vericiguat is likely very low. This information suggests that prescribers appear knowledgeable of HF medications with embryo-fetal risk as most patients were discontinued off of these HF medications during pregnancy. DRM and DCN concluded that labeling can adequately communicate this risk.

Bone formation abnormalities

Proliferative effects (hyperostosis) was noted on toxicology studies of vericiguat. The effect appears to be common to all sGC stimulators, though the magnitude of the effect is likely dependent on each specific drug's penetration into the bone (i.e., the magnitude of the hyperostotic effect is likely to be molecule specific). This effect was prominently demonstrated in the riociguat toxicology evaluation and

¹ The Sentinel System is a national distributed data network of electronic healthcare databases used by the FDA for active surveillance of medical product safety. The data sets contain person-level information on beneficiaries' demographics, diagnoses, and procedures associated with outpatient visits and inpatient stays, and outpatient-filled prescriptions.

was addressed in a consult from the Division of Bone, Reproductive, and Urologic Products (DBRUP) that is appended to the clinical review of that NDA in DARRTS. In accordance with that DBRUP consult, there is agreement with the clinical reviewers that it would be reasonably safe to conduct pediatric studies in older (adolescent) children with dilated cardiomyopathy (DCM), and then gate the decision to study younger DCM patients based on comprehensive juvenile animal assessments of the hyperostosis risk in young, rapidly growing bones of younger animals. This recommendation has been discussed with the Division of Pediatrics and Maternal Health (DPMH) and reviewed by the Pediatric Review Committee (PeRC). This review was influenced by the submission of a Pediatric Study Request during the NDA review cycle, further calling into question the rationale for waiving PREA requirements. Accordingly, a PMR for PREA studies will be issued for adolescent children, as well as a PMR for comprehensive juvenile animal studies to assess the risk of hyperostosis in young rapidly growing bone. Those preclinical toxicology studies will specifically examine vericiguat effects on the growth plates of the long bones to assess potential risks for vericiguat-induced growth abnormalities, as well as hyperostosis effects on the small bony foramina through which axial and cranial nerves traverse to assess potential risks for vericiguat-induced neurological compression syndromes. The decision to study younger children (versus a partial PREA waiver for study in younger children) with DCM will be predicated on the outcomes of these toxicology assessments.

Increased CV deaths

An adverse trend for CV deaths were observed among vericiguat-treated subjects within the highest quartile of baseline NT-proBNP. The BNP-related findings were extensively evaluated. There was no evidence of adverse cardiac interval effects from the TQT study or the surface ECGs from VICTORIA, no evidence of important channel interactions from the CiPA-compliant cardiac channel studies, and no excess in the occurrence of adverse events from VICTORIA suggestive of vericiguat-induced life-threatening ventricular arrhythmias. Regardless the observation regarding the adverse trend for CV deaths will be included in labeling.

In summary, the risk for embryo-fetal toxicity will be communicated through labeling. Although, vericiguat is in the same drug class as riociguat, which has a REMS to mitigate the risk of embryo-fetal toxicity, the clinical use, intended population, and prescribing practices differ. Vericiguat is recommended for approval in adults only pending pediatric toxicology studies that will guide the scope of the PREA waiver that will address the risks of hyperostosis. No pro-arrhythmic interactions with vericiguat were found and the observation of an adverse trend in CV deaths seen in subjects with elevated NT-proBNP will be included in labeling. Based on the proposed indication a REMS is not necessary to ensure the benefits outweigh the risks for vericiguat.

9 Conclusion & Recommendations

The overall efficacy showed benefit of vericiguat in improving CV death and hospitalization. AEs, SAEs, and SAEs with fatal outcome were similar across treatment groups, with placebo-treated patients having a higher proportion. Prespecified AESIs such as symptomatic hypotension, syncope, anemia, hepatic AEs, and liver function test occurred more frequently in vericiguat treatment group compared to

placebo. However, most cases, the events were manageable, did not require specific therapy, and did not result in an increase in study treatment discontinuation.

The review team identified two safety concerns: risk of embryo-fetal toxicity and abnormalities in bone formation such as hyperostosis. Several well-established GDMT for HF (ACE- inhibitors, ARBs, ARNIs) are known to have embryo-fetal toxicity risk. Based on prescribing patterns for other medicines used to treat HF, the data suggests prescribers who manage patients with heart failure appear to be familiar with embryo-fetal toxicity risk and discontinue HF therapies with this risk during pregnancy. Additionally, Vericiguat’s intended population is older and of male gender instead of younger females of childbearing age. Epidemiological data showed very low population of HFREF who become pregnant or are on HF medications with embryo-fetal risk during pregnancy. Similar to other medicines used to treat HF with the risk of embryo-fetal toxicity, labeling will include a boxed warning, contraindication, as well as warning and precaution statements.

The potential risks of vericiguat-induced effects on bone growth in young children will be addressed by a PMR for comprehensive juvenile animal studies that will guide the scope of a potential age-based PREA waiver.

No pro-arrhythmic interactions with vericiguat were found; however, the observation of an adverse trend in CV deaths seen in subjects with elevated NT-proBNP will be included in the clinical study (Section 14) of labeling.

Should DCN have any concerns or questions or if new safety information becomes available, please send a consult to DRM.

10 Appendices

10.1 PHARMACOLOGICAL THERAPY FOR HEART FAILURE WITH REDUCED EJECTION FRACTION (HFREF)^{12,27-29}

Drug Class	Drug	Initial Dose(s)	Targeted maximum dose	Selected Safety Concern and Prescribing Highlights
Renin Angiotensin System Blockers				
ACE inhibitor (most common)	Captopril	6.25 mg TID	50 mg TID	BW: • fetal toxicity and Pregnancy W&P: • angioedema • hypotension and hyperkalemia CI: • angioedema
	Enalapril	2.5 mg BID	10-20 mg BID	
	Lisinopril	2.5-5 mg QD	40 mg QD	
	Ramipril	1.25 mg QD	10 mg QD	
ARB	Candesartan	4-8 mg QD	32 mg QD	
	Losartan	25-50 mg QD	150 mg QD	
	Valsartan	20-40 mg BID	160 mg BID	
ARNI	Entresol (sacubitril-valsartan)	24/26 mg BID	97/103 mg BID	

Beta blocker				
	Carvedilol	3.125 mg BID	If < 85 kg: 25 mg BID If > 85 kg: 50 mg BID	BW: <ul style="list-style-type: none"> should not be withdrawn abruptly Caution: <ul style="list-style-type: none"> patients with diabetes, conduction abnormalities, myasthenia gravis, peripheral vascular disease (PVD) Pregnancy: <ul style="list-style-type: none"> teratogenic effects in Carvedilol labeling All beta blockers for HFrEF with pregnancy category C. CI: <ul style="list-style-type: none"> bronchial asthma, second- or third degree anterior ventricular block, sick sinus syndrome or severe bradycardia cardiogenic shock, decompensated HF requiring IV inotropic therapy
	Carvedilol CR	10 mg once daily	80 mg QD	
	Metoprolol succinate extended release (metoprolol CR/XL)	12.5 – 25 mg QD	200 mg QD	
	Bisoprolol	1.25 mg QD	10 mg QD	
Hydralazine and Isosorbide Dinitrate				
	Fixed dose combination	20 mg isosorbide dinitrate/ 37.5 mg hydralazine TID	40 mg isosorbide dinitrate/ 75 mg hydralazine TID	CI: <ul style="list-style-type: none"> use with PDE-5 inhibitors and sGC stimulator Use in Specific Populations <ul style="list-style-type: none"> Pregnancy category C
	Combined use of isosorbide dinitrate and hydralazine	20-30 mg isosorbide dinitrate TID or QID + 25- 50 mg hydralazine TID or QID	40 mg isosorbide dinitrate TID and 100 mg hydralazine TID	
Mineralocorticoid Receptor Antagonist (MRA) or Aldosterone Antagonist				
	Spirolactone	12.5-25 mg QD	25 mg QD or BID	W&P: <ul style="list-style-type: none"> hyperkalemia hypotension and worsening renal function electrolyte and metabolic abnormalities gynecomastia CI: <ul style="list-style-type: none"> Hyperkalemia, Addison disease
	Eplerenone	25 mg QD	50 mg QD	
Selective I _f inhibitor				
	Corlanor (ivabradine)	5 mg BID	7.5 mg BID	W&P: <ul style="list-style-type: none"> fetal toxicity atrial fibrillation

				<ul style="list-style-type: none"> • bradycardia CI: <ul style="list-style-type: none"> • decompensated HF, hypotension, bradycardia, hepatic impairment Use in Specific Populations <ul style="list-style-type: none"> • Pregnancy - may cause fetal harm
Sodium-glucose cotransporter 2 (SGLT2) inhibitor				
	Farxiga (dapagliflozin)	10 mg QD		W&P: <ul style="list-style-type: none"> • hypotension • ketoacidosis • acute kidney injury CI: <ul style="list-style-type: none"> • hypersensitivity, severe renal impairment/ERSD/ dialysis Use in Specific Populations <ul style="list-style-type: none"> • Pregnancy – potential risk to a fetus especially during the second and third trimester
ACE: angiotensin converting enzyme; ARNI: angiotensin receptor-neprilysin inhibitor; ARB: angiotensin receptor blocker; If: f-channels Inhibitor; QD: daily; BID: twice daily, TID: three times a day; QID: four times a day; BW: box warning; CI: contraindication; ESRD: End-stage renal disease; PDE-5: phosphodiesterase-5; sGC: soluble guanylate cyclase				

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