Summary Report of Benefit-Risk Assessment

VERQUVO FILM-COATED TABLET 10MG, 5MG, 2.5MG

NEW DRUG APPLICATION

Active Ingredient(s)	Vericiguat
Product Registrant	Bayer (South East Asia) Pte Ltd
Product Registration Number	SIN16340P, SIN16342P, SIN16343P
Application Route	Full evaluation
Date of Approval	01 October 2021

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A INTRODUCTION

Verquvo is indicated for the treatment of symptomatic chronic heart failure (HF) in adult patients with reduced ejection fraction, who are stabilised after a recent decompensation event requiring intravenous (IV) therapy. Verquvo is administered in combination with other HF therapies.

The active substance, vericiguat, is a stimulator of soluble guanylate cyclase (sGC). HF is associated with impaired synthesis of nitric oxide (NO) and decreased activity of its receptor, sGC. sGC catalyses the synthesis of intracellular cyclic guanosine monophosphate (cGMP), an important signalling molecule that regulates critical physiological processes such as cardiac contractility, vascular tone, and cardiac remodelling. Deficiency in sGC-derived cGMP contributes to myocardial and vascular dysfunction. Vericiguat restores the relative deficiency in this signalling pathway by directly stimulating sGC, independently of and synergistically with NO, to augment the levels of intracellular cGMP, which may improve both myocardial and vascular function. The complementary cardiovascular benefits of vericiguat in heart failure patients are therefore attributed to the active restoration of the deficient NO-sGC-cGMP pathway driving heart failure progression.

Verquvo is available as film-coated tablets containing 2.5mg, 5mg and 10mg of vericiguat. Other ingredients in the tablet core are cellulose microcrystalline, croscarmellose sodium, hypromellose, lactose monohydrate, magnesium stearate and sodium laurilsulfate. Ingredients in the film coating include hypromellose, talc, titanium dioxide (E171), ferric oxide red (E172) for 5mg tablets and ferric oxide yellow (E172) for 10mg tablets.

B ASSESSMENT OF PRODUCT QUALITY

The drug substance, vericiguat, is manufactured at [redacted] The drug product, Verquvo, is manufactured at Bayer AG, Leverkusen, Germany.

Drug substance:

Adequate controls have been presented for the starting materials, intermediates and reagents. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance are considered appropriate.

The characterisation of the drug substance and its impurities are in accordance with ICH guidelines. Potential and actual impurities are adequately controlled.

The drug substance specifications are established in accordance with ICH Q6A and the impurity limits are considered appropriately qualified. The analytical methods used are adequately described and non-compendial methods were appropriately validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing is presented.

The stability data presented for Bayer AG was adequate to support the approved storage condition and re-test period. The container closure system proposed for the drug substance is assessed to be appropriate. The drug substance does not require special storage condition and is approved with a re-test period of 24 months.

Drug product:

The tablet is manufactured using a wet granulation approach, followed by tablet compression and film-coating. The process is considered to be standard.

All manufacturing sites involved are compliant with Good Manufacturing Practice (GMP). Proper development and validation studies are conducted. It has been demonstrated that the manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications are established in accordance with ICH Q6A and impurity limits are considered adequately qualified. The analytical methods used are adequately described and non-compendial methods were appropriately validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing is presented.

The stability data submitted was adequate to support the approved shelf-life of 24 months when stored at or below 30 ºC. The tablets are packed in either PP/Alu blisters or PVC/PVDC/Alu blisters containing 14 tablets per blister.

C ASSESSMENT OF CLINICAL EFFICACY

The clinical efficacy of vericiguat was supported by one pivotal study, VICTORIA. This was a Phase III, randomised, placebo-controlled, parallel-group, multi-centre, double-blind, event-driven study comparing the addition of vericiguat or placebo to standard of care in subjects with symptomatic chronic HF and left ventricular ejection fraction (EF) <45% following a worsening HF event. A worsening HF event was defined as HF hospitalisation within 6 months before randomisation or use of outpatient IV diuretics for HF within 3 months before randomisation.

Subjects in the study were randomised in a 1:1 ratio to receive placebo or vericiguat at a starting dose of 2.5mg and titrated to 10 mg daily. The randomisation was stratified according to geographical region and race. Study medication was to be taken in addition to standard of care HF therapy following locally relevant guidelines.

The primary efficacy endpoint was the time to the first event of the composite endpoint of cardiovascular (CV) death or HF hospitalisation. Only clinical events confirmed by the independent Clinical Events Committee (CEC) were included in the efficacy analyses. Primary analysis was conducted when the protocol-specified number of 782 CV death events were anticipated to have occurred.

The full analysis set population comprised 2,526 subjects in the vericiguat group and 2,524 subjects in the placebo group. The median length of follow-up for the primary endpoint was 10.8 months, resulting in 5,240.9 patient years of follow-up.

The demographics and baseline characteristics were generally balanced between treatment groups. The mean age of the subjects was 67.3 years, and nearly one-quarter (23.9%) of the subjects were female. As per the study entry criteria, all subjects had evidence of HF decompensation within 6 months of randomisation. At randomisation, 58.9% of subjects were

categorised as New York Heart Association (NYHA) Class II, and 39.7% of subjects were categorised as NYHA Class III. The median N-terminal pro-brain natriuretic peptide (NT-proBNP) level was 2816.0 pg/mL (range: 10.0 to >175000.0 pg/mL). The use of background standard of care treatments at baseline and during follow-up were balanced between treatment groups.

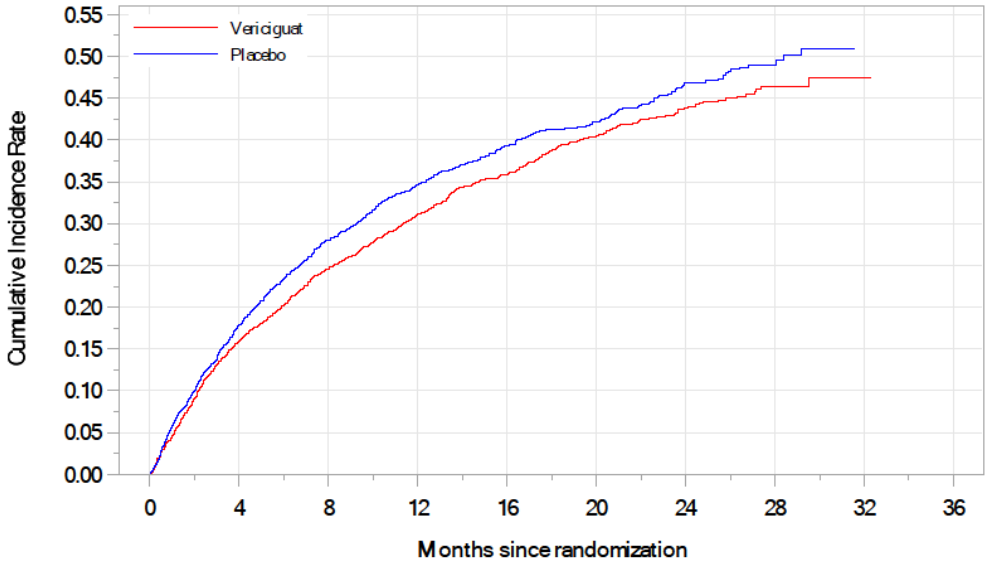
Summary of key efficacy results

Endpoints	**Vericiguat** (N=2,526)		**Placebo** (N=2,524)		**Hazard ratio** (95% CI)	**p-value**
	n (%)	Annualised event rate^	n (%)	Annualised event rate^		
Primary composite endpoint						
CV death or HF hospitalisation	897 (35.5)	33.6	972 (38.5)	37.8	0.90 (0.82, 0.98)	0.019
CV death#	206 (8.2)		225 (8.9)			
HF hospitalisation	691 (27.4)		747 (29.6)			
Secondary endpoints						
CV death	414 (16.4)	12.9	441 (17.5)	13.9	0.93 (0.81, 1.06)	0.269
HF hospitalisation	691 (27.4)	25.9	747 (29.6)	29.1	0.90 (0.81, 1.00)	0.048
Total HF hospitalisations (first and recurrent)	1223	38.3	1336	42.4	0.91 (0.84, 0.99)	0.023
All-cause mortality or HF hospitalisation	957 (37.9)	35.9	1032 (40.9)	40.1	0.90 (0.83, 0.98)	0.021
All-cause mortality#	266 (10.5)		285 (11.3)			
HF hospitalisation	691 (27.4)		747 (29.6)			
All-cause mortality	512 (20.3)	16.0	534 (21.2)	16.9	0.95 (0.84, 1.07)	0.377

Based on data up to the primary completion date (18 Jun 2019).
^Total subjects with an event per 100 subject years at risk.
#Deaths included in the composite endpoint were not preceded by HF hospitalisation.

Treatment with vericiguat resulted in a statistically significant reduction in the risk of CEC-confirmed CV death or HF hospitalisation compared with placebo (hazard ratio [HR] 0.90; 95% CI 0.82-0.98; p=0.019). The treatment effect was mainly driven by a reduction in the risk of HF hospitalisation. The annualised absolute risk reduction was 4.2 events per 100 patient-years with vericiguat relative to placebo.

Kaplan-Meier Plot for cumulative event rate of the primary endpoint of CV death or HF hospitalisation



Number of subjects at risk

Vericiguat	2526	2099	1621	1154	826	577	348	125	1	0
Placebo	2524	2053	1555	1097	772	559	324	110	0	0

Cumulative number of events up to the time point

Vericiguat	0	402	609	733	803	857	885	896	897	897
Placebo	0	448	694	823	890	924	960	969	972	972

Results with respect to the endpoints on time to CV death and time to first HF hospitalisation were consistent with the primary endpoint, with a marginally statistically significant relative risk reduction of 10% in first HF hospitalisation (HR 0.90; 95% CI 0.81-1.00; p=0.048), and a 7% relative risk reduction in CV death which was not statistically significant (HR 0.93; 95% CI 0.81-1.06; p=0.269).

Similar results were observed with respect to the reduction in the risk of total HF hospitalisation (first and recurrent) (HR 0.91; 95% CI 0.84-0.99; p=0.023) as well as the composite of all-cause mortality or HF hospitalisation compared with placebo (HR 0.90; 95% CI 0.83-0.98; p=0.021). For the all-cause mortality endpoint, no significant difference was observed compared to placebo (HR 0.95; 95% CI 0.84-1.07; p=0.377).

In the subgroup analysis of the primary composite endpoint, unfavourable HR was observed for the subgroup with baseline NT-proBNP values in the highest quartile (>5314 pg/mL) (HR 1.16; 95% CI 0.99-1.35); while post-hoc multivariate analyses showed that among patients with high NT-proBNP above 4230 pg/mL, patients with serum chloride levels ≤99 mEq/L benefited from vericiguat treatment. As low serum chloride levels may be associated with volume depletion when diuretic therapy is optimised, the findings suggested that patients with very high NT-proBNP level would require further optimisation of volume status, diuretic therapy and other HF therapies before treatment initiation with vericiguat, in order to derive benefit from vericiguat. This observation was in congruence with the post-hoc analysis results which showed that the efficacy of vericiguat differed based on the time between index event and randomisation, where the risk reduction in the composite primary endpoint was the least among patients enrolled less than 3 months after a prior hospitalisation for HF. Therefore,

vericiguat should only be used in patients who are stabilised after a decompensation event. The package insert had included information on the need to optimise volume status and diuretic therapy, as well as other guideline-directed heart failure therapies, to stabilise patients after the decompensation event, particularly in patients with very high NT-proBNP levels, before initiating vericiguat.

In summary, while the treatment effect of vericiguat in reduction of composite of CV death or first HF hospitalisation was modest and mainly driven by the reduction in HF hospitalisations, the treatment effect was considered clinically relevant in the context of high-risk population who has recent HF decompensation events and is at significant risk for CV mortality and repeated HF hospitalisations. The data presented was reasonable to support the efficacy of vericiguat for the treatment of symptomatic chronic HF in adult patients with reduced EF who are stabilised after a recent decompensation event requiring IV therapy, in combination with other HF therapies.

D ASSESSMENT OF CLINICAL SAFETY

The clinical safety of vericiguat was based primarily on data derived from the pivotal Phase III VICTORIA study, comprising a total of 5,034 subjects (2,519 subjects in the vericiguat group and 2,515 subjects in the placebo group) who had received at least one dose of study medication. As of the primary completion date of the study (18 Jun 2019), the mean duration of exposure to any dose of vericiguat was 375.5 days (max. 964 days) and to 10 mg vericiguat was 362 days (max. 935 days). The mean duration of exposure to placebo was 374.7 days (max. 966 days).

Overview of safety profile

	Vericiguat (N=2,519)	**Placebo (N=2,515)**
Any AE	2,027 (80.5%)	2,036 (81.0%)
Drug-related AE	367 (14.6%)	294 (11.7%)
Serious AE	826 (32.8%)	876 (34.8%)
Serious drug-related AE	30 (1.2%)	20 (0.8%)
Discontinuations due to AE	167 (6.6%)	158 (6.3%)
Deaths due to non-CV causes	98 (3.9%)	93 (3.7%)

The incidences of adverse events (AEs) were similar in the vericiguat and placebo groups (80.5% vs 81.0%). The AE profile of vericiguat was predominantly associated with its mechanism of action (i.e., relaxation of smooth muscle leading to hemodynamic changes and gastrointestinal side effects). Few AEs with incidences ≥2% were reported with a higher frequency in the vericiguat group compared with the placebo group: anaemia (7.6% vs 5.7%), dyspepsia (2.7% vs 1.1%), nausea (3.8% vs 2.7%), and headache (3.4% vs 2.4%).

The overall incidences of serious AEs (SAEs) were similar in the vericiguat and placebo groups (32.8% vs 34.8%), and the SAEs with incidences ≥2% had similar incidences between treatment groups. The incidences of drug-related SAEs were low and similar between the treatment groups (1.2% vs 0.8%). The incidences of discontinuations due to AEs (6.6% vs 6.3%) and non-CV deaths (3.9% vs 3.7%) were similar between the treatment groups.

The AEs of special interest reported with vericiguat included gastrointestinal AEs, hypotension, syncope and anaemia. The incidence of gastrointestinal AEs was higher in the vericiguat group compared with the placebo group (25.3% vs 21.7%). These AEs included diarrhoea (5.2% vs 4.9%), dyspepsia (2.7% vs 1.1%), nausea (3.8% vs 2.7%), vomiting (2.2% vs 1.8%) and

constipation (2.9% vs 3.1%). The imbalances in the proportions of subjects with these gastrointestinal AEs between treatment groups were small and the events were generally infrequent and non-serious.

The incidence of hypotension was slightly higher in the vericiguat group compared with the placebo group (15.4% vs 14.1%). Similar results were observed for orthostatic hypotension (1.3% vs 1.0%) and symptomatic hypotension (9.1% vs 7.9%). Most symptomatic hypotension events were categorised as non-serious and were mild in intensity. Likewise for syncope, the incidence was slightly higher in the vericiguat group compared with the placebo group (4.0% vs 3.5%). However, the proportions of subjects with SAE of syncopal events, drug-related syncopal events, or syncopal events leading to treatment discontinuation were low and similar between the treatment groups. In addition, there was no evidence that the symptomatic hypotension events or syncope events were associated with contemporaneous fall or fracture.

The incidence of anaemia was higher in the vericiguat group compared with the placebo group (7.6% vs 5.7%). Anaemia-related SAE was more frequently reported in the vericiguat group compared with the placebo group (1.6% vs 0.9%). No serious drug-related AEs of anaemia were also reported. The proportion of subjects who experienced a haematocrit below the lower limit of normal with a decrease of ≥10 percentage points from baseline was higher in the vericiguat group compared with the placebo group (3.9% vs 2.2%). Similar findings were noted for subjects who experienced a haemoglobin value below the lower limit of normal with a decrease ≥3 g/dL (5.0% vs 3.2%). The possible mechanism contributing to the higher percentage of anaemia AEs in the vericiguat group is not well understood, but anaemia has been previously reported with another sGC stimulator.

Overall, the safety profile of vericiguat was generally non-serious and manageable. The AEs of special interest included gastrointestinal AEs, hypotension, syncope and anaemia. These safety concerns were adequately addressed in the package insert.

E ASSESSMENT OF BENEFIT-RISK PROFILE

HF is a is a chronic, progressive disease that is characterised by frequent hospital admissions and ultimately, high mortality rates. The current guideline-recommended standard of care for HF with reduced EF includes angiotensin-converting enzyme inhibitors, beta-blockers, and/or mineralocorticoid receptor antagonists. Despite treatment with the current standard of care, there is substantial risk of morbidity and mortality in these patients, especially for patients with worsening HF events, which are associated with poor prognosis.

Vericiguat had demonstrated statistically significant reduction in CV death or HF hospitalisation (HR 0.90; 95% CI 0.82-0.98; p=0.019), with an absolute risk reduction of 4.2 events per 100 patient-years relative to placebo. The treatment effect was mainly driven by a reduction in the risk of HF hospitalisation. Overall, the results were considered clinically relevant in the context of high-risk patient population who has recent HF decompensation events despite receiving standard of care HF treatments.

The results of the key secondary endpoints were consistent with respect to risk reduction in total HF hospitalisation and the composite of all-cause mortality or HF hospitalisation compared with placebo. There was a lack of treatment benefit in patients with very high NT-proBNP level (> 4230 pg/mL) at baseline. However, exploratory analyses suggested that that patients with very high elevations in NT-proBNP might require further optimisation of their

underlying HF therapies and volume status in order to derive benefit from additional therapies such as vericiguat. The recommendation to initiate vericiguat after optimising volume status and diuretic therapy, as well as other HF therapies, to stabilise patients after the decompensation event, particularly in patients with very high NT-proBNP levels had been included in the package insert.

The safety profile of vericiguat was considered acceptable relative to the benefits. The safety risks such as gastrointestinal AEs, hypotension and anaemia have been adequately described in the package insert.

Overall, the benefit-risk profile of vericiguat for the treatment of symptomatic chronic HF in adult patients with reduced EF who are stabilised after a recent decompensation event requiring IV therapy, in combination with other HF therapies, was considered positive.

F CONCLUSION

Based on the review of quality, safety and efficacy data, the benefits of Verquvo in combination with other HF therapies for the treatment of symptomatic chronic HF in adult patients with reduced EF, who are stabilised after a recent decompensation event requiring IV therapy outweighed the risks and approval of the product registration was granted on 01 October 2021.

APPROVED PACKAGE INSERT AT REGISTRATION

VERQUVO (vericiguat)

1. INDICATIONS AND USAGE

VERQUVO (vericiguat) is indicated for the treatment of symptomatic chronic heart failure in adult patients with reduced ejection fraction, who are stabilised after a recent decompensation event requiring IV therapy. Vericiguat is administered in combination with other HF therapies *[see 9. CLINICAL STUDIES].*

2. DOSAGE AND ADMINISTRATION

Before starting VERQUVO, care should be taken to optimise volume status and diuretic therapy, as well as other guideline-directed heart failure therapies, to stabilise patients after the decompensation event, particularly in patients with very high NT-proBNP levels *[see 9. CLINICAL STUDIES].*

2.1 Adults

- The recommended starting dose of VERQUVO is 2.5 mg once daily, taken with food.
- Double the dose of VERQUVO approximately every 2 weeks to reach the target maintenance dose of 10 mg once daily, as tolerated by the patient.
- For patients who are unable to swallow whole tablets, VERQUVO may be crushed and mixed with water immediately before administration *[see 10. CLINICAL PHARMACOLOGY, 10.4 Pharmacokinetics]*.

Missed Dose

If a dose is missed, it should be taken as soon as the patient remembers on the same day of the missed dose. Patients should not take two doses of VERQUVO on the same day.

2.2 Pediatric Patients

Safety and efficacy of VERQUVO have not been established in patients less than 18 years of age *[see 6. USE IN SPECIFIC POPULATIONS, 6.3 Pediatric Use and 10. CLINICAL PHARMACOLOGY, 10.4 Pharmacokinetics]*.

2.3 Geriatric Patients

No dosage adjustment of VERQUVO is required for geriatric patients *[see 6. USE IN SPECIFIC POPULATIONS, 6.4 Geriatric Use and 10. CLINICAL PHARMACOLOGY, 10.4 Pharmacokinetics]*.

2.4 Renal Impairment

No dose adjustment of VERQUVO is required in patients with estimated glomerular filtration rate (eGFR) ≥15 mL/min/1.73m^2 (without dialysis). VERQUVO has not been studied in patients with eGFR <15 mL/min/1.73m^2 at treatment initiation or on dialysis and is therefore not recommended in these patients *[see 6. USE IN SPECIFIC POPULATIONS, 6.5 Renal Impairment, 9. CLINICAL STUDIES, and 10. CLINICAL PHARMACOLOGY, 10.4 Pharmacokinetics]*.

2.5 Hepatic Impairment

No dose adjustment of VERQUVO is required in patients with mild or moderate hepatic impairment. VERQUVO has not been studied in patients with severe hepatic impairment and is therefore not recommended in these patients *[see 6. USE IN SPECIFIC POPULATIONS, 6.6 Hepatic Impairment and 10. CLINICAL PHARMACOLOGY, 10.4 Pharmacokinetics]*.

3. CONTRAINDICATIONS

VERQUVO is contraindicated in patients with concomitant use of other soluble guanylate cyclase (sGC) stimulators, such as riociguat *[see 5. DRUG INTERACTIONS AND OTHER FORMS OF INTERACTIONS, 5.2 Other Soluble Guanylate Cyclase Stimulators]*.

Hypersensitivity to the active substance or to any of the excipients listed in section *14.2 Composition*.

4. WARNINGS AND PRECAUTIONS

4.1 Symptomatic Hypotension

VERQUVO may cause symptomatic hypotension. In the VICTORIA clinical trial, adverse events determined by the investigator to be events of symptomatic hypotension were reported in 9.1% of patients treated with VERQUVO and 7.9% of patients treated with placebo and were considered serious in 1.2% of patients treated with VERQUVO and 1.5% of patients treated with placebo *[see 7. ADVERSE REACTIONS, 7.1 Clinical Trials Experience]*. VERQUVO has not been studied in patients with systolic blood pressure less than 100 mmHg or symptomatic hypotension at treatment initiation.

Consider the potential for symptomatic hypotension in patients with hypovolemia, severe left ventricular outflow obstruction, resting hypotension, autonomic dysfunction, history of hypotension, or concomitant treatment with antihypertensives or organic nitrates *[see 10. CLINICAL PHARMACOLOGY, 10.5 Drug Interaction Studies]*. If symptomatic hypotension occurs, consider dose adjustment of diuretics and treatment of other causes of hypotension (e.g., hypovolemia). If symptomatic hypotension persists despite such measures, temporary reduction in dose or interruption of VERQUVO should be considered.

Concomitant use of VERQUVO and phosphodiesterase-5 (PDE-5) inhibitors, such as sildenafil, has not been studied in patients with heart failure and is therefore not recommended due to the potential increased risk for symptomatic hypotension *[see 5. DRUG INTERACTIONS AND OTHER FORMS OF INTERACTIONS, 5.1 PDE-5 Inhibitors and 10. CLINICAL PHARMACOLOGY, 10.5 Drug Interaction Studies]*.

5. DRUG INTERACTIONS AND OTHER FORMS OF INTERACTIONS

5.1 PDE-5 Inhibitors

Concomitant use of VERQUVO and PDE-5 inhibitors, such as sildenafil, has not been studied in patients with heart failure and is therefore not recommended due to the potential increased risk for symptomatic hypotension *[see 4. WARNINGS AND PRECAUTIONS, 4.1 Symptomatic Hypotension and 10. CLINICAL PHARMACOLOGY, 10.5 Drug Interaction Studies]*.

5.2 Other Soluble Guanylate Cyclase Stimulators

VERQUVO is contraindicated in patients with concomitant use of other soluble guanylate cyclase (sGC) stimulators, such as riociguat *[see 3. CONTRAINDICATIONS]*.

6. USE IN SPECIFIC POPULATIONS

6.1 Pregnancy
There are no data from the use of VERQUVO in pregnant women**.** Studies in animals have shown reproductive toxicity in presence of maternal toxicity *[see section 11.6 Development].* Given the potential for mechanism-based hemodynamic effects, VERQUVO is not recommended during pregnancy and in women of childbearing potential not using contraception.

6.2 Nursing Mothers
There is no information regarding the presence of vericiguat in human milk, the effects on the breast-fed infant, or the effects on milk production. Vericiguat is present in the milk of lactating rats. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from VERQUVO therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

6.3 Pediatric Use
Safety and efficacy of VERQUVO have not been established in patients less than 18 years of age *[see section 11.2 Chronic Toxicity].*

6.4 Geriatric Use
No dosage adjustment of VERQUVO is required in geriatric patients. In VICTORIA, a total of 1,596 (63%) patients treated with VERQUVO were 65 years and older and 783 (31%) patients treated with VERQUVO were 75 years and older. No overall differences in safety or efficacy of VERQUVO were observed between patients aged 65 years and older compared to younger patients, but greater sensitivity of some older individuals cannot be ruled out *[see 9. CLINICAL STUDIES and 10. CLINICAL PHARMACOLOGY, 10.4 Pharmacokinetics]*.

6.5 Renal Impairment
No dose adjustment of VERQUVO is required in patients with eGFR ≥15 mL/min/1.73m^2 (without dialysis). VERQUVO has not been studied in patients with eGFR <15 mL/min/1.73m^2 at treatment initiation or on dialysis and is therefore not recommended in these patients *[see 2. DOSAGE AND ADMINISTRATION, 2.4 Renal Impairment, 9. CLINICAL STUDIES, and 10. CLINICAL PHARMACOLOGY, 10.4 Pharmacokinetics]*.

6.6 Hepatic Impairment
No dose adjustment of VERQUVO is required in patients with mild or moderate hepatic impairment. VERQUVO has not been studied in patients with severe hepatic impairment and is therefore not recommended in these patients *[see 2. DOSAGE AND ADMINISTRATION, 2.5 Hepatic Impairment and 10. CLINICAL PHARMACOLOGY, 10.4 Pharmacokinetics]*.

7. ADVERSE REACTIONS

7.1 Clinical Trials Experience

VERQUVO was evaluated in VICTORIA, a Phase 3 randomized, placebo-controlled, double-blind, clinical trial in adult patients with symptomatic chronic heart failure and ejection fraction less than 45% following a worsening heart failure event, which included a total of 2,519 patients treated with VERQUVO (up to 10 mg once daily) and 2,515 patients treated with matching placebo *[see 9. CLINICAL STUDIES]*. The mean duration of VERQUVO exposure was 1 year, and the maximum duration was 2.6 years. Table 1 lists adverse drug reactions occurring in patients treated with VERQUVO and greater than placebo in VICTORIA.

Table 1: Adverse Drug Reactions Occurring in Patients Treated with VERQUVO and Greater than Placebo in VICTORIA by System Organ Class (SOC)

Adverse Drug Reaction	VERQUVO N=2,519 n (%)	Placebo N=2,515 n (%)
Blood and lymphatic system disorders		
Anemia*	243 (9.6)	185 (7.4)
Gastrointestinal disorders		
Nausea	96 (3.8)	67 (2.7)
Dyspepsia	67 (2.7)	27 (1.1)
Vomiting	56 (2.2)	45 (1.8)
Gastroesophageal reflux disease	44 (1.7)	17 (0.7)
Nervous system disorders		
Dizziness	169 (6.7)	150 (6.0)
Headache	86 (3.4)	61 (2.4)
Vascular disorders		
Hypotension†	412 (16.4)	375 (14.9)

*Includes: anemia, anemia macrocytic, anemia of chronic disease, autoimmune hemolytic anemia, blood loss anemia, hemolytic anemia, hypochromic anemia, iron deficiency anemia, microcytic anemia, nephrogenic anemia, normochromic anemia, normochromic normocytic anemia, normocytic anemia, pancytopenia, pernicious anemia, hematocrit decreased, hemoglobin decreased, and red blood cell count decreased

†Includes: blood pressure decreased, blood pressure diastolic decreased, blood pressure systolic decreased, hypotension, and orthostatic hypotension

8. OVERDOSAGE

Limited data are available with regard to overdosage in human patients treated with VERQUVO. In VICTORIA, doses up to 10 mg have been studied. In a study of patients with preserved ejection fraction heart failure (left ventricular ejection fraction ≥45%), multiple doses of vericiguat 15 mg have been studied and were generally well tolerated. In the event of an overdose, hypotension may result. Symptomatic treatment should be provided. VERQUVO is unlikely to be removed by hemodialysis because of high protein binding.

9. CLINICAL STUDIES

VICTORIA was a randomized, parallel-group, placebo-controlled, double-blind, event-driven, multi-center trial comparing VERQUVO and placebo in 5,050 adult patients 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.

The primary objective of VICTORIA was to determine whether VERQUVO in combination with other heart failure therapies is superior to placebo in reducing the risk of cardiovascular (CV) death or heart failure hospitalization in adults with symptomatic chronic heart failure and ejection fraction less than 45% following a worsening heart failure event.

Patients were treated up to the target maintenance dose of VERQUVO 10 mg once daily or matching placebo. Therapy was initiated at VERQUVO 2.5 mg once daily and increased in approximately 2-week intervals to 5 mg once daily and then 10 mg once daily, as tolerated. After approximately 1 year, 90% of patients in both the VERQUVO and placebo arms were treated with the 10 mg target dose.

The primary endpoint was the time to first event of the composite of CV death or hospitalization for heart failure. The median follow-up for the primary endpoint was 11 months.

The population was 64% Caucasian, 22% Asian, and 5% Black. The mean age was 67 years and 76% were male. 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 (EF) was 29% and approximately half of all patients had an EF <30%, and 14% of patients had an EF 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 62 mL/min/1.73 m^2; the majority of patients (88%) had an eGFR >30 mL/min/1.73 m^2, and 10% of patients had an eGFR ≤30 mL/min/1.73 m^2. Sixty-seven percent of the patients in VICTORIA were enrolled within 3 months of a HF-hospitalization index event; 17% were enrolled within 3 to 6 months of HF hospitalization, and 16% were enrolled within 3 months of outpatient treatment with IV diuretics for worsening HF. The median NT-proBNP level was 2816 pg/mL at randomization.

At baseline, more than 99% of patients were treated with other heart failure therapies; 93% of patients were on a beta blocker, 73% of patients were on an angiotensin-converting enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB), 70% of patients were on a mineralocorticoid receptor antagonist (MRA), 15% of patients were on a combination of an angiotensin receptor and neprilysin inhibitor (ARNI), 28% of patients had an implantable cardiac defibrillator, and 15% had a biventricular pacemaker. Ninety-one percent of patients were treated with 2 or more heart failure medications (beta blocker, any renin-angiotensin system [RAS] inhibitor, or MRA) and 60% of patients were treated with all 3. At baseline, 6% of patients were on ivabradine and 3% of patients were on a sodium glucose co-transporter 2 (SGLT2) inhibitor.

In VICTORIA, VERQUVO was superior to placebo in reducing the risk of CV death or heart failure hospitalization based on a time-to-event analysis (hazard ratio [HR]: 0.90, 95% confidence interval [CI], 0.82-0.98; p=0.019). Over the course of the study, there was a 4.2% annualized absolute risk reduction (ARR) with VERQUVO compared with placebo. Therefore, 24 patients would need to be treated over an average of 1 year to prevent 1 primary endpoint event. The treatment effect reflected a reduction in the risk of both cardiovascular death and heart failure hospitalization; see Table 2.

VERQUVO (vericiguat)

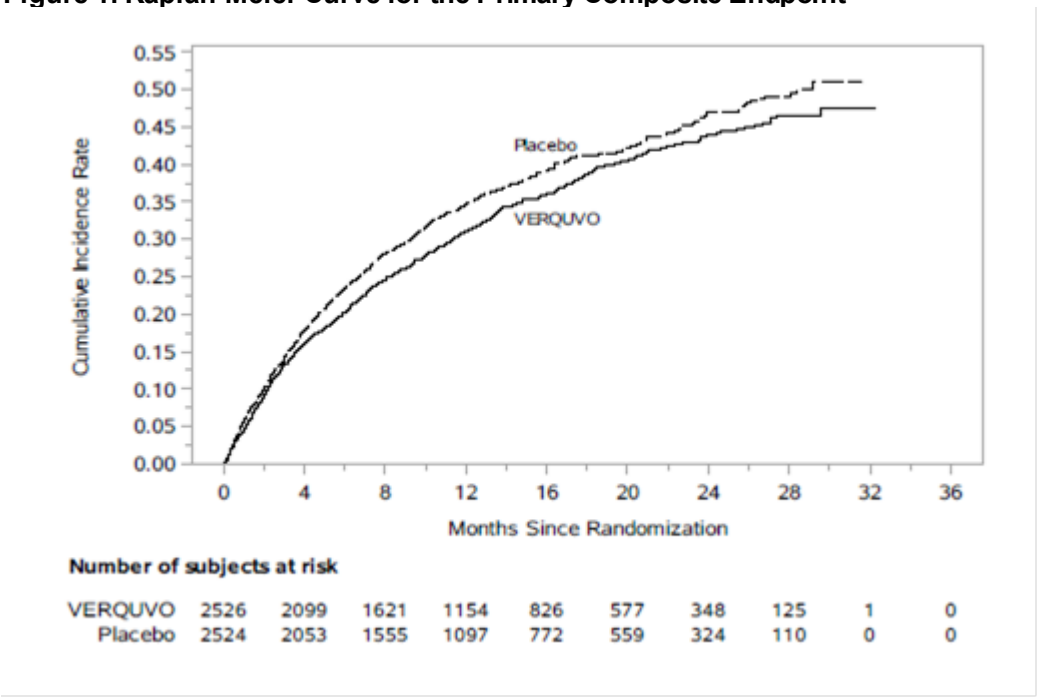
Table 2: Treatment Effect for the Primary Composite Endpoint, Its Components, and the Secondary Endpoints of Cardiovascular Death and Heart Failure Hospitalizations

	VERQUVO N=2,526		Placebo N=2,524		Treatment Comparison		
	n (%)	Annual %*	n (%)	Annual %*	Hazard Ratio (95% CI)†	p-value‡	Annualized ARR %§
Primary endpoint							
Composite of cardiovascular death or heart failure hospitalization¶	897 (35.5)	33.6	972 (38.5)	37.8	0.90 (0.82, 0.98)	0.019	4.2
Cardiovascular death	206 (8.2)		225 (8.9)				
Heart failure hospitalization	691 (27.4)		747 (29.6)				
Secondary endpoints							
Cardiovascular death	414 (16.4)	12.9	441 (17.5)	13.9	0.93 (0.81, 1.06)		
Heart failure hospitalization	691 (27.4)	25.9	747 (29.6)	29.1	0.90 (0.81, 1.00)		

*Total patients with an event per 100 patient years at risk.
†Hazard ratio (VERQUVO over Placebo) and confidence interval from a Cox proportional hazards model.
‡From the log-rank test.
§Annualized absolute risk reduction, calculated as difference (Placebo-VERQUVO) in annual %.
¶For patients with multiple events, only the first event contributing to the composite endpoint is counted.
N=Number of patients in Intent-to-Treat (ITT) population; n=Number of patients with an event.

The Kaplan-Meier curve (Figure 1) shows time to first occurrence of the primary composite endpoint of cardiovascular death or heart failure hospitalization.

Figure 1: Kaplan-Meier Curve for the Primary Composite Endpoint



In VICTORIA, VERQUVO was superior to placebo in reducing the risk of all-cause mortality or HF hospitalization (HR 0.90 [95% CI, 0.83-0.98]) and total events (first and recurrent) of HF hospitalization (HR 0.91 [95% CI, 0.84-0.99]); see Tables 3 and 4. The total number of HF hospitalization events was greater in the placebo group (1,336 events) than the VERQUVO group (1,223 events).

Table 3: Treatment Effect for All-Cause Mortality or Heart Failure Hospitalizations

	VERQUVO N=2,526		Placebo N=2,524		Hazard Ratio (95% CI)†
	n (%)	Annual %*	n (%)	Annual %*	
Composite of all-cause mortality or heart failure hospitalization‡	957 (37.9)	35.9	1,032 (40.9)	40.1	0.90 (0.83, 0.98)
All-cause mortality	266 (10.5)		285 (11.3)		
Heart failure hospitalization	691 (27.4)		747 (29.6)		

*Total patients with an event per 100 patient years at risk.
†Hazard ratio (VERQUVO over Placebo) and confidence interval from a Cox proportional hazards model.
‡For patients with multiple events, only the first event contributing to the composite endpoint is counted.
N=Number of patients in ITT population; n=Number of patients with an event.

Table 4: Treatment Effect for Total Events (First and Recurrent) of Heart Failure Hospitalization

	VERQUVO N=2,526			Placebo N=2,524			Hazard Ratio (95% CI)†
	n	Total Follow-up Time (years)	Annual %*	n	Total Follow-up Time (years)	Annual %*	
Total number of heart failure hospitalizations (first and recurrent)	1,223	3,190.7	38.3	1,336	3,151.0	42.4	0.91 (0.84, 0.99)
Patients‡ with:							
One event	415			431			
Two events	160			179			
Three events	55			75			
≥Four events	61			62			

*Total events per 100 patient years of follow up.

†Hazard ratio (VERQUVO over Placebo) and confidence interval from an Andersen-Gill model.

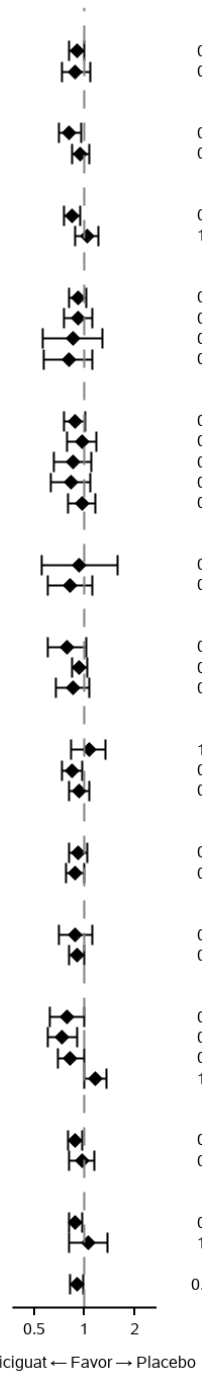
‡Patients with events are counted only once.

N=Number of patients in ITT population.

A wide range of demographic characteristics, baseline disease characteristics, and baseline concomitant medications were examined for their influence on outcomes. The results of the prespecified subgroup analysis for the primary composite endpoint are shown in Figure 2. The results of the primary composite endpoint were generally consistent across subgroups. However, among patients in the highest baseline NT-proBNP quartile, the estimated HRs 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]) were unfavorable, in contrast to the estimated HRs for patients in the three quartiles with lower NT-proBNP levels. Patients with very high NT-proBNP may not be fully stabilised and require further optimisation of volume status and diuretic therapy [see 1. INDICATION AND USAGE and 2. DOSAGE AND ADMINISTRATION].

Figure 2: Primary Composite Endpoint (CV Death or HF Hospitalization) - Subgroup Analysis

	% of Total Population	Vericiguat n (%)	Placebo n (%)	Hazard Ratio (95% CI)
Gender				
Male	76.1	704 (36.6)	762 (39.7)	0.90 (0.81,1.00)
Female	23.9	193 (31.9)	210 (34.8)	0.88 (0.73,1.08)
Age Group 1 (years)				
< 65	37.1	290 (31.3)	348 (36.7)	0.81 (0.70,0.95)
=> 65	62.9	607 (37.9)	624 (39.6)	0.94 (0.84,1.06)
Age Group 2 (years)				
< 75	69.0	579 (33.3)	669 (38.4)	0.84 (0.75,0.94)
=> 75	31.0	318 (40.5)	303 (38.7)	1.04 (0.88,1.21)
Race				
White	64.1	593 (36.6)	635 (39.2)	0.91 (0.81,1.02)
Asian	22.4	199 (34.9)	207 (36.9)	0.91 (0.75,1.11)
Black	4.9	41 (33.3)	50 (39.7)	0.85 (0.56,1.28)
Other	8.5	64 (30.5)	80 (36.5)	0.80 (0.57,1.11)
Geographic Region				
Eastern Europe	33.5	310 (36.6)	345 (40.8)	0.87 (0.75,1.01)
Western Europe	17.6	173 (39.1)	178 (39.9)	0.96 (0.78,1.18)
North America	11.1	103 (36.7)	117 (41.9)	0.85 (0.65,1.10)
Latin and South America	14.3	100 (27.6)	116 (32.0)	0.83 (0.63,1.08)
Asia Pacific	23.4	211 (35.6)	216 (36.5)	0.96 (0.79,1.16)
Race in North America				
Black	2.4	26 (41.9)	29 (47.5)	0.93 (0.55,1.58)
Non-Black	8.7	77 (35.2)	88 (40.4)	0.82 (0.60,1.11)
Index Event				
IV diuretic < 3 months	15.9	96 (24.1)	120 (29.9)	0.78 (0.60,1.02)
Hospitalization < 3 months	66.9	660 (39.5)	701 (41.1)	0.93 (0.84,1.04)
Hospitalization 3-6 Months	17.2	141 (31.1)	151 (36.2)	0.85 (0.67,1.07)
eGFR at Baseline (mL/min/1.73 m^2)				
<=30	10.0	143 (55.2)	128 (51.8)	1.06 (0.83,1.34)
>30 to <=60	41.9	392 (37.2)	455 (42.8)	0.84 (0.73,0.96)
>60	46.2	346 (29.8)	372 (31.7)	0.92 (0.80,1.07)
NYHA Class at Baseline				
Class I/II	59.0	445 (30.1)	484 (32.3)	0.91 (0.80,1.04)
Class III/IV	41.0	451 (43.2)	487 (47.6)	0.87 (0.77,0.99)
Use of Sacubitril/Valsartan at Baseline				
Yes	14.5	134 (37.2)	153 (41.2)	0.88 (0.70,1.11)
No	85.3	760 (35.2)	818 (38.1)	0.90 (0.81,0.99)
NT-proBNP at Baseline by Quartiles (pg/mL)				
Q1 (<=1556)	23.8	128 (21.4)	161 (26.7)	0.78 (0.62,0.99)
Q2 (1556 - 2816)	23.8	165 (26.9)	201 (34.1)	0.73 (0.60,0.90)
Q3 (2816 - 5314)	23.7	213 (36.3)	257 (41.9)	0.82 (0.69,0.99)
Q4 (>5314)	23.8	355 (57.6)	302 (51.6)	1.16 (0.99,1.35)
Ejection Fraction at Screening				
<35%	68.6	637 (36.9)	703 (40.4)	0.88 (0.79,0.97)
=>35%	31.1	255 (32.2)	265 (34.0)	0.96 (0.81,1.14)
<40%	85.5	773 (35.8)	851 (39.4)	0.88 (0.80,0.97)
=>40%	14.3	119 (33.2)	117 (32.3)	1.05 (0.81,1.36)
Overall	100.0	897 (35.5)	972 (38.5)	0.90 (0.82, 0.98)



10. CLINICAL PHARMACOLOGY

10.1 Therapeutic Class
Soluble guanylate cyclase (sGC) stimulator.

Pharmacotherapeutic group: Cardiac therapy, ATC code: C01DX22.

10.2 Mechanism of Action
Vericiguat is a stimulator of soluble guanylate cyclase (sGC). Heart failure is associated with impaired synthesis of nitric oxide (NO) and decreased activity of its receptor, sGC. Soluble guanylate cyclase catalyzes synthesis of intracellular cyclic guanosine monophosphate (cGMP), an important signaling molecule that regulates critical physiological processes such as cardiac contractility, vascular tone, and cardiac remodeling. Deficiency in sGC-derived cGMP contributes to myocardial and vascular dysfunction. Vericiguat restores the relative deficiency in this signaling pathway by directly stimulating sGC, independently of and synergistically with NO, to augment the levels of intracellular cGMP, which may improve both myocardial and vascular function. The complementary cardiovascular benefits of vericiguat in heart failure patients are therefore attributed to the active restoration of the deficient NO-sGC-cGMP pathway driving heart failure progression.

10.3 Pharmacodynamics
The pharmacodynamic effects of vericiguat were evaluated after single and multiple dose administrations in healthy subjects and in patients with heart failure and are consistent with the mode of action of an sGC stimulator resulting in smooth muscle relaxation and vasodilation. Over the course of the VICTORIA study, the mean reduction in systolic blood pressure was approximately 1 to 2 mmHg greater in patients who received VERQUVO compared with placebo.

In a 12-week placebo-controlled dose-finding study (SOCRATES-REDUCED) in patients with heart failure, vericiguat demonstrated a dose-dependent reduction in NT-proBNP, a biomarker in heart failure, compared to placebo when added to standard of care. In VICTORIA, the estimated reduction from baseline NT-proBNP at week 32 was greater in patients who received VERQUVO compared with placebo *[see 9. CLINICAL STUDIES]*.

Cardiac Electrophysiology
In a dedicated QT study in patients with stable coronary artery disease, administration of vericiguat 10 mg at steady-state did not prolong the QT interval to a clinically relevant extent, i.e. the maximum mean prolongation of the QTcF interval did not exceed 6 ms (upper bound of the 90%CI <10 ms). Supratherapeutic exposures have not been tested.

10.4 Pharmacokinetics
General Introduction
Vericiguat shows slightly less than dose proportional, time-independent pharmacokinetics, with low to moderate variability when administered with food. Vericiguat accumulates in plasma up to 155-171% and reaches pharmacokinetic steady-state after approximately 6 days. The mean steady-state population pharmacokinetic (PK) parameters of vericiguat in heart failure patients are summarized in Table 5.

Table 5: Population Pharmacokinetic Model Based Steady-state Geometric Mean (CV%) Plasma Pharmacokinetic Parameters of Vericiguat 2.5 mg, 5 mg, or 10 mg in Heart Failure Patients (N=2,321)

PK Parameters	2.5 mg	5 mg	10 mg
C_{max} (µg/L)	120 (29.0)	201 (29.0)	350 (29.0)
AUC (µg•h/L)	2,300 (33.9)	3,850 (33.9)	6,680 (33.9)

Absorption
The absolute bioavailability of vericiguat is high (93%) when taken with food. Bioavailability (AUC) and peak plasma levels (C_{max}) of vericiguat administered orally as a crushed tablet in water is comparable to that of a whole tablet *[see 2. DOSAGE AND ADMINISTRATION, 2.1 Adults]*.

Effect of Food
Administration of vericiguat with a high-fat, high-calorie meal increases T_{max} from about 1 hour (fasted) to about 4 hours (fed), reduces PK variability, and increases vericiguat exposure by 19% (AUC) and 9% (C_{max}) for the 5 mg tablet and by 44% (AUC) and 41% (C_{max}) for the 10 mg tablet as compared with the fasted state. Similar results were obtained when vericiguat was administered with a low-fat, high-carbohydrate meal. Therefore, VERQUVO should be taken with food *[see 2. DOSAGE AND ADMINISTRATION, 2.1 Adults]*.

Distribution
The mean steady-state volume of distribution of vericiguat in healthy subjects is approximately 44 L. Plasma protein binding of vericiguat is about 98%, with serum albumin being the main binding component. Plasma protein binding of vericiguat is not altered by renal or hepatic impairment.

Metabolism
Glucuronidation is the major biotransformation pathway of vericiguat to form an N-glucuronide, which is pharmacologically inactive and the major drug related component in plasma. N-glucuronidation is catalyzed predominantly by UGT1A9, as well as UGT1A1. CYP-mediated metabolism is a minor clearance pathway (<5%).

Elimination
Vericiguat is a low-clearance drug (1.6 L/h in healthy subjects). The half-life is about 20 hours in healthy subjects and 30 hours in heart failure patients. Following oral administration of [^{14}C]-vericiguat to healthy subjects, approximately 53% of the dose was excreted in urine (primarily as the N-glucuronide) and 45% of the dose was excreted in feces (primarily as vericiguat).

Special Populations

Renal Impairment
No relevant increase in exposure (AUC) was observed for heart failure patients with moderate and severe renal impairment not requiring dialysis. In patients with heart failure with moderate (eGFR ≥30 to <60 mL/min/1.73m^2) and severe renal impairment (eGFR ≥15 to <30 mL/min/1.73m^2) not requiring dialysis, the mean exposure (AUC) of vericiguat was increased by 13% and 20%, respectively, compared to patients with normal renal function. The pharmacokinetics of vericiguat have not been studied in patients with eGFR <15 mL/min/1.73m^2 at treatment initiation or on dialysis *[see 2. DOSAGE AND ADMINISTRATION, 2.4 Renal Impairment and 6. USE IN SPECIFIC POPULATIONS, 6.5 Renal Impairment]*.

Hepatic Impairment
No relevant increase in exposure (unbound AUC) was observed for subjects with mild hepatic impairment (Child Pugh A) with mean exposure to vericiguat 21% higher compared to healthy subjects with normal hepatic function. In subjects with moderate hepatic impairment (Child Pugh B), mean exposure to vericiguat was approximately 47% higher compared to their healthy subjects with normal hepatic function. The pharmacokinetics of vericiguat have not been studied in patients with severe hepatic impairment (Child-Pugh C) *[see 2. DOSAGE AND ADMINISTRATION, 2.5 Hepatic Impairment and 6. USE IN SPECIFIC POPULATIONS, 6.6 Hepatic Impairment]*.

Pediatric
No studies with VERQUVO have been performed in pediatric patients.

Body Weight
In a population pharmacokinetic analysis of vericiguat, the steady-state AUC values were approximately 27% higher in heart failure patients with a body weight <60 kg and approximately 20% lower in heart failure patients with a body weight >90 kg, compared to heart failure patients with a body weight between 60 and 90 kg. The effect of body weight on vericiguat exposure is not clinically meaningful.

Effects of Age, Gender, Ethnicity, Race, and Baseline NT-proBNP
Based on a population pharmacokinetic analysis, age, gender, ethnicity, race, and baseline NT-proBNP do not have a clinically meaningful effect on the pharmacokinetics of vericiguat.

10.5 Drug Interaction Studies
***In Vitro* Assessment of Drug Interactions**
In vitro studies indicate that vericiguat and its N-glucuronide are neither inhibitors of major CYP isoforms (CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4) or UGT isoforms (UGT1A1, 1A4, 1A6, 1A9, 2B4, and 2B7), nor inducers of CYP1A2, 2B6, and 3A4, at clinically relevant concentrations.

Vericiguat is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) transporters and is not a substrate of organic cation transporter (OCT1), or organic anion transporting polypeptides (OATP1B1 and OATP1B3). Vericiguat and its N-glucuronide are not inhibitors of drug transporters, including P-gp, BCRP, BSEP, OATP1B1/1B3, OAT1, OAT3, OCT1, OCT2, MATE1, and MATE2K, at clinically relevant concentrations.

Overall, these data indicate that the administration of VERQUVO is unlikely to affect the pharmacokinetics of concurrently administered medications that are substrates of these enzymes or transporters.

***In Vivo* Assessment of Drug Interactions**
No dose adjustment of VERQUVO is recommended when coadministered with commonly prescribed medicinal products. There was no clinically relevant effect on vericiguat pharmacokinetics with coadministration of drugs increasing gastric pH (e.g. proton pump inhibitors, H2-receptor antagonists, antacids) in heart failure patients; or with coadministration of mefenamic acid, ketoconazole, rifampicin, digoxin, warfarin, aspirin, sildenafil, or the combination of sacubitril/valsartan in healthy subjects. There was no clinically relevant effect on vericiguat pharmacokinetics with coadministration of atazanavir based on physiologically-based PK (PBPK) modeling. Vericiguat also had no clinically relevant effect on the pharmacokinetics of midazolam, digoxin, warfarin, sildenafil, and the combination of sacubitril/valsartan when coadministered in healthy subjects.

Effects of Other Drugs on the Pharmacokinetics of Vericiguat
The effects of coadministered drugs on the pharmacokinetics of vericiguat have been assessed in clinical drug-drug interaction studies.

Drugs Increasing Gastric pH (e.g. Proton Pump Inhibitors, H2-receptor Antagonists, Antacids)

Co-treatment with drugs that increase gastric pH, such as proton pump inhibitors, H2-receptor antagonists, or antacids, did not affect vericiguat exposure when vericiguat was taken as directed with food in heart failure patients *[see 2. DOSAGE AND ADMINISTRATION, 2.1 Adults]*.

Multi-pathway CYP and Transporter Inhibitor (Ketoconazole)
Multiple-dose administration of ketoconazole 200 mg twice daily was not associated with a clinically relevant effect on the exposure of vericiguat 1.25 mg. The vericiguat mean AUC and mean C_{max} following coadministration with ketoconazole were increased by approximately 12%.

UGT1A9 Inhibitor (Mefenamic Acid)
A starting dose of mefenamic acid 500 mg followed by multiple-dose administration of 250 mg every 6 hours over 48 hours was not associated with a clinically relevant effect on the exposure of vericiguat 2.5 mg. The vericiguat mean AUC was increased by 20% and mean C_{max} was decreased by 3%, following coadministration with mefenamic acid.

UGT1A1 Inhibitor (Atazanavir)
Co-administration of atazanavir 400 mg once daily was not associated with a clinically relevant effect on the exposure of vericiguat 10 mg based on physiologically-based PK (PBPK) modeling. The predicted vericiguat mean AUC and mean C_{max} were increased by 12% and 4%, respectively.

Broad Spectrum Inducer (Rifampicin)
Multiple-dose administration of rifampicin 600 mg once daily for 8 days was not associated with a clinically relevant effect on the exposure of vericiguat 10 mg. The vericiguat mean AUC and mean C_{max} following coadministration with rifampicin were decreased by 29% and 9%, respectively.

PDE-5 Inhibitor (Sildenafil)
Single-dose administration of sildenafil 25, 50, and 100 mg was not associated with a clinically relevant effect on the exposure of multiple doses of vericiguat 10 mg once daily. The vericiguat mean AUC and mean C_{max} following coadministration with sildenafil 25, 50, and 100 mg were changed by less than 4% and less than 9%, respectively. No dose-dependent effect on the pharmacokinetics of vericiguat was observed with the different sildenafil doses.

Effects of Vericiguat on the Pharmacokinetics of Other Drugs
The effects of vericiguat on the pharmacokinetics of coadministered drugs have been assessed in clinical drug-drug interaction studies.

CYP3A Substrate (Midazolam)
Multiple-dose administration of vericiguat 10 mg once daily for 4 days was not associated with a clinically relevant effect on the exposure of a single-dose of midazolam 7.5 mg. The midazolam mean AUC and mean C_{max} following coadministration with vericiguat were decreased by 18% and 23%, respectively.

PDE-5 Inhibitor (Sildenafil)
Multiple-dose administration of vericiguat 10 mg once daily was not associated with a clinically relevant effect on the exposure of a single-dose of sildenafil 25, 50, and 100 mg. The sildenafil 25, 50, and 100 mg mean AUC and mean C_{max} following coadministration with vericiguat were increased by 13-22% and 14-20%, respectively.

Concomitant Use with Medicinal Products Commonly Prescribed to Heart Failure Patients
P-gp Substrate (Digoxin)
Multiple-dose administration of digoxin 0.375 mg together with multiple doses of vericiguat 10 mg once daily was not associated with clinically relevant effects on the exposure (AUC and C_{trough}) of digoxin. Multiple-dose administration of digoxin 0.375 mg together with a single-dose of vericiguat 10 mg was not associated with clinically relevant effects on the exposure (AUC and C_{max}) of vericiguat.

VERQUVO (vericiguat)

Anticoagulant (Warfarin)
Single-dose administration of warfarin 25 mg together with multiple doses of vericiguat 10 mg once daily was not associated with clinically relevant effects on the exposure (AUC and C_{max}) of either drug.

Antiplatelet Agent (Aspirin)
Multiple-dose administration of aspirin 500 mg once daily together with a single-dose of vericiguat 15 mg was not associated with clinically relevant effects on the exposure (AUC and C_{max}) of vericiguat.

Neprilysin Inhibitor/Angiotensin II Receptor Blocker (Combination of Sacubitril/Valsartan)
Multiple-dose administration of the fixed dose combination of sacubitril 97 mg and valsartan 103 mg twice daily together with a single-dose of vericiguat 2.5 mg was not associated with clinically relevant effects on the exposure (AUC and C_{max}) of vericiguat. The vericiguat mean AUC and mean C_{max} following coadministration with sacubitril/valsartan were decreased by 7% and 9%, respectively. Multiple-dose administration of the fixed dose combination of sacubitril 97 mg and valsartan 103 mg twice daily together with multiple doses of vericiguat 2.5 mg once daily was not associated with clinically relevant effects on the exposure (AUC and C_{max}) of sacubitril, LBQ657 (active metabolite of sacubitril), or valsartan. The sacubitril mean AUC and mean C_{max} following coadministration with vericiguat were increased by 8% and 18%, respectively. The LBQ657 mean AUC and mean C_{max} following coadministration with vericiguat were increased by 1% and 2%, respectively. The valsartan mean AUC and mean C_{max} following coadministration with vericiguat were increased by 12% and 13%, respectively.

Pharmacodynamic Interactions
Acetylsalicylic Acid (Aspirin)
Administration of a single-dose of vericiguat 15 mg in healthy subjects did not alter the effect of acetylsalicylic acid 500 mg on bleeding time or platelet aggregation. Bleeding time or platelet aggregation did not change under treatment with vericiguat 15 mg alone.

Warfarin
Administration of multiple doses of vericiguat 10 mg once daily in healthy subjects did not alter the effect of a single-dose of warfarin 25 mg on prothrombin time and the activities of Factors II, VII, and X.

Combination of Sacubitril/Valsartan
Addition of multiple doses of vericiguat 2.5 mg to multiple doses of sacubitril/valsartan 97/103 mg in healthy subjects had no additional effect on seated blood pressure (BP) compared to administration of sacubitril/valsartan alone.

Sildenafil
Addition of single doses of sildenafil (25, 50, or 100 mg) to multiple doses of vericiguat 10 mg once daily in healthy subjects was associated with additional seated BP reduction of less than or equal to 5.4 mmHg (systolic/diastolic BP, MAP) compared to administration of vericiguat alone. No dose-dependent trend was observed with the different sildenafil doses *[see 4. WARNINGS AND PRECAUTIONS, 4.1 Symptomatic Hypotension]*.

Organic Nitrates
Co-administration of multiple doses of vericiguat increased to 10 mg once daily did not significantly alter the seated BP effects of short- and long-acting nitrates (nitroglycerin spray and isosorbide mononitrate [ISMN] modified release 60 mg) in patients with coronary artery disease. In patients with heart failure, concomitant use of short-acting nitrates was well tolerated. There is limited experience with concomitant use of vericiguat and long-acting nitrates in patients with heart failure *[see 4. WARNINGS AND PRECAUTIONS, 4.1 Symptomatic Hypotension]*.

11. ANIMAL TOXICOLOGY

11.1 Acute Toxicity
No acute toxicity was observed in pivotal repeat-dose oral toxicity studies in rats up to 60 mg/kg/day and in dogs up to 25 mg/kg/day (approximately 75 or 12 times the human exposure [unbound AUC] at the maximum recommended human dose [MRHD] of 10 mg/day).

11.2 Chronic Toxicity
Repeat-dose oral toxicity studies were conducted in rats and dogs for up to 26 and 39 weeks, respectively. In the chronic toxicity studies, no adverse signs of toxicity were observed up to exposures equal to approximately 50 (rat) or 8 (dog) times the human exposure (unbound AUC) at the MRHD of 10 mg/day.

The toxicological profile was characterized by effects secondary to exaggerated pharmacodynamics. Secondary to smooth muscle relaxation hemodynamic and gastrointestinal effects were noted in all species investigated. In adolescent rapidly-growing rats, reversible bone effects consisting of hypertrophy of growth plate and hyperostosis and remodeling of metaphyseal and diaphyseal bone were seen that were mediated by a mode of action-related intracellular cGMP increase. These effects were not observed after chronic administration of vericiguat to adult rats up to exposures of approximately 50 times the human exposure at the MRHD. In addition, no comparable findings were seen with dogs which were almost full-grown at start of treatment up to exposures of 15 times the human exposure at the MRHD.

11.3 Carcinogenesis
Carcinogenicity was evaluated in 2-year studies conducted in CD1 mice and Wistar rats. Vericiguat did not show a carcinogenic effect in mice dosed up to 150 mg/kg/day (males) or up to 250 mg/kg/day (females). These doses were associated with exposures 149 (males) or 286 (females) times the human exposure (unbound AUC) at the MRHD of 10 mg/day.

In the carcinogenicity study in rats, no vericiguat-related tumor or hyperplastic findings were seen up to exposures of 12 times the human exposure at the MRHD. A non-statistical numerical increase of benign pheochromocytomas and Leydig cell tumors as well as respective hyperplasias were observed in males after administration of the high dose of 20 mg/kg/day leading to exposure of 41 times the human exposure at the MRHD. This is considered a consequence of a compensatory and recurrent activation of the renin angiotensin aldosterone and the adrenergic system due to a marked daily decrease in blood pressure over 2 years. Based on the known sensitivity of rats to develop these two tumor types in contrast to humans and a documented pharmacological-based mechanism (seen also with other antihypertensive drugs) at supratherapeutic doses as well as adequate safety margins this is considered not relevant for patients.

Non-clinical data revealed no carcinogenic risk for humans at clinical doses.

11.4 Genotoxicity
Vericiguat was not genotoxic in the *in vitro* microbial mutagenicity (Ames) assay, the *in vitro* mouse lymphoma assay, and the *in vivo* rat and mouse micronucleus assay.

11.5 Reproduction
In a 4-week repeat dose fertility and early embryonic development study in male and female rats, vericiguat when administered orally at doses of 5, 15 or 50 mg/kg/day had no effects on fertility or reproductive performance at up to the highest dose tested of 50 mg/kg/day (66 times the human exposure at the MRHD of 10 mg/day, unbound AUC).

11.6 Development

A study in pregnant rats showed that vericiguat is transferred to the fetus through the placenta. Development toxicity studies in rats with vericiguat administered orally during organogenesis showed no development toxicity up to 50 mg/kg/day (75 times the human unbound AUC at the MRHD of 10 mg). Exaggerated pharmacodynamic-mediated maternal toxicity was observed ≥21 times the human unbound AUC at the MRHD; there was no maternal toxicity at 9 times the human exposure at MRHD. In rabbits, the exaggerated pharmacodynamic-mediated maternal toxicity was observed at 2.5 mg/kg/day and above (≥6 times the human unbound AUC at the MRHD) resulting in secondary late spontaneous abortions and resorptions. In addition, at this dose, a low incidence of malformation of the heart and major vessels was seen. While this could not be unambiguously attributed to vericiguat treatment, cardiac and major vessel abnormalities were observed following maternal administration of a structurally related compound (riociguat) to rats. No maternal, embryofetal or developmental toxicity was seen in rabbits following maternal oral doses of 0.75 mg/kg/day, respectively (approximately equivalent to the human exposure, based on unbound AUC, at the MRHD).

In a pre/postnatal toxicity study, vericiguat administered orally to rats during gestation through lactation showed exaggerated pharmacodynamic-mediated maternal toxicity at approximately ≥9 times the human exposure at the MRHD (based on unbound AUC), which resulted in decreased pup body weight gain (≥21 times the MRHD) and pup mortality (45 times the MRHD) during the preweaning period.

VERQUVO (vericiguat)

12. NAME OF THE DRUG

VERQUVO Film-coated Tablet 2.5 mg (vericiguat 2.5 mg)
VERQUVO Film-coated Tablet 5 mg (vericiguat 5 mg)
VERQUVO Film-coated Tablet 10 mg (vericiguat 10 mg)

13. PHARMACEUTICAL FORM

Film-coated tablets.

VERQUVO 2.5 mg film-coated tablets
Round, biconvex, white film-coated tablet with a diameter of 7 mm, debossed with "2.5" on one side and "VC" on the other side.

VERQUVO 5 mg film-coated tablets
Round, biconvex, brown-red film-coated tablet with a diameter of 7 mm, debossed with "5" on one side and "VC" on the other side.

VERQUVO 10 mg film-coated tablets
Round, biconvex, yellow-orange film-coated tablet with a diameter of 9 mm, debossed with "10" on one side and "VC" on the other side.

14. PHARMACEUTICAL PARTICULARS

14.1 Chemistry

The chemical name of vericiguat is methyl {4,6-diamino-2-[5-fluoro-1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b] pyridin-3-yl] pyrimidin-5-yl} carbamate. The molecular formula is $C_{19}H_{16}F_2N_8O_2$ and the molecular weight is 426.39 g/mol.

The chemical structure is:

Vericiguat is a white to yellowish powder that is freely soluble in dimethyl sulfoxide, slightly soluble in acetone, very slightly soluble in ethanol, acetonitrile, methanol, ethyl acetate, and practically insoluble in 2-propanol.

VERQUVO (vericiguat)

14.2 Composition

Active Ingredient
VERQUVO 2.5 mg film-coated tablets
Each film-coated tablet contains 2.5 mg vericiguat.

VERQUVO 5 mg film-coated tablets
Each film-coated tablet contains 5 mg vericiguat.

VERQUVO 10 mg film-coated tablets
Each film-coated tablet contains 10 mg vericiguat.

Inactive Ingredients (List of excipients)
VERQUVO tablets contain the inactive ingredients:
VERQUVO 2.5, 5, and 10 mg film-coated tablets
Cellulose microcrystalline
Croscarmellose sodium
Hypromellose 5 cP
Lactose monohydrate
Magnesium stearate
Sodium laurilsulfate

The film coating contains:
VERQUVO 2.5 mg film-coated tablets
Hypromellose 5 cP
Talc
Titanium dioxide (E171)

VERQUVO 5 mg film-coated tablets
Ferric oxide red (E172)
Hypromellose 5 cP
Talc
Titanium dioxide (E171)

VERQUVO 10 mg film-coated tablets
Ferric oxide yellow (E172)
Hypromellose 5 cP
Talc
Titanium dioxide (E171)

14.3 Storage
Do not store above 30°C

14.4 Incompatibilities
Not applicable

14.5 Shelf Life
2 years

14.6 Availability (a.k.a. Nature and contents of container)
VERQUVO 2.5 mg film-coated tablets
PP/Al- or PVC/PVDC/Al- foil blister in cartons of 14 or 28 film-coated tablets

VERQUVO (vericiguat)

VERQUVO 5 and 10 mg film-coated tablets
PP/Al- or PVC/PVDC/Al- foil blister in cartons of 14, 28 or 98 film-coated tablets

Not all presentations may be available locally

14.7 Manufacturer
Bayer AG
Kaiser-Wilhelm-Allee
51368 Leverkusen
Germany

Date of Revision of the Text
September 2021