# VERQUVO®

## Film-coated tablet

## NAME OF THE DRUG

VERQUVO 2.5 mg (vericiguat 2.5 mg)
VERQUVO 5 mg (vericiguat 5 mg)
VERQUVO 10 mg (vericiguat 10 mg)

## 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.

## INDICATIONS AND USAGE

Verquvo is indicated for the treatment of symptomatic chronic heart failure in adult patients with reduced ejection fraction less than 45% who are stabilized with IV diuretic therapy after hospitalization for heart failure, occurring on guideline-based medical therapy, including angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARB), betablockers, mineralocorticoid receptor antagonists (MRA), and a combination of an angiotensin receptor and neprilysin inhibitor (ARNI).

## DOSAGE AND ADMINISTRATION

**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.
- If patients experience tolerability issues (symptomatic hypotension or systolic blood pressure [SBP] less than 90 mmHg), temporary down-titration or discontinuation of vericiguat is recommended
- For patients who are unable to swallow whole tablets, VERQUVO may be crushed and mixed with water immediately before administration *[see CLINICAL PHARMACOLOGY, Pharmacokinetics]*.

Verquvo is administered in conjunction with other heart failure therapies (see Clinical Studies).

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.

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

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

**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 USE IN SPECIFIC POPULATIONS, Renal Impairment, CLINICAL STUDIES, and CLINICAL PHARMACOLOGY, Pharmacokinetics]*.

**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 USE IN SPECIFIC POPULATIONS, Hepatic Impairment and CLINICAL PHARMACOLOGY, Pharmacokinetics]*.

## CLINICAL PHARMACOLOGY

**Therapeutic Class**
Soluble guanylate cyclase (sGC) stimulator.

Pharmacotherapeutic group: Cardiac therapy, ATC code: C01DX22.

**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.

**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 CLINICAL STUDIES]*.

Cardiac Electrophysiology
There was no evidence of proarrhythmic risk in an *in vitro* assessment of vericiguat or its major N-glucuronide metabolite. No inhibition of cardiac ion channels (hERG, hNav1.5, or hKvLQT1/mink) was observed at substantial multiples of their unbound $C_{max}$ values at the recommended target dose of 10 mg.

The integrated risk assessment of nonclinical and clinical data supports that administration of vericiguat 10 mg is not associated with clinically meaningful QTc prolongation.

**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 1.

**Table 1: 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 DOSAGE AND ADMINISTRATION, 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 DOSAGE AND ADMINISTRATION, Adults]*.

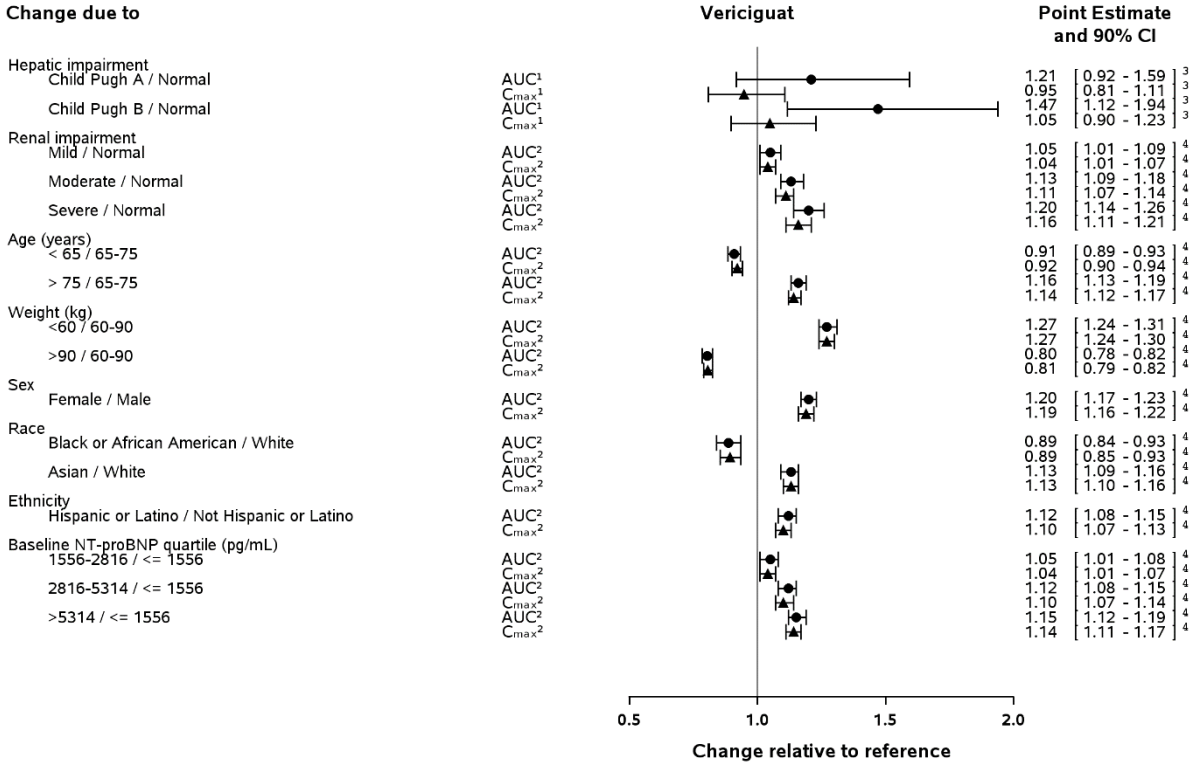
**Distribution**
The mean steady-state volume of distribution of vericiguat in healthy subjects is approximately 44 L. Plasma protein binding of vericiguat is about 98%, with serum albumin being the main binding component. Plasma protein binding of vericiguat is not altered by renal or hepatic impairment.

**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**
Effects of specific populations on the pharmacokinetics of vericiguat are shown in Figure 1.

**Figure 1: Pharmacokinetics of Vericiguat in Specific Populations**




CI: Confidence Interval.
1. Dose and body weight normalized AUC and dose and body weight normalized $C_{max}$ of unbound concentrations after single dose administration.
2. AUC over the dosing interval after multiple dose administration. $C_{max}$ after multiple dose administration.
3. Based on data from healthy subjects (phase I trial).
4. Based on population-pharmacokinetic (POP-PK) modeling of VICTORIA and SOCRATES-REDUCED.

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 mild, moderate, and severe renal impairment not requiring dialysis, the mean exposure (AUC) of vericiguat was increased by 5%, 13%, and 20% respectively, compared to patients with normal renal function. These differences in exposure are not considered clinically relevant. The pharmacokinetics of vericiguat have not been studied in patients with eGFR less than 15 mL/min/1.73m2 at treatment initiation or on dialysis.

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 DOSAGE AND ADMINISTRATION, Hepatic Impairment and USE IN SPECIFIC POPULATIONS, 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.

**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 (see Figure 2 and Table 2). There was no clinically relevant effect on vericiguat pharmacokinetics with coadministration of atazanavir based on physiologically-based PK (PBPK) modeling (see Figure 2 and Table 2). 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 (see Figure 3 and Table 3).

**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 (see Figure 2 and Table 2).
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 DOSAGE AND ADMINISTRATION, 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 (see Figure 3 and Table 3).

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.

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.

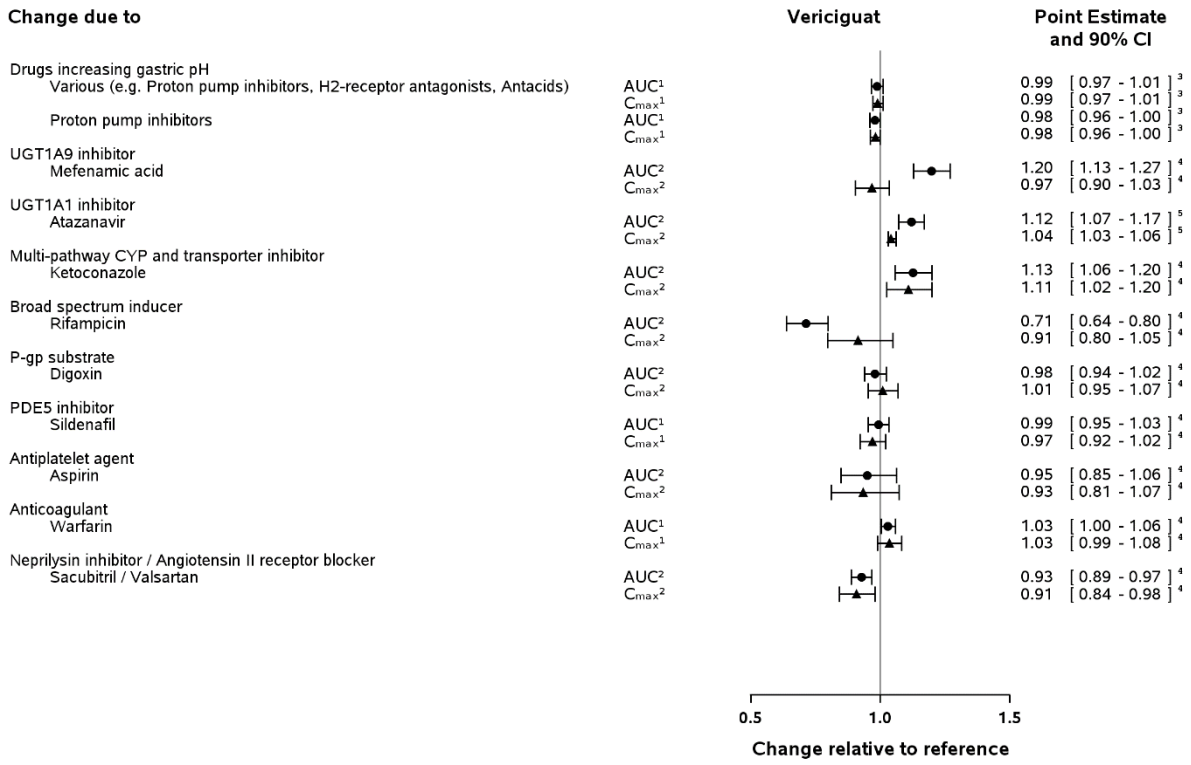
Antiplatelet Agent (Aspirin)

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.

**Figure 2: Effects of Other Drugs on the Pharmacokinetics of Vericiguat**




CI: Confidence Interval.
1. AUC over the dosing interval after multiple dose administration. $C_{max}$ after multiple dose administration.
2. AUC and $C_{max}$ after single dose administration.
3. Based on population-pharmacokinetic (POP-PK) modeling of VICTORIA and SOCRATES-REDUCED.
4. Based on data from healthy subjects (phase I trial).
5. Based on physiologically-based PK (PBPK) modeling, interval represents 90% population interval.

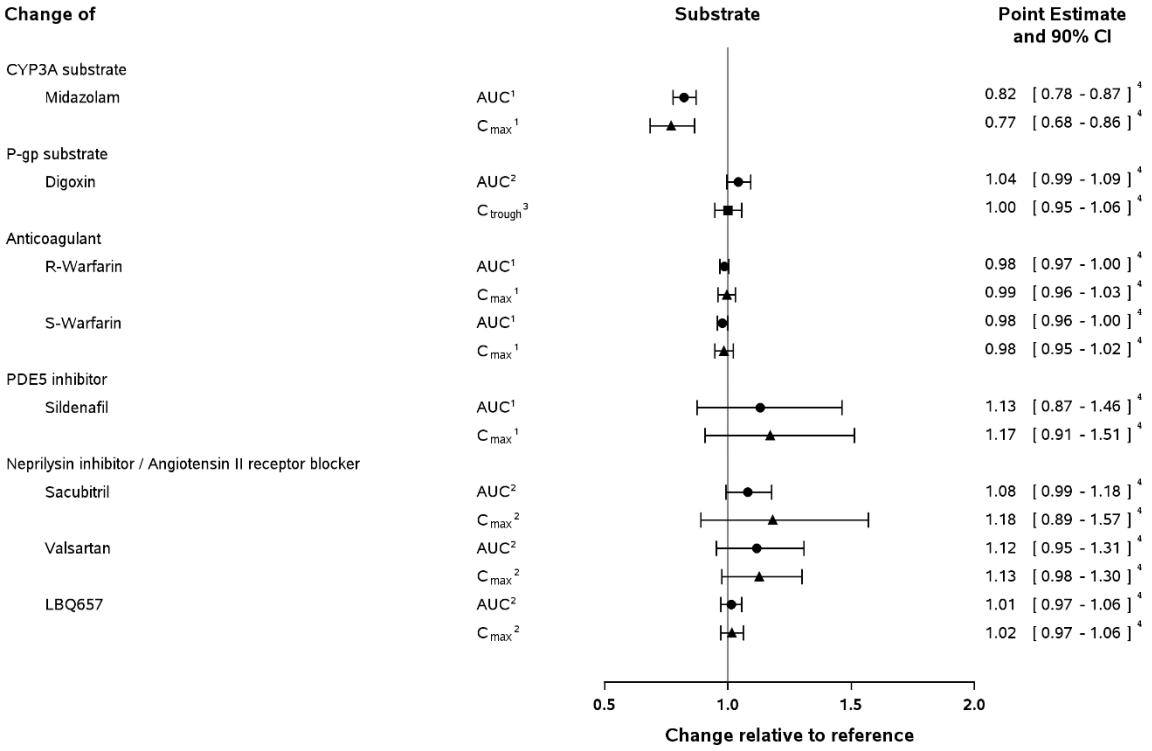
**Table 2: Effects of Other Drugs on the Pharmacokinetics of Vericiguat**

| Co-administered Drug | Regimen of Co-administered Drug | Vericiguat Regimen | N | Geometric Mean Ratio (90% CI) of Vericiguat PK with/without Co-administered Drug (No Effect=1.00) | | Dosing Recommendation |
|---|---|---|---|---|---|---|
| | | | | AUC | $C_{max}$ | |
| Drugs Increasing Gastric pH (e.g. Proton Pump Inhibitors, H2-Receptor Antagonists, Antacids)* | | 2.5-10 mg, multiple-dose | 1,362 | 0.99 (0.97, 1.01) | 0.99 (0.97, 1.01) | No dose adjustment of VERQUVO. |
| Proton Pump Inhibitors* | | 2.5-10 mg, multiple-dose | 1,232 | 0.98 (0.96, 1.00) | 0.98 (0.96, 1.00) | No dose adjustment of VERQUVO. |
| Ketoconazole† | 200 mg, twice daily, multiple-dose | 1.25 mg, single-dose | 15 | 1.13 (1.06, 1.20) | 1.11 (1.02, 1.20) | No dose adjustment of VERQUVO. |
| Mefenamic Acid† | Starting dose of 500 mg followed by 250 mg every 6 hours over 48 hours | 2.5 mg, single-dose | 16 | 1.20 (1.13, 1.27) | 0.97 (0.90, 1.03) | No dose adjustment of VERQUVO. |
| Atazanavir‡ | 400 mg, once daily | 10 mg, single-dose | NA | 1.12 (1.07, 1.17) | 1.04 (1.03, 1.06) | No dose adjustment of VERQUVO. |
| Rifampicin† | 600 mg, once daily for 8 days | 10 mg, single-dose | 16 | 0.71 (0.64, 0.80) | 0.91 (0.80, 1.05) | No dose adjustment of VERQUVO. |
| Digoxin† | 0.375 mg, multiple-dose | 10 mg, single-dose | 24 | 0.98 (0.94, 1.02) | 1.01 (0.95, 1.07) | No dose adjustment of VERQUVO. |
| Warfarin† | 25 mg, single-dose | 10 mg, once daily for 9 days | 23 | 1.03 (1.00, 1.06) | 1.03 (0.99, 1.08) | No dose adjustment of VERQUVO. |
| Aspirin† | 500 mg, once daily for 2 days | 15 mg, single-dose | 13 | 0.95 (0.85, 1.06) | 0.93 (0.81, 1.07) | No dose adjustment of VERQUVO. |
| Sildenafil† | 25 mg, single-dose | 10 mg, once daily for 16 days | 16 | 1.01 (0.97, 1.04) | 1.01 (0.97, 1.07) | The concomitant use of VERQUVO and PDE-5 inhibitors, such as sildenafil, is not recommended. |
| | 50 mg, single-dose | | 15 | 0.96 (0.92, 1.00) | 0.91 (0.87, 0.96) | |

| | | | | | | |
|---|---|---|---|---|---|---|
| | 100 mg, single-dose | | 14 | 0.99 (0.95, 1.03) | 0.97 (0.92, 1.02) | |
| Combination of Sacubitril/ Valsartan† | 97/103 mg, twice daily for 14 days | 2.5 mg, single-dose | 15 | 0.93 (0.89, 0.97) | 0.91 (0.84, 0.98) | No dose adjustment of VERQUVO. |

CI: Confidence interval
*Based on population-pharmacokinetic (POP-PK) modeling of VICTORIA and SOCRATES-REDUCED.
†Based on data from healthy subjects.
‡Based on physiologically-based PK (PBPK) modeling, interval represents 90% population interval.

**Figure 3: Effects of Vericiguat on the Pharmacokinetics of Other Drugs**




CI: Confidence Interval.
1. AUC and $C_{max}$ after single dose administration.
2. AUC over the dosing interval after multiple dose administration. $C_{max}$ after multiple dose administration.
3. $C_{trough}$ of digoxin on day 10.
4. Based on data from healthy subjects (phase I trial).

**Table 3: Effects of Vericiguat on the Pharmacokinetics of Other Drugs**

| Co-administered Drug | Regimen of Co-administered Drug | Vericiguat Regimen | N | Geometric Mean Ratio (90% CI) of Co-administered Drug PK with/without Vericiguat (No Effect =1.00) | | | Dosing Recommendation |
|---|---|---|---|---|---|---|---|
| | | | | AUC | $C_{max}$ | $C_{trough}$ | |
| Midazolam* | 7.5 mg, single-dose | 10 mg, once daily for 4 days | 32 | 0.82 (0.78, 0.87) | 0.77 (0.68, 0.86) | -- | No dose adjustment of midazolam. |
| Digoxin* | 0.375 mg, multiple-dose | 10 mg, once daily, for 9 days | 22 | 1.04 (0.99, 1.09) | -- | 1.00† (0.95, 1.06) | No dose adjustment of digoxin. |
| R-Warfarin* | warfarin 25 mg, single-dose | 10 mg, once daily for 9 days | 23 | 0.98 (0.97, 1.00) | 0.99 (0.96, 1.03) | -- | No dose adjustment of warfarin. |
| S-Warfarin* | | | 23 | 0.98 (0.96, 1.00) | 0.98 (0.95, 1.02) | -- | |
| Sildenafil* | 25 mg, single-dose | 10 mg, once daily for 16 days | 32 | 1.22 (0.92, 1.63) | 1.14 (0.85, 1.53) | -- | The concomitant use of VERQUVO and PDE-5 inhibitors, such as sildenafil, is not recommended. |
| | 50 mg, single-dose | | 31 | 1.17 (0.90, 1.52) | 1.20 (0.92, 1.58) | -- | |
| | 100 mg, single-dose | | 30 | 1.13 (0.87, 1.46) | 1.17 (0.91, 1.51) | -- | |
| Sacubitril* | sacubitril/ valsartan 97/103 mg, twice daily for 14 days | 2.5 mg, once daily for 14 days | 14 | 1.08 (0.99, 1.18) | 1.18 (0.89, 1.57) | -- | No dose adjustment of the combination of sacubitril/valsartan. |
| Valsartan* | | | | 1.12 (0.95, 1.31) | 1.13 (0.98, 1.30) | -- | |
| LBQ657 (active | | | | 1.01 (0.97, 1.06) | 1.02 (0.97, 1.06) | -- | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| metabolite of sacubitril)* | | | | | | | |

CI: Confidence interval
*Based on data from healthy subjects.
†$C_{trough}$ of digoxin was calculated on Day 10.

**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 WARNINGS AND PRECAUTIONS, 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 WARNINGS AND PRECAUTIONS, Symptomatic Hypotension]*.

## 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 both cardiovascular death and heart failure hospitalization; see Table 4.

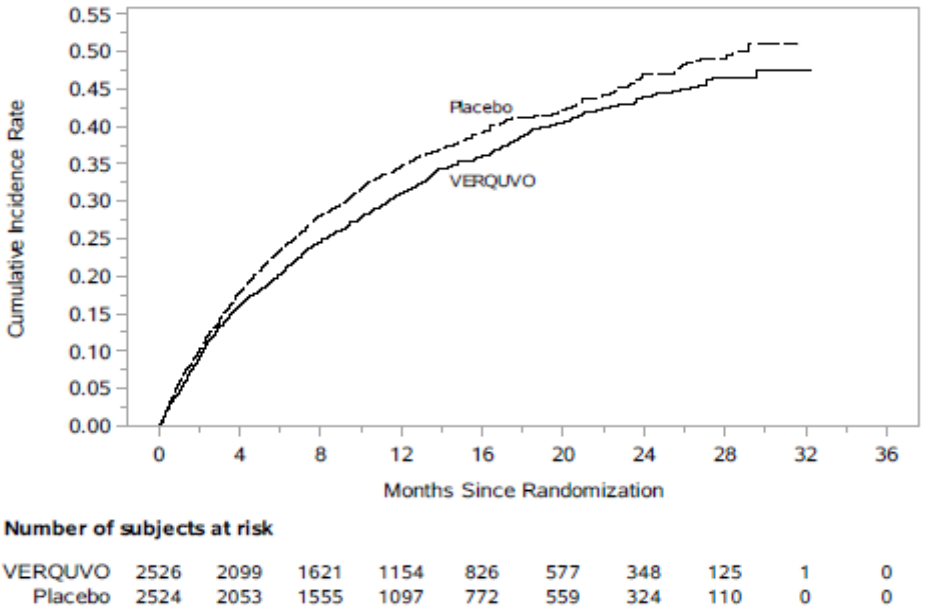
**Table 4: Treatment Effect for the Primary Composite Endpoint, Its Components, and the Secondary Endpoints of Cardiovascular Death and Heart Failure Hospitalizations**

| | 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 4) shows time to first occurrence of the primary composite endpoint of cardiovascular death or heart failure hospitalization.

**Figure 4: 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 5 and 6. The total number of HF hospitalization events was greater in the placebo group (1,336 events) than the VERQUVO group (1,223 events).

**Table 5: 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 6: 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.

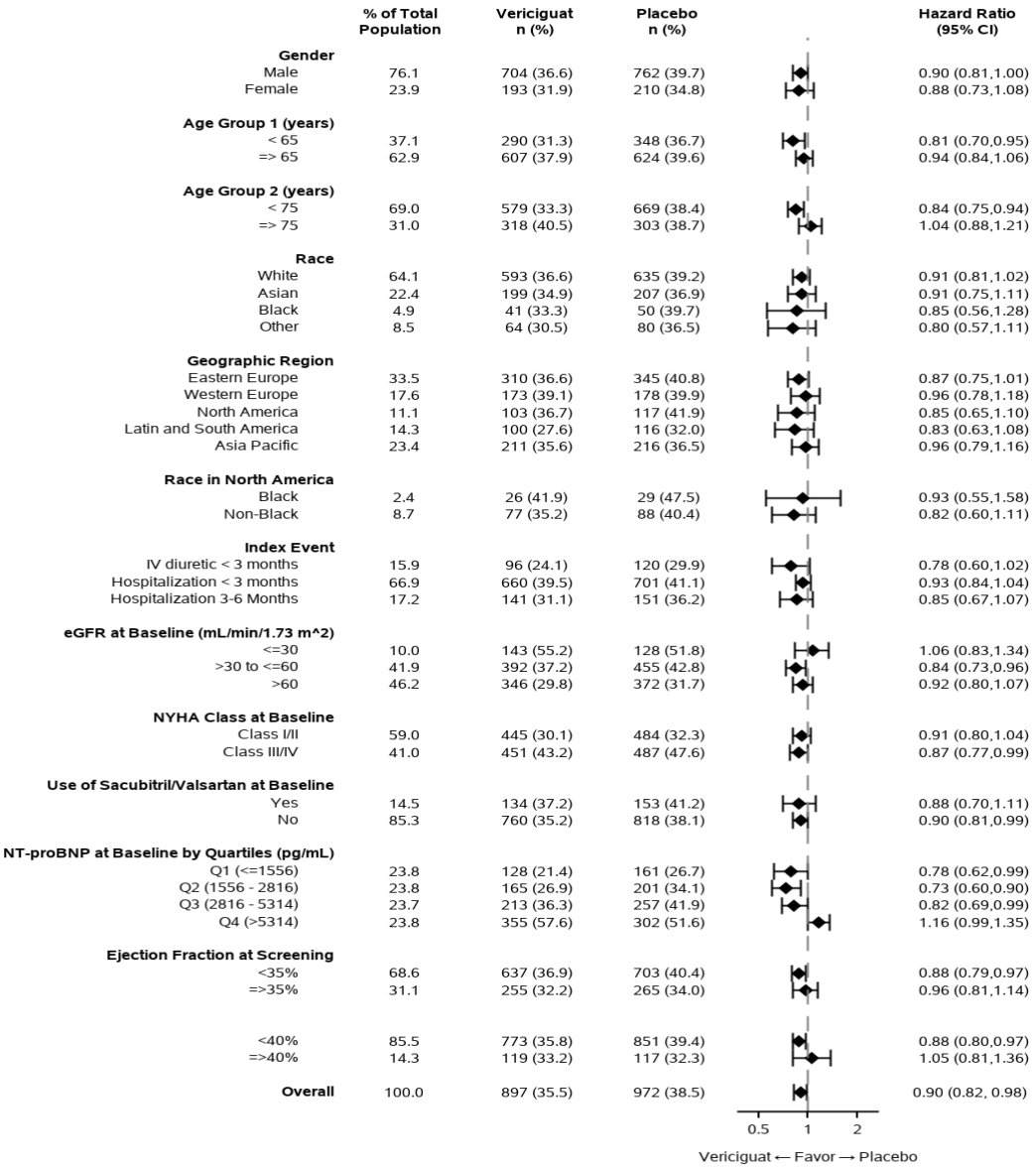
†Hazard ratio (VERQUVO over Placebo) and confidence interval from an Andersen-Gill model.

‡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 5.

**Figure 5: Primary Composite Endpoint (CV Death or HF Hospitalization) - Subgroup Analysis**




## ANIMAL TOXICOLOGY

### 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).

### 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.

**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.

**Mutagenesis**

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.

**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).

**Development**

Reproductive toxicity studies with vericiguat showed no evidence of developmental toxicity (rats, rabbits) or effects on pre/postnatal development (rats).

In a prenatal developmental toxicity study in rats, vericiguat was administered orally to pregnant rats during the period of organogenesis from gestation days (GD) 6 to 17 at doses of 5, 15 or 50 mg/kg/day. No developmental toxicity was observed up to the highest dose (75 times the human exposure at the MRHD, unbound AUC). Exaggerated pharmacodynamic-mediated maternal toxicity (decreased body weight gain and food consumption) was observed at ≥15 mg/kg/day (≥21 times the human exposure at the MRHD). There was no maternal toxicity at 5 mg/kg/day (9 times the human exposure at the MRHD).

In a prenatal developmental toxicity study in rabbits, vericiguat was administered orally to pregnant rabbits during the period of organogenesis from GD 6 to 20 at doses of 0.75, 2.50 or 7.50 mg/kg/day. No developmental toxicity was observed up to the highest dose tested (27 times the human exposure at the MRHD). Exaggerated pharmacodynamic-mediated maternal toxicity (decreased food consumption and body weight loss) resulting in late spontaneous abortions and resorptions was noted at ≥2.50 mg/kg/day (≥6 times the human exposure at the MRHD). There was no maternal toxicity or abortions/resorptions in rabbits at an exposure equivalent to the human exposure at the MRHD.

In a pre-postnatal development study in rats, vericiguat was administered orally at doses of 7.5, 15 or 30 mg/kg/day from GD 6 through lactation day 21. Exaggerated pharmacodynamic-mediated maternal toxicity (decreases in food consumption and body weight gain) was observed at all dose levels (≥9 times at the MRHD) and resulted in decreased pup body weight gain at ≥15 mg/kg/day (≥21 times at the MRHD) and pup mortality at 30 mg/kg/day (49 times at the MHRD).

[$^{14}$C]-vericiguat was administered orally to pregnant rats at a dose of 3 mg/kg. Vericiguat-related material was transferred across the placenta, with fetal plasma concentrations of approximately 67% maternal concentrations on GD 19.

[$^{14}$C]-vericiguat was administered intravenously to lactating rats at a dose of 1 mg/kg. Vericiguat-related material was excreted into milk at concentrations approximately 12% maternal plasma concentrations on LD 8.

## CONTRAINDICATIONS

VERQUVO is contraindicated in patients with concomitant use of other soluble guanylate cyclase (sGC) stimulators, such as riociguat *[see DRUG INTERACTIONS AND OTHER FORMS OF INTERACTIONS, Other Soluble Guanylate Cyclase Stimulators]*.
Hypersensitivity to the active substance or to any of the excipient.

## WARNINGS AND PRECAUTIONS

**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 ADVERSE REACTIONS, 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 CLINICAL PHARMACOLOGY, 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 DRUG INTERACTIONS AND OTHER FORMS OF INTERACTIONS, PDE-5 Inhibitors and CLINICAL PHARMACOLOGY, Drug Interaction Studies]*.

**Excipients**
Lactose
This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucosegalactose malabsorption should not take this medicinal product.

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially “sodium-free”.

## DRUG INTERACTIONS AND OTHER FORMS OF INTERACTIONS

Pharmacodynamic interactions

Vericiguat co-administration with haemodynamic active substances did not result in a more than additive effect. In addition, vericiguat reduced systolic blood pressure by approximately 1 to 2 mmHg when co-administered with other medicinal products used in patients with heart failure.

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

*PDE5 inhibitors*
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 blood pressure (BP) reduction of less than or equal to 5.4 mmHg (systolic/ diastolic BP, mean arterial pressure [MAP]) compared to administration of vericiguat alone. No dose-dependent trend was observed with the different sildenafil doses.
Co-administration was not associated with a clinically relevant effect on the exposure (AUC and Cmax) of either medicinal product.
Concomitant use of vericiguat and PDE5 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.

*Acetylsalicylic acid*
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.
Co-administration of acetylsalicylic acid was not associated with a clinically relevant effect on the exposure (AUC and Cmax) of vericiguat.

*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.
Co-administration was not associated with a clinically relevant effect on the exposure (AUC and Cmax) of either medicinal product.

*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 compared to administration of sacubitril/valsartan alone.
Co-administration was not associated with a clinically relevant effect on the exposure (AUC and Cmax) of either medicinal product.

*Organic nitrates*
Co-administration of multiple doses of vericiguat increased to 10 mg once daily did not significantly alter the seated blood pressure effects of short- and long-acting nitrates (nitroglycerin spray and isosorbide mononitrate [ISMN]) 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.
Pharmacokinetic interactions

Vericiguat is eliminated via multiple routes in humans. The dominant route is glucuronidation via UGT1A9 and UGT1A1, and vericiguat does not affect the pharmacokinetics of other medicinal products.

*UGT1A9/1A1 inhibitors*
Vericiguat is metabolised by UGT1A9 and UGT1A1. Inhibitors of these UGTs may result in increased exposure of vericiguat. No clinically meaningful effect on vericiguat exposure was observed when vericiguat was coadministered with mefenamic acid (weak to moderate UGT1A9 inhibitor).
As strong inhibition of UGT1A9 or combined UGT1A9/1A1 has not been tested in clinical drug-drug interaction studies due to the lack of available inhibitors, the clinical consequences of coadministration with these medicinal products are currently unknown.

*Concomitant use with medicinal products that increase gastric pH*
Co-treatment with medicinal products that increase gastric pH, such as proton pump inhibitors (omeprazole), H2-receptor antagonists or antacids (aluminium hydroxide/magnesium hydroxide) did not affect vericiguat exposure when vericiguat was taken as directed with food in heart failure patients

*No significant interactions*
Concomitant administration of medicinal products affecting one or more of vericiguat´s elimination pathways does not have a clinically relevant effect on the pharmacokinetics of vericiguat.
No clinically meaningful effect on vericiguat exposure was observed when vericiguat was co-administered with ketoconazole (multi-pathway CYP and transporter inhibitor), or rifampicin (multi-pathway UGT, CYP and transporter inducer).
No clinically meaningful effect on midazolam (CYP3A substrate) or digoxin (P-gp substrate) exposure was observed when vericiguat was co-administered with these medicinal products.

## USE IN SPECIFIC POPULATIONS

**Pregnancy**
There are no data from the use of VERQUVO in pregnant women**.** Given the potential for mechanism-based hemodynamic effects, VERQUVO is not recommended during pregnancy and in women of childbearing potential not using contraception. Developmental toxicity studies in rats and rabbits with vericiguat administered orally during organogenesis showed no developmental toxicity up to 75 or 27 times, respectively, the human exposure (unbound AUC) at the maximum recommended human dose (MRHD) of 10 mg. Exaggerated pharmacodynamic-mediated maternal toxicity was observed in rats and rabbits at ≥21 and ≥6 times, respectively, the human exposure at the MRHD resulting in secondary late spontaneous abortions and resorptions in rabbits. There was no maternal toxicity in rats at 9 times the human exposure at the MRHD, and no maternal toxicity or abortions/resorptions in rabbits at an exposure equivalent to the human exposure 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, which resulted in decreased pup body weight gain (≥21 times the MRHD) and pup mortality (49 times the MRHD) during the preweaning period.

**Females and Males of Reproductive Potential**
Pregnancy Testing
Verify the pregnancy status in females of reproductive potential prior to initiating
VERQUVO
Contraception
Females

VERQUVO may cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment and for one month after the final dose

**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.

**Pediatric Use**
Safety and efficacy of VERQUVO have not been established in patients less than 18 years of age.

**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 CLINICAL STUDIES and CLINICAL PHARMACOLOGY, Pharmacokinetics]*.

**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 DOSAGE AND ADMINISTRATION, Renal Impairment, CLINICAL STUDIES, and CLINICAL PHARMACOLOGY, Pharmacokinetics]*.

**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 DOSAGE AND ADMINISTRATION, Hepatic Impairment and CLINICAL PHARMACOLOGY, Pharmacokinetics]*.

## EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Vericiguat has minor influence on the ability to drive or use machines. When driving vehicles or operating machines it should be taken into account that dizziness may occur occasionally.

## ADVERSE REACTIONS

**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 CLINICAL STUDIES]*. The mean duration of VERQUVO exposure was 1 year, and the maximum duration was 2.6 years. Table 7 lists adverse drug reactions occurring in patients treated with VERQUVO and greater than placebo in VICTORIA.

**Table 7: 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

**Description of selected adverse reactions** Hypotension
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 vericiguat compared with placebo. In VICTORIA, hypotension was reported in 16.4% of vericiguat-treated patients compared with 14.9% of placebo-treated patients. This includes also orthostatic hypotension that was reported in 1.3% of vericiguat-treated patients compared with 1.0% of placebo-treated patients. Symptomatic hypotension was reported in 9.1% of vericiguat-treated and 7.9% of placebo-treated patients, and was considered as a serious adverse event in 1.2% of vericiguat-treated patients and 1.5% of placebo-treated patients.

**Reporting of suspected adverse reactions**
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

## 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.

## LIST OF EXCIPIENTS

Tablet core
Microcrystalline cellulose
Croscarmellose sodium
Hypromellose 2910
Lactose monohydrate
Magnesium stearate
Sodium laurilsulfate
Film-coat
Hypromellose 2910
Talc
Titanium dioxide (E 171)
Iron oxide red (E 172) (Verquvo 5 mg only)
Iron oxide yellow (E 172) (Verquvo 10 mg only)

## INCOMPATIBILITES

Not applicable

## STORAGE

Do not store above 30°C

## PRESENTATION

**Verquvo 2.5 mg**
Box, 1 Blister @ 14 Film-coated tablets : Reg. No. XXXXXXXXX
Box, 2 Blisters @ 14 Film-coated tablets : Reg. No. XXXXXXXXX

**Verquvo 5 mg**
Box, 1 Blister @ 14 Film-coated tablets : Reg. No. XXXXXXXXX
Box, 2 Blisters @ 14 Film-coated tablets : Reg. No. XXXXXXXXX

**Verquvo 10 mg**
Box, 1 Blister @ 14 Film-coated tablets : Reg. No. XXXXXXXXX
Box, 2 Blisters @ 14 Film-coated tablets : Reg. No. XXXXXXXXX

## INSTRUCTION FOR USE/HANDLING

None

**Harus dengan resep dokter**

**Manufactured by Bayer AG, Leverkusen – Germany**
**Imported by PT Bayer Indonesia, Depok – Indonesia**

**LEMBAR INFORMASI UNTUK PASIEN**

**VERQUVO 2,5 mg tablet salut selaput**
**VERQUVO 5 mg tablet salut selaput**
**VERQUVO 10 mg tablet salut selaput**
**Vericiguat**

Bacalah informasi ini dengan saksama sebelum mulai mengonsumsi obat meskipun Anda telah membeli kembali obat resep Anda. Beberapa informasi mungkin telah diubah.

Perlu diingat bahwa dokter meresepkan obat ini hanya untuk Anda. Jangan pernah memberikannya kepada orang lain.

## 1. APA ITU VERQUVO?

VERQUVO (vericiguat) adalah tablet salut selaput yang dikonsumsi melalui mulut. VERQUVO mengandung 2,5 mg, 5 mg, atau 10 mg vericiguat sebagai kandungan aktif.

VERQUVO adalah stimulan siklase guanilat (sGC). Cara kerja obat ini adalah dengan melebarkan arteri sehingga memperlancar aliran darah dan oksigen dari jantung ke seluruh tubuh.

Tablet salut selaput

VERQUVO 2.5 mg tablet salut selaput
Bulat, cembung pada kedua sisi, tablet salut selaput berwarna putih dengan diameter 7 mm, bertanda “2.5” di satu sisi dan “VC” di sisi lain

VERQUVO 5 mg tablet salut selaput
Bulat, cembung pada kedua sisi, tablet salut selaput berwarna putih dengan diameter 7 mm, bertanda “5” di satu sisi dan “VC” di sisi lain

VERQUVO 10 mg tablet salut selaput
Bulat, cembung pada kedua sisi, tablet salut selaput berwarna putih dengan diameter 9 mm, bertanda “10” di satu sisi dan “VC” di sisi lain

## 2. MENGAPA DOKTER SAYA MERESEPKAN VERQUVO?

VERQUVO adalah obat resep bagi orang dewasa penderita gagal jantung kronis yang gejalanya, seperti sesak napas, pembengkakan, atau kelelahan, terasa makin parah baru-baru ini dan mungkin sudah berobat ke rumah sakit.

- VERQUVO dapat menurunkan risiko sakit parah atau dirawat inap.
- VERQUVO dikonsumsi bersama dengan obat gagal jantung lainnya.
- Keamanan dan keefektifan VERQUVO pada anak-anak masih belum diketahui.

Gagal jantung terjadi ketika jantung Anda lemah dan tidak dapat memompa cukup darah ke seluruh tubuh.

## 3. BAGAIMANA ATURAN PAKAI VERQUVO?

- Minum VERQUVO sesuai dengan aturan pakai yang disampaikan oleh penyedia layanan kesehatan Anda.
- Minum 1 tablet pada waktu yang sama setiap harinya bersama-sama dengan makanan.
- Jangan berhenti mengonsumsi VERQUVO atau mengubah dosis tanpa berkonsultasi dengan dokter Anda.
- Dokter mungkin perlu mengubah dosis Anda — terutama sekitar 2 minggu pertama setelah Anda mulai mengonsumsi VERQUVO.
- Jika tidak dapat menelan tablet, Anda dapat mengonsumsinya dengan menggerus dan mencampurkan VERQUVO dengan air.

***3.1 Apa yang harus dilakukan jika saya mengonsumsi lebih dari dosis yang dianjurkan?***

- Jika Anda mengonsumsi VERQUVO lebih dari dosis yang dianjurkan, segera hubungi dokter Anda atau segera pergi ke ruang gawat darurat di rumah sakit terdekat.

***3.2 Apa yang harus dilakukan jika ada dosis yang terlewat?***

- Jika ada dosis yang terlewat dan segera setelah Anda mengingatnya, langsung konsumsi dosis tersebut pada hari yang sama.
- Jangan gandakan dosis VERQUVO dan meminumnya sekaligus untuk menggantikan dosis yang terlewat.

**3.3 Jika Anda menghentikan konsumsi Verquvo**

Jangan berhenti mengkonsumsi obat ini tanpa berbicara dengan dokter Anda terlebih dahulu. Jika Anda berhenti mengkonsumsi obat ini, kondisi Anda dapat memburuk.

Jika Anda ragu mengenai cara mengonsumsi VERQUVO, hubungi dokter atau apoteker Anda.

## 4. APA YANG HARUS SAYA KETAHUI SEBELUM MENGONSUMSI VERQUVO?

***4.1 Siapa yang dilarang mengonsumsi VERQUVO?***

**Jangan konsumsi VERQUVO jika Anda:**

- sedang mengonsumsi riociguat.
- hipersensitif terhadap zat aktif atau zat tambahan

***4.2 Apa yang harus saya sampaikan kepada dokter sebelum dan selama mengonsumsi VERQUVO?***

**Sebelum mengonsumsi VERQUVO, sampaikan kepada penyedia layanan kesehatan tentang semua kondisi medis Anda, termasuk jika Anda:**

- memiliki tekanan darah rendah.
- memiliki masalah hati.
- memiliki masalah ginjal atau sedang menjalani dialisis.

***4.3 Kehamilan***

Beri tahu penyedia layanan kesehatan jika Anda sedang hamil atau merencanakan kehamilan. Efek samping VERQUVO terhadap bayi di dalam kandungan belum diketahui.

***4.4 Menyusui***

Beri tahu penyedia layanan kesehatan jika Anda sedang menyusui atau berencana untuk menyusui. Efek samping dari VERQUVO yang tercampur dengan ASI dan diminum bayi belum

diketahui. Anda dan dokter harus memutuskan bersama tindakan yang perlu diprioritaskan: mengonsumsi VERQUVO atau menyusui. Jangan konsumsi obat ini selama menyusui.

***4.5 Anak-anak***
Keamanan dan keefektifan VERQUVO pada anak-anak masih belum diketahui.

***4.6 Bolehkah saya mengonsumsi VERQUVO bersama obat, suplemen makanan, produk herbal, atau makanan lainnya?***
**Beri tahu penyedia layanan kesehatan tentang semua obat yang sedang Anda konsumsi,** termasuk obat resep dan obat bebas, vitamin, serta suplemen herbal.

**Beri tahu penyedia layanan kesehatan, khususnya apabila Anda sedang mengonsumsi:**
- sildenafil
- tadalafil
- vardenafil
- riociguat

Tanyakan kepada penyedia layanan kesehatan jika Anda ragu sedang mengonsumsi salah satu obat ini.
Ketahui obat-obat yang Anda konsumsi. Catat dan tunjukkan kepada penyedia layanan kesehatan dan apoteker saat Anda menerima obat baru.

***4.7. Mengemudi dan mengoperasikan mesin***
Jika Anda merasa pusing ketika mengonsumsi obat ini, jangan mengemudikan kendaraan, bersepeda atau mengoperasikan mesin

***4.8. VERQUVO mengandung laktosa and natrium***
Obat ini mengandung laktosa. Jika Anda pernah diberi tahu oleh dokter bahwa Anda memiliki intoleransi terhadap beberapa jenis gula tertentu, hubungi dokter sebelum mengonsumsi obat ini. Obat ini mengandung kurang dari 1 mmol natrium (23 mg) per tablet, dengan kata lain obat ini pada dasarnya 'bebas natrium'.

## 5. APA SAJA EFEK TIDAK DIINGINKAN YANG DITIMBULKAN VERQUVO?

Semua obat memiliki efek yang tidak dikehendaki atau tidak diinginkan. Efek ini disebut efek samping.

**VERQUVO dapat menimbulkan efek samping yang serius, termasuk:**
- **tekanan darah rendah (hipotensi)**. Hubungi dokter jika Anda merasa pusing atau kliyengan.

**Efek samping yang paling umum dari VERQUVO antara lain:**
- perut tidak nyaman
- mual
- muntah
- nyeri ulu hati
- pusing
- sakit kepala
- tekanan darah rendah
- sel darah merah rendah (anemia)

Efek samping lainnya juga mungkin terjadi meskipun jarang dan seperti obat resep lain, beberapa efek sampingnya mungkin serius.
Tanyakan kepada dokter atau apoteker jika Anda memerlukan informasi lebih lanjut. Keduanya memiliki daftar efek samping yang lebih lengkap. Segera beri tahu dokter atau apoteker Anda tentang gejala ini atau gejala lain yang tidak biasa.

**Pelaporan efek samping**
Jika Anda mendapatkan efek samping di atas, hubungi dokter atau apoteker Anda. Hal yang sama berlaku untuk efek samping yang tidak tercantum dalam leaflet ini. Dengan melaporkan efek samping, Anda dapat membantu memberikan informasi lebih lanjut tentang keamanan obat ini.

## 6. BAGAIMANA CARA MENYIMPAN VERQUVO?

Jauhkan dari jangkauan dan pandangan anak-anak.

Jangan minum VERQUVO setelah tanggal kadaluarsa yang tercantum pada karton pembungkus dan pada setiap blister obat, setelah tulisan EXP.
Tanggal kadaluarsa merujuk pada hari terakhir pada bulan tersebut.

Obat ini tidak memerlukan kondisi penyimpanan khusus.

Obat ini tidak boleh dihancurkan melalui sistem pembuangan air atau sampah rumah tangga. Tanyakan pada apoteker anda bagaimana cara menghancurkan atau membuang obat-obatan yang tidak lagi digunakan. Hal ini dapat membantu melindungi lingkungan anda.

Jangan disimpan pada suhu di atas 30°C

## 7. APA KANDUNGAN VERQUVO?

- Zat aktifnya adalah vericiguat. Setiap tablet salut selaput mengandung 2.5 mg, 5 mg atau 10 mg vericiguat.
- Bahan lainnya adalah:

*Inti tablet*: microcrystalline cellulose, croscarmellose sodium, hypromellose 2910, lactose monohydrate, magnesium stearate, sodium laurilsulfate (lihat "VERQVUVO mengandung laktosa dan natrium")
*Salut tablet*: hypromellose 2910, talc, titanium dioxide (E 171), iron oxide red (E 172) (hanya dalam VERQUVO 5 mg), iron oxide yellow (E 172) (hanya dalam VERQUVO 10 mg).

## 8. BAGAIMANA CARA MENDAPATKAN INFORMASI LENGKAP TENTANG VERQUVO DAN KONDISI SAYA?

Dapatkan informasi selengkapnya dari dokter atau apoteker Anda.

VERQUVO 2,5 mg tersedia dalam kemasan :
- Dus, 1 blister @ 14 tablet salut selaput; No. Reg. XXXXX
- Dus, 2 blister @ 14 tablet salut selaput; No. Reg. XXXXX

VERQUVO 5 mg tersedia dalam kemasan :
- Dus, 1 blister @ 14 tablet salut selaput; No. Reg. XXXXX
- Dus, 2 blister @ 14 tablet salut selaput; No. Reg. XXXXX

VERQUVO 10 mg tersedia dalam kemasan :
- Dus, 1 blister @ 14 tablet salut selaput; No. Reg. XXXXX
- Dus, 2 blister @ 14 tablet salut selaput; No. Reg. XXXXX

**Harus dengan resep dokter**

**Dibuat oleh Bayer AG, Leverkusen – Germany**
**Diimpor oleh PT Bayer Indonesia, Depok – Indonesia**