▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

# AUSTRALIAN PRODUCT INFORMATION
# VERQUVO® (VERICIGUAT) FILM-COATED TABLETS

## 1 NAME OF THE MEDICINE

Vericiguat

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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.

Excipient with known effect

Each 2.5 mg film-coated tablet contains 58.14 mg lactose (as monohydrate).

Each 5 mg film-coated tablet contains 55.59 mg lactose (as monohydrate).

Each 10 mg film-coated tablet contains 111.15 mg lactose (as monohydrate).

For the full list of excipients, see Section 6.1 List of excipients.

## 3 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.

# 4 CLINICAL PARTICULARS

## 4.1 THERAPEUTIC INDICATIONS

VERQUVO® is indicated in addition to standard of care therapy for the treatment of symptomatic chronic heart failure in adult patients with reduced ejection fraction less than 45% who are stabilised after a recent heart failure decompensation event requiring admission and/or IV diuretic therapy (see Section 5.1 Pharmacodynamic properties – Clinical trials).

## 4.2 DOSE AND METHOD OF ADMINISTRATION

### Adults

VERQUVO® should be initiated under the supervision of a cardiologist. The recommended starting dose of VERQUVO® is 2.5 mg once daily. The dose should be doubled approximately every 2 weeks to reach the target maintenance dose of 10 mg once daily, as tolerated by the patient.

Before starting VERQUVO®, care should be taken to optimise volume status and diuretic therapy to stabilise patients after the decompensation event, particularly in patients with very high NT-proBNP levels (see Section 5.1 Pharmacodynamic properties – Clinical trials).

If patients experience symptomatic hypotension, dose adjustment of concomitant diuretics and treatment of other causes of hypotension (e.g. hypovolaemia) should be considered. If symptomatic hypotension persists despite such measures, temporary reduction in dose or interruption of VERQUVO® should be considered (see Section 4.4 Special warnings and precautions for use).

Treatment should not be initiated in patients with SBP <100 mmHg (see Section 4.4 Special warnings and precautions for use).

*Method of administration*

For oral use. VERQUVO® should be taken with food (see Section 5.2 Pharmacokinetic properties).

For patients who are unable to swallow whole tablets, VERQUVO® may be crushed and mixed with water immediately before administration (see Section 5.2 Pharmacokinetic properties).

*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.

### 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 Section 4.4 Special warnings and precautions for use – Use in renal impairment,

Section 5.1 Pharmacodynamic properties – Clinical trials and Section 5.2 Pharmacokinetic properties – Special populations).

### 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 Section 4.4 Special warnings and precautions for use – Use in hepatic impairment and Section 5.2 Pharmacokinetic properties – Special populations).

### Geriatric Patients

No dosage adjustment of VERQUVO® is required for geriatric patients (see Section 4.4 Special warnings and precautions for use – Use in the elderly and Section 5.2 Pharmacokinetic properties – Special populations).

### Paediatric Patients

Safety and efficacy of VERQUVO® have not been established in patients less than 18 years of age (see Section 4.4 Special warnings and precautions for use – Paediatric use and Section 5.2 Pharmacokinetic properties – Special populations).

## 4.3 CONTRAINDICATIONS

VERQUVO® is contraindicated in patients with:

- hypersensitivity to the active substance or any of the excipients listed in section 6.1 List of excipients.
- concomitant use of other soluble guanylate cyclase (sGC) stimulators, such as riociguat (see Section 4.5 Interactions with other medicines and other forms of interactions).

## 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

### 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 vericiguat and 7.9% of patients treated with placebo and were considered serious in 1.2% of patients treated with vericiguat and 1.5% of patients treated with placebo (see Section 4.8 Adverse effects (Undesirable effects)). 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 Section 4.5 Interactions with other medicines and other forms of interactions). 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 Section 4.5 Interactions with other medicines and other forms of interactions).

### Use in 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 Section 4.2 Dose and method of administration – Renal Impairment, Section 5.1 Pharmacodynamic properties – Clinical trials and Section 5.2 Pharmacokinetic properties – Special populations).

### Use in 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 Section 4.2 Dose and method of administration – Hepatic Impairment and Section 5.2 Pharmacokinetic properties – Special populations).

### Use in the elderly

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 Section 4.2 Dose and method of administration – Geriatric Patients, Section 5.1 Pharmacodynamic properties – Clinical trials and Section 5.2 Pharmacokinetic properties – Special populations).

### Paediatric use

Safety and efficacy of VERQUVO® have not been established in patients less than 18 years of age (see Section 4.2 Dose and method of administration – Paediatric Patients and Section 5.2 Pharmacokinetic properties – Special populations). Undesirable effects were observed on growing bone in non-clinical studies (see Section 5.3 Preclinical safety data - Toxicity).

### Effects on laboratory tests

No data available.

## 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

### Contraindications of concomitant use

*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 Section 4.3 Contraindications).

### Concomitant use not recommended

*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 $C_{max}$) of either medicinal product.

Concomitant use of VERQUVO® 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 (see Section 4.4 Special warnings and precautions for use – Symptomatic Hypotension).

### Other interactions

*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 $C_{max}$) of either medicinal product.

*Concomitant use with drugs 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 (see Section 4.2 Dose and method of administration).

*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 $C_{max}$) 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 $C_{max}$) 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 (see Section 4.4 Special warnings and precautions for use – Symptomatic Hypotension).

*No significant interactions*

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.

No clinically meaningful effect on vericiguat exposure was observed when vericiguat was co-administered with ketoconazole (multi pathway CYP and transporter inhibitor), mefenamic acid (UGT1A9 inhibitor), rifampicin (multi pathway UGT, CYP and transporter inducer), or digoxin.

No clinically meaningful effect on vericiguat exposure was predicted when vericiguat is co-administered with atazanavir (UGT1A1 inhibitor), based on physiologically based PK (PBPK) modelling.

***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, 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 vericiguat is unlikely to affect the pharmacokinetics of concurrently administered medications that are substrates of these enzymes or transporters.

## 4.6 FERTILITY, PREGNANCY AND LACTATION

### Effects on fertility

There are no data available on the effect of vericiguat on human fertility. In a 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 (64 times the human exposure at the maximum recommended human dose (MRHD) of 10 mg/day, unbound AUC).

### Use in pregnancy – Pregnancy Category D

There are no data from the use of vericiguat in pregnant women. VERQUVO® should not be used in pregnancy. Women of childbearing potential should use effective forms of contraception during treatment.

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 development toxicity was seen in rabbits following maternal oral doses of 0.75 mg/kg/day (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, which resulted in decreased pup body weight gain (≥21 times the MRHD) and pup mortality (45 times the MRHD) during the preweaning period.

### Use in lactation.

There is no information regarding the presence of vericiguat in human milk, the effects on the breastfed infant, or the effects on milk production. Vericiguat is present in the milk of lactating rats. A risk to the breastfed child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue or abstain from VERQUVO® therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

## 4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

## 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Vericiguat was evaluated in VICTORIA, a Phase 3 randomised, 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 vericiguat (up to 10 mg once daily) and 2,515 patients treated with matching placebo (see Section 5.1 Pharmacodynamic properties – Clinical trials). The mean duration of vericiguat exposure was 1 year, and the maximum duration was 2.6 years. Table 1 lists adverse drug reactions occurring in

patients treated with vericiguat and greater than placebo in VICTORIA. Table 2 lists the frequency of adverse reactions occurring in patients treated with vericiguat in VICTORIA by MedDRA System Organ Class. Frequencies are defined as very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), and very rare (<1/10,000).

**Table 1: Adverse drug reactions occurring in patients treated with vericiguat and greater than placebo in VICTORIA by System Organ Class**

| Adverse Drug Reaction | Vericiguat N=2,519 n (%) | Placebo N=2,515 n (%) |
|---|---|---|
| **Blood and lymphatic system disorders** | | |
| Anemia[1] | 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[2] | 412 (16.4) | 375 (14.9) |

[1]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
[2]Includes: blood pressure decreased, blood pressure diastolic decreased, blood pressure systolic decreased, hypotension, and orthostatic hypotension

**Table 2: Frequency of adverse drug reactions occurring in patients treated with vericiguat in VICTORIA by System Organ Class**

| MedDRA System Organ Class | Very common | Common |
|---|---|---|
| **Blood and lymphatic system disorders** | | Anemia[1] |
| **Gastrointestinal disorders** | | Nausea<br>Dyspepsia<br>Vomiting<br>Gastroesophageal reflux disease |
| **Nervous system disorders** | | Dizziness<br>Headache |
| **Vascular disorders** | Hypotension[2] | |

[1]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
[2]Includes: blood pressure decreased, blood pressure diastolic decreased, blood pressure systolic decreased, hypotension, and orthostatic hypotension

### Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

## 4.9 OVERDOSE

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

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

# 5 PHARMACOLOGICAL PROPERTIES

## 5.1 PHARMACODYNAMIC PROPERTIES

### Therapeutic class

Soluble guanylate cyclase (sGC) stimulator.

Pharmacotherapeutic group: Cardiac therapy, ATC code: C01DX22 vericiguat.

### 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 catalyses 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.

### Pharmacodynamic effects

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 vericiguat 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 vericiguat compared with placebo (see Section 5.1 Pharmacodynamic properties – Clinical trials).

#### *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).

### Clinical trials

The safety and efficacy of vericiguat were evaluated in a randomised, parallel-group, placebo-controlled, double-blind, event-driven, multi-centre trial (VICTORIA) comparing vericiguat and placebo in 5,050 adult patients with symptomatic chronic heart failure (NYHA class II–IV) and left ventricular ejection fraction (LVEF) less than 45% following a worsening heart failure event. A worsening chronic heart failure event was defined as heart failure hospitalisation within 6 months before randomisation or use of outpatient IV diuretics for heart failure within 3 months before randomisation.

Patients were treated up to the target maintenance dose of vericiguat 10 mg once daily or matching placebo in combination with other heart failure therapies. Therapy was initiated at 2.5 mg vericiguat 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 vericiguat and placebo arms were treated with the 10 mg target dose.

The primary endpoint was the time to first event of the composite of cardiovascular (CV) death or hospitalisation for heart failure (HF). The median follow up for the primary endpoint was 11 months. Patients on vericiguat were treated for a mean duration of 1 year and up to 2.6 years.

The mean age of the studied population was 67 years, a total of 1,596 (63%) patients treated with vericiguat were 65 years and older, and 783 (31%) patients treated with vericiguat were 75 years and older. At randomisation, 58.9% of patients were NYHA Class II, 39.7% were NYHA Class III, and 1.3% were NYHA Class IV. The mean LVEF was 28.9%, approximately half of all patients had an LVEF <30%, and 14.3% of patients had an LVEF between 40% and 45%. The most frequently reported medical history conditions other than heart failure included hypertension (79%), coronary artery disease (58%), hyperlipidaemia (57%), diabetes mellitus (47%), atrial fibrillation (45%), and myocardial infarction (42%). At randomisation, the mean eGFR was 62 mL/min/1.73 $m^2$ (88% of patients >30 mL/min/1.73 $m^2$; 10% of patients ≤30 mL/min/1.73 $m^2$). 67% of the patients in VICTORIA were enrolled within 3 months of a HF hospitalisation index event; 17% were enrolled within 3 to 6 months of HF hospitalisation and 16% were enrolled within 3 months of outpatient treatment with IV diuretics for worsening HF. The median NT proBNP level was 2,816 pg/mL at randomisation.

At baseline, more than 99% of patients were treated with other heart failure therapies which included beta blockers (93%), angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARB) (73%), mineralocorticoid receptor antagonists (MRA) (70%), a combination of an angiotensin receptor and neprilysin inhibitor (ARNI) (15%), ivabradine (6%), implantable cardiac defibrillators (28%), and biventricular pacemakers (15%). 91% 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. 3% of patients were on a sodium glucose co transporter 2 (SGLT2) inhibitor.

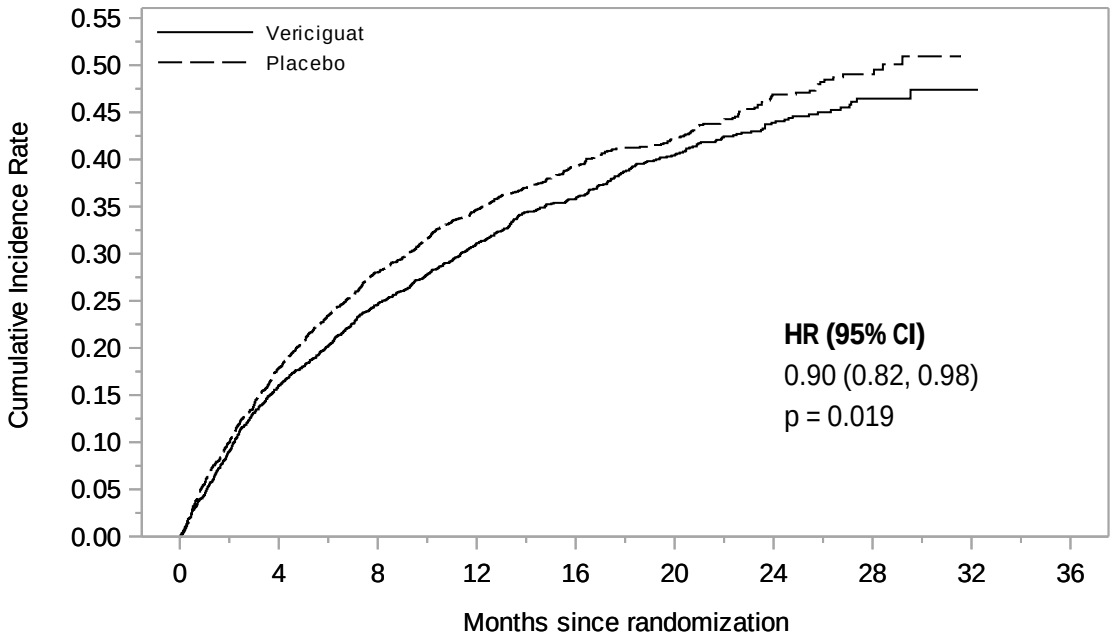
Vericiguat was superior to placebo in reducing the risk of CV death or HF hospitalisation based on a time to event analysis (hazard ratio [HR]: 0.90, 95% confidence interval [CI], 0.82 0.98; p=0.019). Over the course of the study, the annualised absolute risk reduction (ARR) was 4.2% with vericiguat 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 CV death and HF hospitalisation (see Table 3 and Figure 1).

**Table 3: Treatment effect for the primary composite endpoint, its components, and the secondary endpoints of CV death and HF hospitalisation**

| | Vericiguat N=2,526 | | Placebo N=2,524 | | Treatment Comparison | | |
|---|---|---|---|---|---|---|---|
| | n (%) | Annual %[1] | n (%) | Annual %[1] | Hazard Ratio (95% CI)[2] | p-value[3] | Annualised ARR %[4] |
| **Primary endpoint** | | | | | | | |
| Composite of CV death or HF hospitalisation[5] | 897 (35.5) | 33.6 | 972 (38.5) | 37.8 | 0.90 (0.82, 0.98) | 0.019 | 4.2 |
| 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) | | |
| HF hospitalisation | 691 (27.4) | 25.9 | 747 (29.6) | 29.1 | 0.90 (0.81, 1.00) | | |

[1]Total patients with an event per 100 patient years at risk.
[2]Hazard ratio (vericiguat over placebo) and confidence interval from a Cox proportional hazards model.
[3]From the log-rank test. p-value applies to HR only and not annualised ARR.
[4]Annualised absolute risk reduction, calculated as difference (placebo-vericiguat) in annual %.
[5]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.

**Figure 1: Kaplan-Meier curve for the primary composite endpoint: time to first occurrence 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 |

Vericiguat was superior to placebo in reducing the risk of all-cause mortality or HF hospitalisation (HR 0.90 [95% CI, 0.83 0.98]) and total events (first and recurrent) of HF hospitalisation (HR 0.91 [95% CI, 0.84 0.99]) (see Table 4 and Table 5). The total number of HF hospitalisation events was greater in the placebo group (1,336 events) than in the vericiguat group (1,223 events).

**Table 4: Treatment effect for the secondary endpoint of all-cause mortality or HF hospitalisation**

| | **Vericiguat N=2,526** | | **Placebo N=2,524** | | **Hazard Ratio (95% CI)[2]** |
|---|---|---|---|---|---|
| | **n (%)** | **Annual %[1]** | **n (%)** | **Annual %[1]** | |
| Composite of all-cause mortality or HF hospitalisation[3] | 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) | | |
| HF hospitalisation | 691 (27.4) | | 747 (29.6) | | |

[1]Total patients with an event per 100 patient years at risk.

[2]Hazard ratio (vericiguat over placebo) and confidence interval from a Cox proportional hazards model.

[3]For patients with multiple events, only the first event contributing to the composite endpoint is counted in the table.

N=Number of patients in ITT population; n=Number of patients with an event.

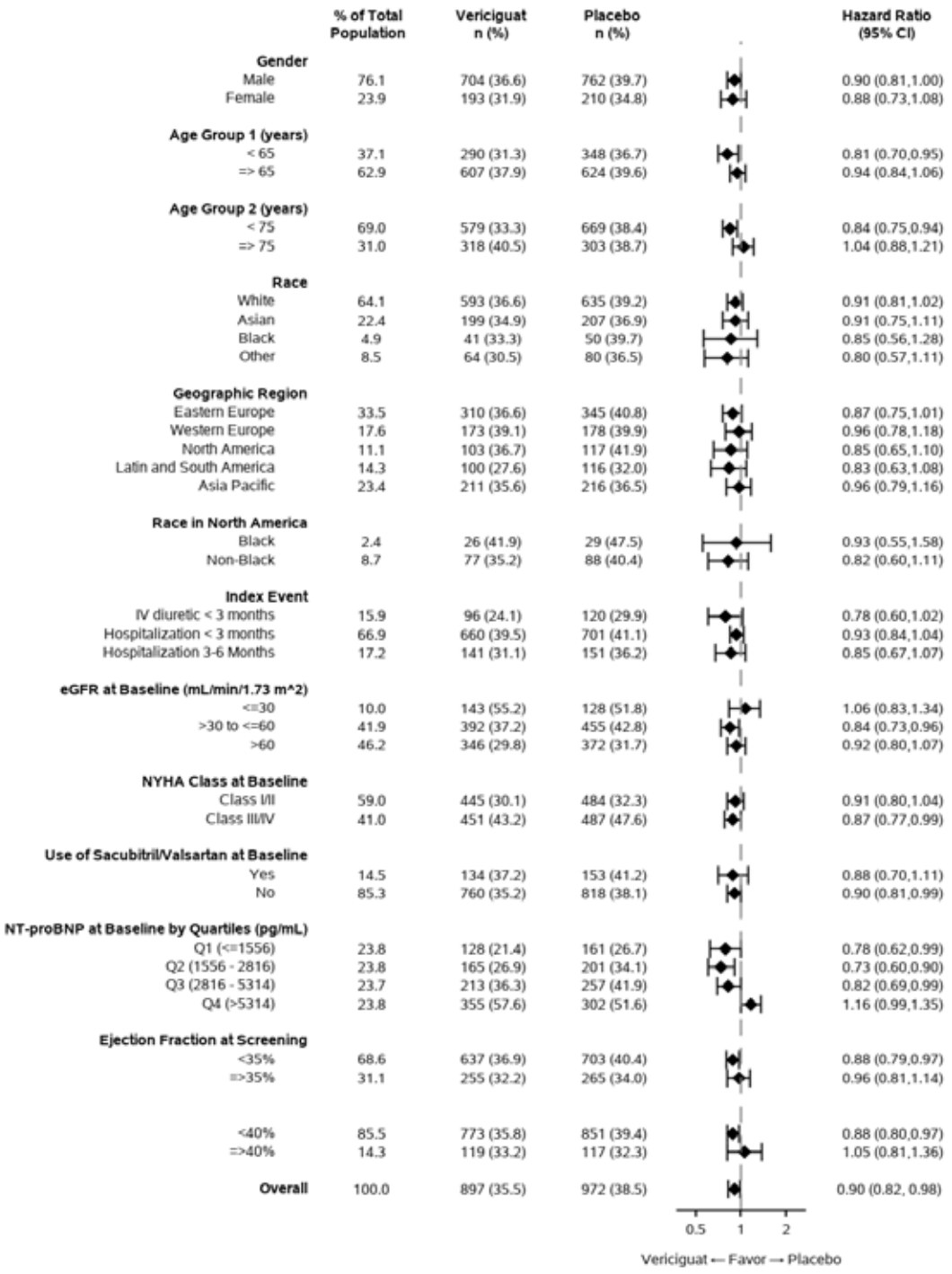
**Table 5: Treatment effect for the secondary endpoint of total events (first and recurrent) of HF hospitalisation**

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

[1]Total events per 100 patient years of follow up.
[2]Hazard ratio (vericiguat over placebo) and confidence interval from an Andersen-Gill model.
[3]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 pre-specified subgroup analysis for the primary composite endpoint are shown in Figure 2.

**Figure 2: Primary composite endpoint (time to first occurrence of CV death or HF hospitalisation) subgroup analysis**



## 5.2 PHARMACOKINETIC PROPERTIES

### 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 summarised in Table 6.

**Table 6: Population pharmacokinetic model based steady state geometric mean (CV%) plasma pharmacokinetic parameters of 2.5 mg, 5 mg, or 10 mg vericiguat 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 Section 4.2 Dose and method of administration).

*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 Section 4.2 Dose and method of administration).

### 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 catalysed predominantly by UGT1A9, as well as UGT1A1. CYP-mediated metabolism is a minor clearance pathway (<5%).

### Excretion

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 faeces (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 Section 4.2 Dose and method of administration – Renal Impairment and Section 4.4 Special warnings and precautions for use – Use in 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 Section 4.2 Dose and method of administration – Hepatic Impairment and Section 4.4 Special warnings and precautions for use – Use in hepatic impairment).

*Paediatric*

No studies with vericiguat have been performed in paediatric 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.

## 5.3 PRECLINICAL SAFETY DATA

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity or carcinogenic potential.

### Toxicity

In rapidly-growing adolescent rats, reversible bone effects consisting of hypertrophy of growth plate and hyperostosis and remodelling 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 and almost full-grown dogs.

### 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.

### Carcinogenicity

Carcinogenicity was evaluated in 2-year studies conducted in CD1 mice and Wistar rats. Vericiguat did not show a carcinogenic effect in mice dosed in the diet at 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 tumour 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 tumours as well as respective hyperplasias were observed in males after oral 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 tumour 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.

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 LIST OF EXCIPIENTS

*Tablet core*

Microcrystalline cellulose
Croscarmellose sodium
Hypromellose 5 cP
Lactose monohydrate
Magnesium stearate
Sodium lauryl sulfate

*Film-coat*
Hypromellose 5 cP
Purified talc
Titanium dioxide (E 171)
Iron oxide red (E 172) (VERQUVO® 5 mg only)
Iron oxide yellow (E 172) (VERQUVO® 10 mg only)

## 6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

## 6.3 SHELF LIFE

24 months

## 6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C

## 6.5 NATURE AND CONTENTS OF CONTAINER

PVC/PVDC/Aluminium foil blisters in cartons of 14 or 28 film-coated tablets or perforated unit dose blisters in cartons of 100 × 1 film-coated tablets.

PP/Aluminium foil blisters in cartons of 14 or 28 film-coated tablets or perforated unit dose blisters in cartons of 100 × 1 film-coated tablets.

Not all pack sizes may be marketed.

## 6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

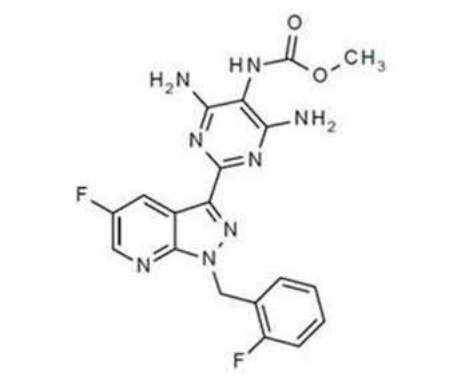
## 6.7 PHYSICOCHEMICAL PROPERTIES

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.

### Chemical name

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.

### Chemical structure



The molecular formula is $C_{19}H_{16}F_2N_8O_2$ and the molecular weight is 426.39 g/mol.

### CAS number

1350653-20-1

## 7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription Only Medicine

## 8 SPONSOR

Bayer Australia Ltd
ABN 22 000 318 714
875 Pacific Highway
Pymble NSW 2073
www.bayer.com.au

## 9 DATE OF FIRST APPROVAL

15 November 2021

## 10 DATE OF REVISION

Not applicable.

**SUMMARY TABLE OF CHANGES**

| Section Changed | Summary of new information |
|---|---|
| | |