SUMMARY OF PRODUCT CHARASTERISTICS

1. Name of the medicinal product
Vericiguat 10mg film-coated tablets
Verquvo 10mg

2. Qualitative and quantitative composition
Each film-coated tablet contains 10mg vericiguat.
Excipient with known effect
Each film-coated tablet contains 61.20mg lactose (as monohydrate), see section 4.4.
For the full list of excipients, see section 6.1.

3. Pharmaceutical form
Film-coated tablet (tablet)
Round, biconvex, yellow-orange film-coated tablet with a diameter of 9 mm, marked with "10" on one side and "VC" on the other side.

4. Clinical particulars
4.1 Therapeutic indications
Verquvo is indicated for the treatment of symptomatic chronic heart failure in adult patients with reduced ejection fraction who are stabilised after a recent decompensation event requiring IV therapy (see section 5.1).

4.2 Posology and method of administration
Posology
Vericiguat is administered in conjunction with other heart failure therapies.
Before starting vericiguat, 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).
The recommended starting dose is 2.5mg vericiguat once daily. The dose should be doubled approximately every 2 weeks to reach the target maintenance dose of 10mg 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 (see section 4.4).
Treatment should not be initiated in patients with SBP <100 mmHg (see section 4.4).
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 vericiguat on the same day.
Special populations
Elderly
No dose adjustment is required for elderly patients (see sections 5.1 and 5.2).
Renal impairment

No dose adjustment is required in patients with estimated glomerular filtration rate (eGFR) ≥15 mL/min/1.73 m^2 (without dialysis). Treatment with vericiguat is not recommended in patients with eGFR <15 mL/min/1.73 m^2 at treatment initiation or on dialysis (see sections 4.4 and 5.2).

Hepatic impairment

No dose adjustment is required in patients with mild or moderate hepatic impairment. Treatment with vericiguat is not recommended in patients with severe hepatic impairment (see sections 4.4 and 5.2).

Paediatric population

The safety and efficacy of vericiguat in children and adolescents aged below 18 years have not yet been established. No clinical data are available. Undesirable effects were observed on growing bone in non-clinical studies (see section 5.3).

Method of administration

For oral use. Verquvo should be taken with food (see section 5.2).

Crushed tablets

For patients who are unable to swallow whole tablets, Verquvo may be crushed and mixed with water immediately before administration (see section 5.2).

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Concomitant use of other soluble guanylate cyclase (sGC) stimulators, such as riociguat (see section 4.5).

4.4 Special warnings and precautions for use

Symptomatic hypotension

Vericiguat may cause symptomatic hypotension (see section 4.8). Patients with SBP less than 100 mmHg or symptomatic hypotension at treatment initiation were not studied.

The potential for symptomatic hypotension should be considered in patients with hypovolaemia, severe left ventricular outflow obstruction, resting hypotension, autonomic dysfunction, history of hypotension, or concomitant treatment with antihypertensives or organic nitrates (see section 4.5).

If patients experience tolerability issues (symptomatic hypotension or SBP less than 90 mmHg), temporary down-titration or discontinuation of vericiguat is recommended (see section 4.2).

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 (see section 4.5).

Renal impairment

Patients with eGFR <15 mL/min/1.73 m^2 at treatment initiation or on dialysis have not been studied, therefore treatment with vericiguat is not recommended in these patients (see sections 4.2 and 5.2).

Hepatic impairment

Patients with severe hepatic impairment have not been studied, therefore treatment with vericiguat is not recommended in these patients (see sections 4.2 and 5.2).

Excipients

Lactose

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

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

4.5 Interaction with other medicinal products and other forms of interaction
Pharmacodynamic interactions
Vericiguat co-administration with haemodynamic active substances did not result in a more than additive effect (see sections 4.4 and 5.1). 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 (see section 4.8).
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).
PDE5 inhibitors
Addition of single doses of sildenafil (25, 50, or 100mg) to multiple doses of vericiguat (10mg) 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 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 (see section 4.4).
Acetylsalicylic acid
Administration of a single dose of vericiguat (15mg) in healthy subjects did not alter the effect of acetylsalicylic acid (500mg) on bleeding time or platelet aggregation. Bleeding time or platelet aggregation did not change under treatment with vericiguat (15mg) 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 (10mg) once daily in healthy subjects did not alter the effect of a single dose of warfarin (25mg) 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.
Combination of sacubitril/valsartan
Addition of multiple doses of vericiguat (2.5mg) to multiple doses of sacubitril/valsartan (97/103mg) 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.
Organic nitrates
Co-administration of multiple doses of vericiguat increased to 10mg 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).

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 (see section 5.2).

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 co-administered 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 co-administration 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 (see section 4.2).

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.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of vericiguat in pregnant women. Studies in animals have shown reproductive toxicity in presence of maternal toxicity (see section 5.3). As a precautionary measure, vericiguat should not be used during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding

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 vericiguat therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

There are no data available on the effect of vericiguat on human fertility. In a study with male and female rats, vericiguat showed no impairment of fertility (see section 5.3).

4.7 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.

4.8 Undesirable effects

Summary of the safety profile

The most frequently reported adverse reaction under treatment with vericiguat was hypotension (16.4%).

Tabulated list of adverse reactions

The safety of vericiguat was evaluated in a phase III study (VICTORIA) which included a total of 2,519 patients treated with vericiguat (up to 10mg once daily) (see section 5.1). The mean duration of vericiguat exposure was 1 year and the maximum duration was 2.6 years.

The adverse reactions reported with vericiguat obtained from clinical studies are listed in the table below by MedDRA system organ class and by frequency. 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 reactions

MedDRA system organ class	**Very common**	**Common**
Blood and lymphatic system disorders		Anaemia
Nervous system disorders		Dizziness Headache
Vascular disorders	Hypotension	
Gastrointestinal disorders		Nausea Dyspepsia Vomiting Gastro-oesophageal reflux disease

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 (see section 4.4).

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 e-PV desktop applications (https://drive.google.com/file/d/16hwTz0587ZWtSWadbBAMwQPOD_KSExZP/view) or search for e-PV Mobile applications on the Google Play or Apple App Store.

4.9 Overdose
Overdose of vericiguat may lead to hypotension. If necessary, symptomatic treatment should be provided. The medicinal product is unlikely to be removed by haemodialysis due to high protein binding.

5. Pharmacological properties
5.1 Pharmacodynamic properties
Pharmacological Classification: 12.9 Other cardiovascular drugs

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. Deficiency in sGC-derived cyclic guanosine monophosphate (cGMP) contributes to myocardial and vascular dysfunction. Vericiguat restores the relative deficiency in the NO-sGC-cGMP 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.
Pharmacodynamic effects
The pharmacodynamic effects of vericiguat are consistent with the mode of action of a sGC stimulator resulting in smooth muscle relaxation and vasodilation.
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 clinical efficacy and safety).
Cardiac electrophysiology
In a dedicated QT study in patients with stable coronary artery disease, administration of 10mg of vericiguat 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 efficacy and safety
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 (HF) event. A worsening chronic HF 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 10mg once daily or matching placebo in combination with other HF therapies. Therapy was initiated at 2.5mg vericiguat once daily and increased in approximately 2 week intervals to 5mg once daily and then 10mg once daily, as tolerated. After approximately 1 year, 89% of vericiguat-treated patients and 91% of placebo-treated patients received the 10mg target dose in addition to other HF therapies.
The primary endpoint was the time to first event of the composite of cardiovascular (CV) death or hospitalisation for 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 HF 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; 17% were enrolled within 3 to 6 months of HF hospitalisation and 16% were enrolled within 3 months of outpatient treatment with IV diuretics. The median NT-proBNP level was 2,816 pg/mL at randomisation.

At baseline, more than 99% of patients were treated with other HF 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 HF medicinal products (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. 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 the risk of CV death, HF hospitalisation, all-cause mortality or HF hospitalisation and total number of HF hospitalisation (see table 2 and figure 1).

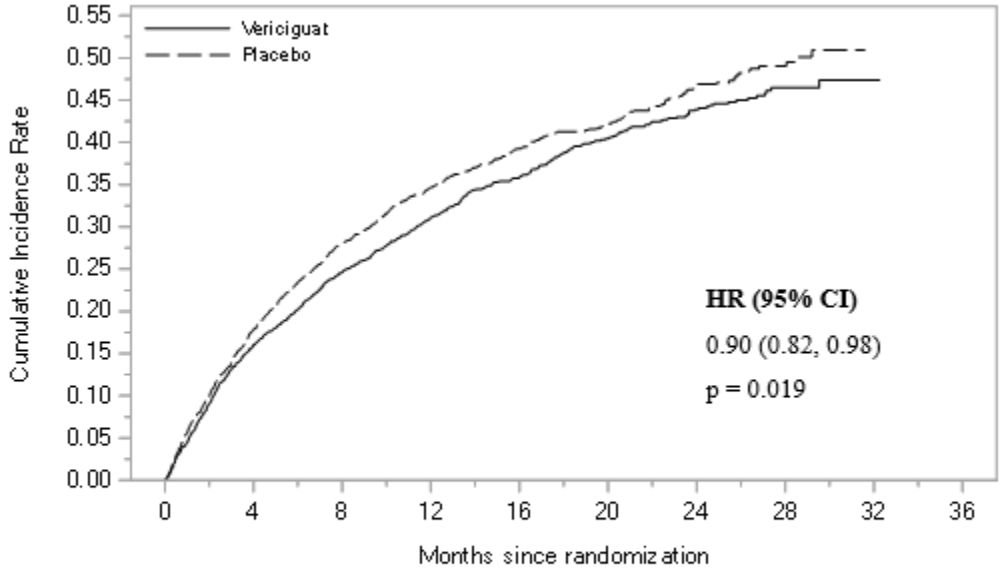
Table 2: Treatment effect for the primary composite endpoint, its components, and the secondary endpoints

	Vericiguat N=2,526	**Placebo N=2,524**	**Treatment comparison**
	n (%) [Annual %[1]]	**n (%) [Annual %[1]]**	**Hazard Ratio (95% CI)[2] [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) p = 0.019[3] [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)

Composite of all-cause mortality or HF hospitalisation[5]	957 (37.9) [35.9]	1,032 (40.9) [40.1]	0.90 (0.83, 0.98)
Total number of HF hospitalisations (first and recurrent)	1,223 [38.3]	1,336 [42.4]	0.91 (0.84, 0.99)[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] 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.
[6] Hazard ratio (vericiguat over placebo) and confidence interval from an Andersen-Gill model.
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

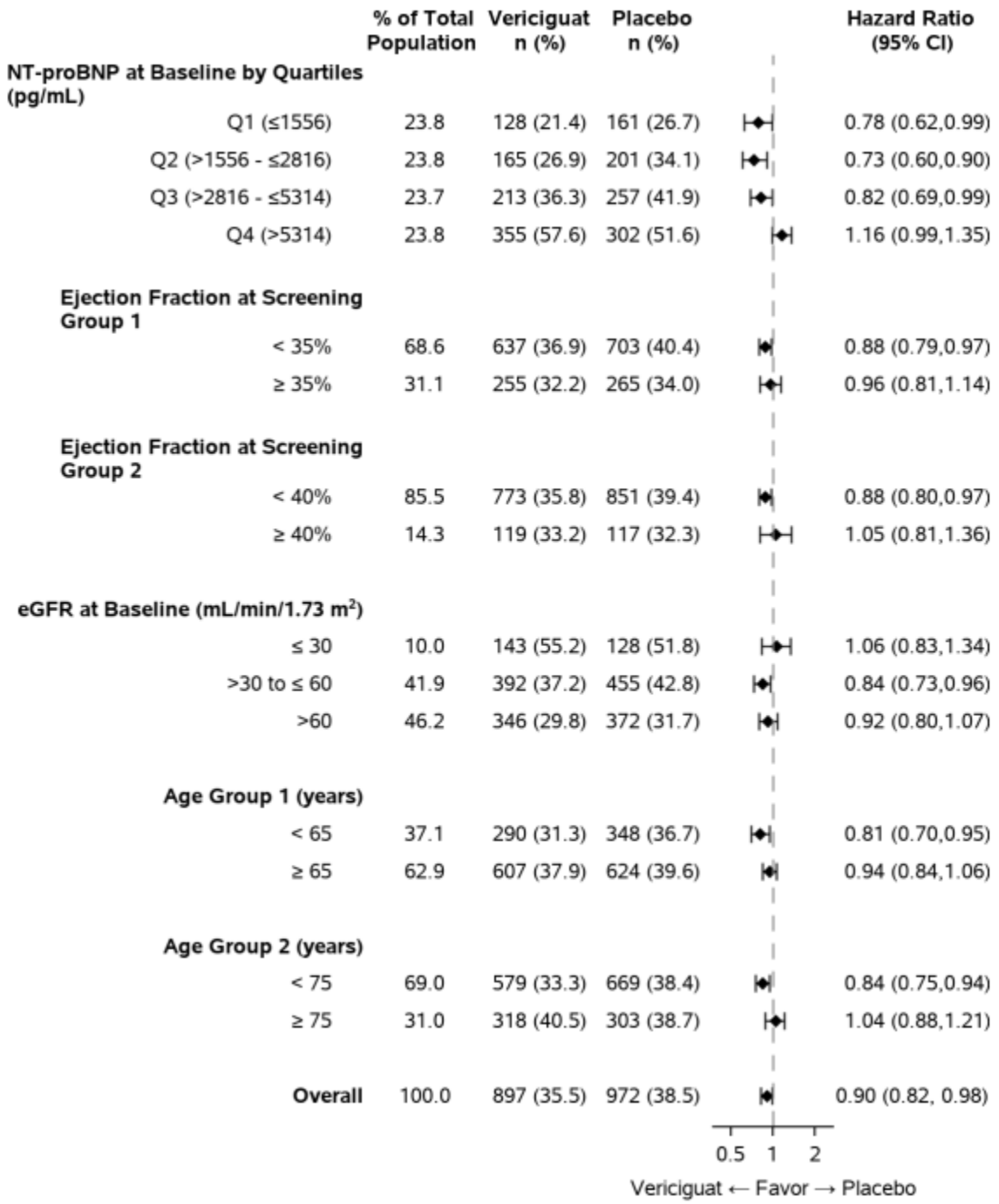


Number of subjects at risk

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

A wide range of demographic characteristics, baseline disease characteristics and baseline concomitant medicinal products were examined for their influence on outcomes. The results of the primary composite endpoint were generally consistent across subgroups. Results of select pre-specified subgroup analyses are shown in figure 2.

Figure 2: Primary composite endpoint (time to first occurrence of CV death or HF hospitalisation) - select subgroups of the pre-specified analyses



Patients with very high NT-proBNP may not be fully stabilised and require further optimisation of volume status and diuretic therapy (see sections 4.1 and 4.2).

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Verquvo in one or more subsets of the paediatric population in the treatment of left ventricular failure (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

General introduction

Vericiguat shows time-independent pharmacokinetics with low to moderate variability when administered with food. Pharmacokinetics are dose proportional in healthy volunteers and slightly less than dose proportional in heart failure patients. Vericiguat accumulates in plasma up to 155-171% and reaches pharmacokinetic steady state after approximately 6 days. The mean steady-state population pharmacokinetic parameters of vericiguat in heart failure patients are summarised in table 3. Steady-state exposure is estimated to be about 20% higher in heart failure patients when compared to healthy volunteers.

Table 3*: Population pharmacokinetic model based steady-state geometric mean (CV%) plasma pharmacokinetic (PK) parameters of 2.5mg, 5mg, or 10mg vericiguat in heart failure patients (N=2,321)*

PK Parameters	**2.5mg**	**5mg**	**10mg**
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 are comparable to that of a whole tablet (see section 4.2).

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 5mg tablet and by 44% (AUC) and 41% (C_{max}) for the 10mg 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).

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.

Biotransformation

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, accounting for 72% of the total drug-related AUC, with the parent vericiguat accounting for 28% of the total drug-related AUC. N-glucuronidation is catalysed predominantly by UGT1A9, as well as UGT1A1. CYP-mediated metabolism is a minor clearance pathway (<5%).

The potential effect of UGT-related genetic polymorphism has not been investigated given the low-to-moderate inter-individual variability of vericiguat (see table 3). Titration of vericiguat mitigates the clinical impact of potential changes in exposure (see section 4.2).

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 faeces (primarily as vericiguat, likely due to excretion of the N-glucuronide into bile followed by hydrolysis back to vericiguat by intestinal microflora).

Special populations

Renal impairment

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 <15 mL/min/1.73 m^2 at treatment initiation or on dialysis (see sections 4.2 and 4.4).

In a dedicated clinical pharmacology study, otherwise healthy participants with mild, moderate, and severe renal impairment, had 8%, 73%, and 143% respectively, higher mean vericiguat exposure (unbound AUC normalised for body weight) after a single dose compared to healthy controls.

The apparent discrepancy of the effect of renal impairment on vericiguat exposure between the dedicated clinical pharmacology study and the analysis in patients with heart failure may be attributed to differences in study design and size.

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 sections 4.2 and 4.4).

Effects of age, body weight, gender, ethnicity, race and baseline NT-proBNP

Based on an integrated population pharmacokinetic analysis of vericiguat in patients with heart failure, age (23-98 years), body weight, gender, ethnicity, race and baseline NT-proBNP do not have a clinically meaningful effect on the pharmacokinetics of vericiguat (see section 5.1).

Paediatric population

No studies with vericiguat have been performed yet in paediatric patients.

In vitro assessment of medicinal product interactions

Vericiguat is a substrate for UGT1A9, as well as UGT1A1 (see section 4.5). *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 medicinal products that are substrates of these enzymes or transporters.

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, carcinogenic potential, and male and female fertility.

In repeat-dose toxicity studies, the toxicological profile was characterised by effects secondary to exaggerated pharmacodynamics. Secondary to smooth muscle relaxation haemodynamic 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 remodelling of metaphyseal and diaphyseal bone were seen. These effects were not observed after chronic administration of vericiguat to adult rats and almost full-grown dogs.
A study in pregnant rats showed that vericiguat is transferred to the foetus through the placenta. Developmental toxicity studies in rats with vericiguat administered orally during organogenesis showed no developmental toxicity up to at least 21 times the human exposure (based on unbound AUC) at the maximum recommended human dose (MRHD) of 10mg. In rabbits, late abortions and resorptions were observed, at maternally toxic doses at ≥6 times the human exposure at the MRHD. In a pre-/postnatal toxicity study in rats, at maternal toxic doses decreased pup body weight gain resulting in a slight delay in incisor eruption and a slight delay in vaginal opening was observed at approximately ≥21 times the human exposure at the MRHD. An increased incidence of stillbirths and decreased pup survival and a delay in balano-preputial separation were observed at 49 times the human exposure at the MRHD.

6. Pharmaceutical particulars

6.1 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 yellow (E 172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/PVDC/Aluminium foil blisters in cartons of 14, 28 or 98 film-coated tablets.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Applicant
Bayer (Pty) Ltd
27 Wrench Road
1609 Isando
South Africa

8. Manufacturer
Bayer Ag
Kaiser-Wilhelm-Allee
51368, Leverkusen
Germany

9. Registration details
Zimbabwe registration number: 2022/12.9/6309
Zimbabwe Category of distribution: Prescription Preparations (P.P.)

10. Date of revision of the text
25 July 2022