*Date: 30 November 2021*
Swissmedic, Swiss Agency for Therapeutic Products

# *Swiss Public Assessment Report*

# Verquvo

**International non-proprietary name:** vericiguat
**Pharmaceutical form:** coated tablets
**Dosage strength(s):** 2.5 mg, 5.0 mg, 10.0 mg
**Route(s) of administration:** oral
**Marketing Authorisation Holder:** Bayer (Schweiz) AG
**Marketing Authorisation No.:** 68001
**Decision and Decision date:** approved on 22.09.2021

**Note:**

Assessment Report as adopted by Swissmedic with all information of a commercially confidential nature deleted.



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## About Swissmedic

Swissmedic is the Swiss authority responsible for the authorisation and supervision of therapeutic products. Swissmedic's activities are based on the Federal Act of 15 December 2000 (Status as of 1 January 2020) on Medicinal Products and Medical Devices (TPA, SR 812.21). The agency ensures that only high-quality, safe and effective drugs are available in Switzerland, thus making an important contribution to the protection of human health.

## About the Swiss Public Assessment Report (SwissPAR)

- The SwissPAR is referred to in Article 67 para. 1 of the Therapeutic Products Act and the implementing provisions of Art. 68 para. 1 let. e of the Ordinance of 21 September 2018 on Therapeutic Products (TPO, SR 812.212.21).
- The SwissPAR provides information about the evaluation of a prescription medicine and the considerations that led Swissmedic to approve or not approve a prescription medicine submission. The report focuses on the transparent presentation of the benefit-risk profile of the medicinal product.
- A SwissPAR is produced for all human medicinal products with a new active substance and transplant products for which a decision to approve or reject an authorisation application has been issued.
- A supplementary report will be published for approved or rejected applications for an additional indication for a human medicinal product for which a SwissPAR has been published following the initial authorisation.
- The SwissPAR is written by Swissmedic and is published on the Swissmedic website. Information from the application documentation is not published if publication would disclose commercial or manufacturing secrets.
- The SwissPAR is a “final” document, which provides information relating to a submission at a particular point in time and will not be updated after publication.
- In addition to the actual SwissPAR, a concise version of SwissPAR that is more comprehensible to lay persons (Public Summary SwissPAR) is also published.



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# 1 Terms, Definitions, Abbreviations

| | |
|---|---|
| ADA | Anti-drug antibody |
| ADME | Absorption, Distribution, Metabolism, Elimination |
| ALT | Alanine aminotransferase |
| API | Active pharmaceutical ingredient |
| ATC | Anatomical Therapeutic Chemical Classification System |
| AUC | Area under the plasma concentration-time curve |
| AUC0-24h | Area under the plasma concentration-time curve for the 24-hour dosing interval |
| CEC | Clinical Events Committee |
| cGMP | cyclic guanosine monophosphate |
| CHF | Chronic heart failure |
| Cmax | Maximum observed plasma/serum concentration of drug |
| CV | cardiovascular |
| CYP | Cytochrome P450 |
| eGFR | Estimated glomerular filtration rate |
| ERA | Environmental Risk Assessment |
| GLP | Good Laboratory Practice |
| HF | Heart failure |
| HFpEF | Heart failure with preserved ejection fraction |
| HFrEF | Heart failure with reduced ejection fraction |
| hHF | hospitalisation for heart failure |
| HR | hazard ratio |
| ICH | International Council for Harmonisation |
| Ig | Immunoglobulin |
| INN | International Nonproprietary Name |
| LoQ | List of Questions |
| LVEF | Left ventricular ejection fraction |
| MAH | Marketing Authorisation Holder |
| Max | Maximum |
| Min | Minimum |
| N/A | Not applicable |
| NO(A)EL | No Observed (Adverse) Effect Level |
| NT-proBNP | N-terminal prohormone of brain natriuretic peptide |
| NYHA | New York Heart Association |
| PD | Pharmacodynamics |
| PIP | Paediatric Investigation Plan (EMA) |
| PK | Pharmacokinetics |
| PLB | Placebo |
| PopPK | Population PK |
| PSP | Pediatric Study Plan (US-FDA) |
| RMP | Risk Management Plan |
| SAE | serious adverse event |
| sGC | soluble guanylate/guanylyl cyclase |
| SGLT2 | sodium-dependent glucose transporter 2 |
| SOC | Standard of care |
| SwissPAR | Swiss Public Assessment Report |
| TPA | Federal Act of 15 December 2000 (Status as of 1 January 2020) on Medicinal Products and Medical Devices (SR 812.21) |
| TPO | Ordinance of 21 September 2018 (Status as of 1 April 2020) on Therapeutic Products (SR 812.212.21) |
| UDP | Uridine diphosphate |
| UGT1A1 | UDP glucuronosyltransferase 1 polypeptide A1 |
| UGT1A9 | UDP glucuronosyltransferase 1 polypeptide A9 |



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# 2 Background Information on the Procedure

## 2.1 Applicant's Request(s)

**New Active Substance status**
The applicant requested the status of a new active entity for the active substance vericiguat of the medicinal product mentioned above.

**Work-sharing procedure**
The applicant requested a work-sharing procedure with Singapore and Australia.
The ACCESS NAS (New Active Substance) work-sharing initiative is a collaboration between regulatory authorities, i.e. Australia's Therapeutic Goods Administration (TGA), Health Canada (HC), Singapore's Health Sciences Authority (HSA), the UK Medicines & Healthcare products Regulatory Agency (MHRA), Swissmedic and the pharmaceutical industry.
The work-sharing initiative coordinates the assessment of a NAS application that has been filed in at least two jurisdictions.

## 2.2 Indication and Dosage

### 2.2.1 Requested Indication

Heart failure

### 2.2.2 Approved Indication

Verquvo is indicated for the treatment of symptomatic, chronic heart failure in adult patients with reduced ejection fraction who have been stabilised after a recent decompensation requiring i.v. therapy.
Vericiguat is used in combination with other treatments for heart failure (see «Dosage/Administration» and «Properties/Effects»).

### 2.2.3 Requested Dosage

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.

### 2.2.4 Approved Dosage

(see appendix)

## 2.3 Regulatory History (Milestones)

| | |
|---|---|
| Application | 15 July 2020 |
| Formal control completed | 12 August 2020 |
| List of Questions (LoQ) | 11 December 2020 |
| Answers to LoQ | 14 March 2021 |
| 1st Predecision | 5 May 2021 |
| Answers to 1st Predecision | 27 May 2021 |
| 2nd Predecision | 22 July 2021 |
| Answers to 2nd Predecision | 7 August 2021 |



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| | |
|---|---|
| Final Decision | 22 September 2021 |
| Decision | approval |



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# 3 Medical Context

Worldwide, the prevalence of chronic heart failure (CHF) among adults is about 2%, rising to 6-10% among people older than 65 years. Heart failure (HF) decompensation has become the leading cause of cardiovascular (CV) hospitalisations in people over 60 years of age [1] . Most of these patients suffer from left ventricular dysfunction, which can be divided into two major forms based primarily on the reduction of the left ventricular ejection fraction (LVEF) [2, 3]: HF with reduced ejection fraction (HFrEF: LVEF <40%) and HF with preserved ejection fraction (HFpEF: LVEF ≥50%).

HFrEF is a progressive medical disorder associated with high morbidity and mortality (5-year mortality rate following hospitalisation for HFrEF exceeds 75% [4]). Thus, there is a medical need for novel therapy options in addition to the current standard of care.

A relative cyclic guanosine monophosphate (cGMP) deficit due to dysfunctional nitric oxide (NO)-cGMP signalling is thought to play a role in the development and progression of CHF (for review see [5, 6]). However, none of the current standard treatments for CHF (renin-angiotensin inhibitors, beta-blockers, and mineralocorticoid-receptor antagonists) tackles this pathophysiological mechanism. Closing this gap (i.e., promoting restoration of physiological cGMP levels), stimulators of soluble guanylyl cyclase (sGC) represent a novel drug development expected to improve left ventricular function in patients with HFrEF.

# 4 Quality Aspects

Swissmedic has not assessed the primary data relating to quality aspects of this application and is adopting the results of the assessment of the foreign reference authority (see section 2.1 Applicant's Request / Work-sharing procedure).

# 5 Nonclinical Aspects

Swissmedic has peered the nonclinical assessment and is adopting the results of the foreign reference authority concerning these aspects (see section 2.1 Applicant's Request / Work-sharing procedure).



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# 6 Clinical and Clinical Pharmacology Aspects

## 6.1 Clinical Pharmacology

**ADME**

The pharmacokinetic and pharmacodynamic characteristics of vericiguat have been studied in a dose range of 0.5 mg to 15 mg in healthy subjects, as well as from 1.25 mg to 10 mg in the intended patient population.

*Absorption*

In healthy volunteers, vericiguat was rapidly absorbed with median $t_{max}$ values of 0.73 to 1.75 hours following administration of an oral solution at single doses of 0.5 – 15 mg.

Following oral administration of 10 mg vericiguat (as 2x 5 mg immediate-release tablets) in combination with a high-fat, high-calorie breakfast, the absolute bioavailability of vericiguat was determined at 93.0%.

Vericiguat AUC and $C_{max}$ increased in a dose-proportional manner following single doses and multiple doses in the investigated dose range.

Following administration of multiple oral doses, the steady-state was reached by days 3-4. Vericiguat accumulated with accumulation ratios for AUC ranging from 155 to 171%, following once daily dosing.

*Dosing recommendations with respect to food and crushed tablets*

Administration of vericiguat with a high-calorie, high-fat meal, caused a 2.5 h delay of median $t_{max}$ from 2 h to 4.5 h and an increase in vericiguat bioavailability (+ 44% for AUC and + 41% for $C_{max}$). In phase 2 and 3 clinical studies, vericiguat was administered under fed conditions and administration in combination with food is recommended

Bioequivalence between crushed immediate-release tablets and intact immediate-release tablets when administered with a high fat, high calorie meal was demonstrated. Thus, vericiguat immediate-release tablets can be administered as crushed tablets in water in combination with food.

*Distribution*

The volume of distribution of vericiguat following i.v. administration has been determined to be approximately 44 L. Vericiguat is highly bound to plasma proteins (97.6% – 97.9%), primarily to albumin.

*Metabolism*

Vericiguat is primarily cleared by UGT1A1- and UGT1A9-mediated metabolism to the N-glucuronide metabolite M-1. Since UGT1A9 is expressed in liver and kidney, metabolism in kidneys could contribute to a relevant extent to vericiguat metabolic clearance.

M-1 was the predominant radioactive species in plasma, accounting on average for 72.1% of AUC of total radioactivity, while vericiguat represented on average 26.6% of AUC of total radioactivity. No further metabolites were detected in plasma.

M-1 is pharmacologically inactive towards the target sGC.

Preclinical data also indicated that several CYPs are capable of metabolising vericiguat, albeit with a low turnover. In a clinical drug-drug interaction study with ketoconazole, only a mild increase in vericiguat exposure was observed, confirming that CYP-dependent metabolism is of minor relevance for vericiguat elimination.



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*Elimination and Excretion*
Vericiguat had a mean systemic plasma clearance of 1.62 L/h after i.v. administration and a terminal half-life of ~20h in healthy subjects.

In a mass balance study, 53.1% of a radioactive vericiguat dose was recovered in urine and 45.2% in faeces.
In urine, the N-glucuronide metabolite M-1 was the predominant component in all subjects, accounting for 41% of the administered dose. Unchanged vericiguat in urine accounted for 9% of the administered dose. Only one minor metabolite was detected in urine, accounting for 1.9% of the dose.
In faeces, unchanged vericiguat was the major radioactive species, accounting for 43% of the administered dose. In addition, one minor metabolite was detected in faeces but this accounted for only 1.6% of the dose.
In vitro experiments indicated that back-conversion of M-1 to vericiguat was mediated by gut microbiota, indicating that (part of) the unchanged vericiguat in faeces might have been secreted as M-1.

**Special Populations / Intrinsic Factors**

*Pharmacokinetics in patients with HFrEF*
Vericiguat exposure was slightly (~18%) higher in patients compared to healthy subjects, which is likely explained by differences in weight and age distributions between the two populations.

*Impaired hepatic function*
Total vericiguat exposure was slightly increased in subjects with mild or moderate hepatic impairment. For details, see the attached information for healthcare professionals (section 8.1). The increased vericiguat exposure is in accordance with theoretical expectations, considering that metabolic elimination is a major clearance pathway for vericiguat. No dose adjustment is recommended for subjects with mildly or moderately impaired hepatic function. In subjects with severely impaired hepatic function, the use of vericiguat is not recommended due to lack of data.

*Impaired renal function*
Vericiguat exposure increased with decreasing renal function. However, this increase was only mild in the intended patient population. For details, see the attached information for healthcare professionals (section 8.1).
No dose adjustment is recommended for subjects with an estimated glomerular filtration rate (eGFR) >15 ml/min/1.73 $m^2$. For subjects with an eGFR <15 ml/min/1.73 $m^2$ at treatment initiation or on dialysis, the use of vericiguat is not recommended due to lack of data.

*Other demographic factors*
Based on dedicated PK studies and a PopPK analysis, no dose adjustments are recommended based on age, body weight, gender or ethnic background.

**Pharmacokinetic Interactions**

The interaction potential of vericiguat with relevant drug-metabolising enzymes and drug transporters has been studied in vitro and in clinical interaction studies. Overall, vericiguat has a low potential for PK-based interactions with other drugs. Details and recommendations with regard to concomitant medications are provided in the attached information for healthcare professionals; see section 8.1 of this report.



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**Pharmacodynamics**

*Mechanism of Action and primary Pharmacology*
Vericiguat is a stimulator of sGC , which catalyses the synthesis of intracellular cGMP.

*Secondary Pharmacology (Safety)*
Potential effects of vericiguat on the QT interval were assessed in a thorough QT/QTc study. Following multiple doses of 10 mg vericiguat at steady state, the ΔΔQTcF values were below the threshold of regulatory concern (Δ=10 msec) at every post dose time point. The highest mean prolongation of QTcF was about 5.7 msec (90 %CI: [1.8 msec; 9.6 msec]) at 2 hours 30 minutes post dose. These study results indicate no clinically relevant effect of vericiguat on the QTcF interval at the therapeutic exposure. However, potential effects on the QT interval at supratherapeutic exposures have not been excluded, as no supratherapeutic dose has been studied.

**Pharmacodynamic Interactions**
Vericiguat has a potential for clinically relevant PD-based interactions with phosphodiesterase 5 – inhibitors and other soluble guanylate cyclase stimulators. Concomitant administration with these medications is contraindicated.
Further details on recommendations with regard to concomitant medications are addressed in the attached information for healthcare professionals; see section 8.1 of this report.

## 6.2 Dose Finding and Dose Recommendation

The 12-week SOCRATES-REDUCED study investigated the effect of pooled vericiguat (doses of 1.25 mg, 2.5 mg, 5 mg, and 10 mg combined) as compared with placebo (PLB) control in patients with HFrEF. Note that tolerance with regard to systolic blood pressure determined dose titration in individual subjects. The study documented a numerical (but not statistically significant) treatment difference for the change in N-terminal prohormone of brain natriuretic peptide (NT-proBNP) from baseline to week 12 (geometric ratio pooled vericiguat/PLB [90% CI]: 0.885 [0.73-1.08]). A prespecified secondary exploratory analysis indicated a dose-response relationship of the effect on NT-proBNP (p=0.0174).

In addition, the risk of clinical efficacy endpoints (e.g., CV mortality, HF hospitalisations) showed a nominal reduction during the short 12-week treatment. The efficacy of vericiguat at a dose beyond 10 mg has not been examined.

## 6.3 Efficacy

Pivotal data regarding the efficacy and safety of the sGC stimulator vericiguat were provided by the VICTORIA trial, a large, multi-centre (694 sites), international (42 countries), randomised, 2-arm, PLB-controlled Phase III study in patients with symptomatic CHF. The VICTORIA study enrolled patients ≥18 years of age in the NYHA classes II to IV with an LVEF ≤45% and markedly increased NT-proBNP. Qualifying patients had to have a recent HF event (hospitalisation for HF [hHF] within the last 6 months or intravenous diuretic treatment for HF without hospitalisation within the last 3 months). No restriction to enter the study only after a particular pre-defined delay from the index event (i.e., the study partially enrolled patients during a hHF prior to discharge). Excluded were unstable patients (per protocol defined as administration of any intravenous treatment within the last 24 hours or systolic blood pressure <100 mm Hg or symptomatic hypotension) and patients with interfering cardiac (e.g., hypertrophic cardiomyopathy, myocarditis, amyloidosis) and non-cardiac (e.g., kidney failure, severe hepatic impairment, malignancy) comorbidities.

All patients received vericiguat or PLB in addition to the standard of care (see Table 2) each titrated from 2.5 to 5 mg to 10 mg based on systolic blood pressure. Table 1 illustrates the primary and key secondary endpoints of the VICTORIA trial and the statistical methods used. The study was powered for CV mortality, and confirmatory testing had to be terminated if CV mortality in the vericiguat group failed to be superior to that in the PLB group.



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**Table 1**

| Endpoint/Variable (Description, Time point) | Statistical Method† | Analysis Population |
|---|---|---|
| **Primary Hypothesis:** | | |
| Time to first occurrence of the composite endpoint of CV death or HF hospitalization | Stratified Log-Rank Test | ITT |
| **Secondary Endpoints:** | | |
| Time to the first occurrence of CV death | Stratified Log-Rank Test | ITT |
| Time to the first occurrence of HF hospitalization | Stratified Log-Rank Test | ITT |
| Time to total HF hospitalizations (including the first and recurrent events) | Andersen-Gill model ‡ | ITT |
| Time to first occurrence of the composite of all-cause mortality or HF hospitalization | Stratified Log-Rank Test | ITT |
| Time to all-cause mortality | Stratified Log-Rank Test | ITT |

Source: SAP Table 1

Overall, 5050 patients (3842 [76%] males and 1208 [24%] females) were randomised (1:1), of whom about 77% completed the study. All patients randomised were included in the efficacy analysis. The discontinuation rate of 23% was accounted for almost completely by cases of death during the study (alternative reasons made up <1.5% in each treatment arm). The VICTORIA study assessed the vital status or the primary endpoint for 99.9% of the study participants (i.e. ≤ 0.1% missing data), which resulted in an amendment of the statistical analysis plan endorsing the omission of any sensitivity analyses.

Patient demographics (sex, age, representation of regions, race and ethnicity) and further important baseline characteristics (e.g., NYHA class, qualifying event, renal function, NT-proBNP level, medical disorders in addition to HF, and concomitant medication for HF and other comorbidities) appeared to be well balanced between treatment arms. The study population had a mean age of 67 years and was mostly in NYHA class II (~59%) or III (~40%). The mean LVEF was ~29% (nearly 50% had a LVEF <30%). The mean eGFR at baseline was ~62 ml/min/1.73m$^2$ (~10% had an eGFR ≤30 ml/min/1.73m$^2$). The mean baseline NT-proBNP levels were 4803.7 pg/ml (vericiguat arm) and 4679.6 pg/ml (PLB arm).

The most common qualifying event (nearly 85% of all index events) was hHF typically within three months prior to randomisation (~66% of all index events). About 11% of these patients were randomised while hospitalised (median time from admission to randomisation 8 days).

Most frequent medical disorders in addition to HF were hypertension (79.1%), coronary artery disease (58.4%), hyperlipidaemia (57.3%), diabetes mellitus (46.9%), atrial fibrillation (45.0%), and prior myocardial infarction (42.1%). The background pharmacotherapy for HF in both arms exemplified in Table 2 below was in accordance with the standard of care (SOC) at the time of study launch. Over 90% of the patients in both arms received a combination of ≥2 HF medications. The proportion of patients treated with a combination of three classes (mineralocorticoid receptor antagonist, any inhibitor of the renin-angiotensin-aldosterone system [angiotensin-converting enzyme inhibitor (ACEI), angiotensin II receptor blocker (ARB), or angiotensin receptor-neprilysin inhibitor (ARNI)], and beta-blocker) was ~60%.



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| Table 2 | Vericiguat | | PLB | | |
|---|---|---|---|---|---|
| | n | % | n | (%) | |
| **≥2 SOC Medications** | | | | | |
| No | 221 | 8.8 | 210 | 8.3 | |
| Yes | 2300 | 91.2 | 2309 | 91.7 | |
| MRA + Any RAS Inhibitor | 91 | 3.6 | 100 | 4.0 | |
| Beta-Blocker + Any RAS inhibitor | 569 | 22.6 | 532 | 21.1 | |
| MRA + Beta-Blocker | 160 | 6.3 | 148 | 5.9 | |
| MRA + Beta-Blocker + Any RAS inhibitor | 1480 | 58.7 | 1529 | 60.7 | Source: CSR Table 10-9 |

The mean treatment duration with the maximum dose of 10 mg vericiguat was 362 days (total days at any dose from 2.5 mg – 10 mg: 375.5 days). During the entire course of the trial, >80% of the patients reached the target dose of 10 mg vericiguat, and ~62% stayed on this dose until the end of the treatment period. Overall, the mean dose of vericiguat over the course of the study was 7.8 mg.

VICTORIA met its primary endpoint (composite of CV death and hospitalisation for HF). There was a significant reduction in the number and rate (per 100 patient-years) of primary endpoint events confirmed by the Clinical Events Committee (CEC) in the vericiguat arm as compared with the PLB arm, equivalent to a modest 10% relative risk reduction (hazard ratio (HR) [95% CI]: 0.90 [0.82; 0.98]; p=0.019). The absolute risk reduction was 3% and 4.2 events per 100 patient-years.

| Outcome | Vericiguat (N=2526) | | Placebo (N=2524) | | Hazard Ratio (95% CI)‡ |
|---|---|---|---|---|---|
| | *no. (%)* | *events/100 patient-yr* | *no. (%)* | *events/100 patient-yr* | |
| **Primary composite outcome and components** | | | | | |
| Death from cardiovascular causes or first hospitalization for heart failure | 897 (35.5) | 33.6 | 972 (38.5) | 37.8 | 0.90 (0.82–0.98) |
| Death from cardiovascular causes§ | 206 (8.2) | | 225 (8.9) | | |
| Hospitalization for heart failure | 691 (27.4) | | 747 (29.6) | | |

Taken from Ref. [7]

The treatment effect of vericiguat relative to PLB persisted throughout the study. It should be noted that the relative short median treatment duration of just ~1 year resulted in an undesirably high number of censored patients (~25% and ~50% at 1 and 2 years, respectively) which may explain partial fading of the effect at later time points (failure to meet proportional hazard rule).



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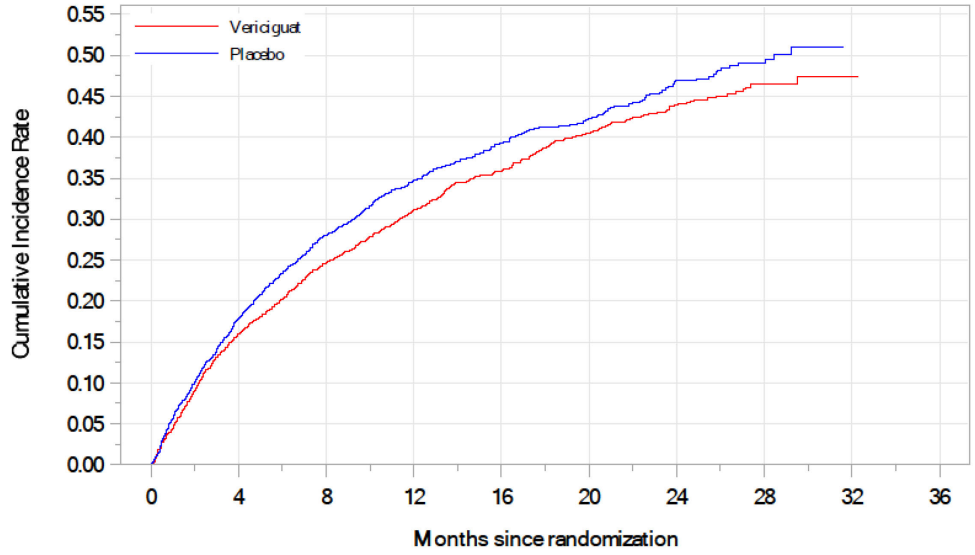



Number of subjects at risk

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

Cumulative number of events up to the time point

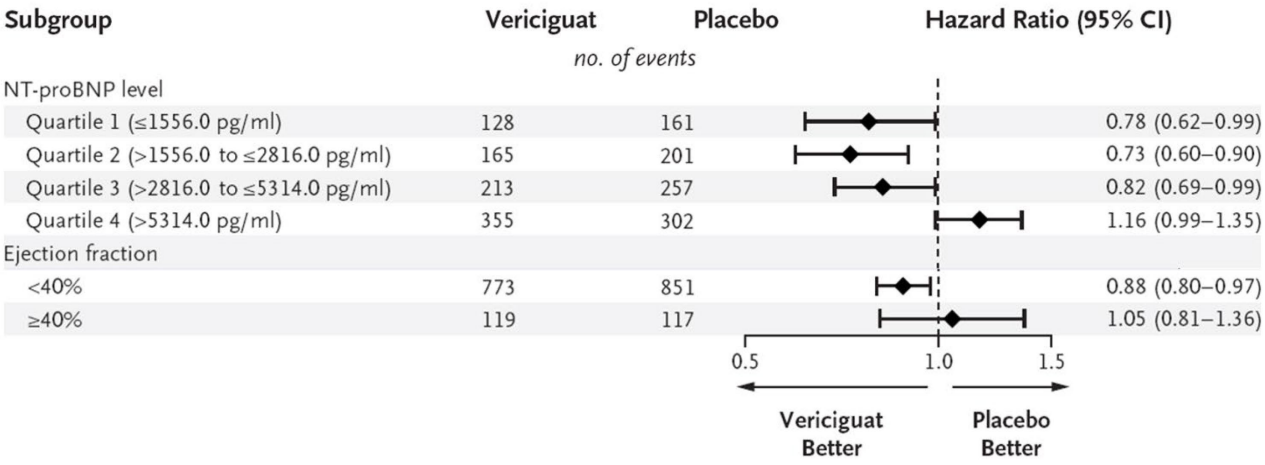
| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Vericiguat | 0 | 402 | 609 | 733 | 803 | 857 | 885 | 896 | 897 | 897 |
| Placebo | 0 | 448 | 694 | 823 | 890 | 924 | 960 | 969 | 972 | 972 |

*KM-Plot for the primary composite endpoint (ITT Population)*

*Source: CSR [Figure 11-1]*

Both components of the primary endpoint contributed to this effect, but none of them showed a significant reduction in the vericiguat arm despite the fact that (i) the study was powered for CV mortality and (ii) the number of patients randomised substantially exceeded the sample size pre-defined per protocol (cf. also secondary outcomes below).

The effect of vericiguat on the composite primary endpoint was consistent across most predefined subgroups except for some apparent exceptions, most noticeably patients with very high NT-proBNP levels and LVEF ≥40%.




Taken from Ref. [7]

The point estimates for patients with baseline NT-proBNP ≤5314 pg/mL (quartiles 1, 2, and 3) were clearly in favour of vericiguat treatment as opposed to those with baseline NT-proBNP >5314 pg/mL (quartile 4), who did not share the benefit from vericiguat treatment (interaction test p-value 0.001). A comprehensive post hoc analysis systematically covering the range of NT-proBNP and including modelling of the HR as a continuous function of NT-proBNP further corroborated a potentially



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detrimental effect of vericiguat in patients with very high NT-proBNP at baseline [8]. Supplemental post hoc analyses further revealed that these patients were typically of older age, in higher NYHA classes, and had a lower eGFR than patients who had lower baseline NT-proBNP. Importantly, patients with very high NT-proBNP at baseline clustered largely in the subcategory of patients randomised during their index event, i.e. shortly after HF hospitalisation.

| | Vericiguat | Placebo | Total |
|---|---|---|---|
| Subjects in population | 2526 | 2524 | 5050 |
| **Overall population** | | | |
| Subjects with Data | 2414 | 2391 | 4805 |
| Mean | 4803.7 | 4679.6 | 4741.9 |
| SD | 7549.4 | 6053.6 | 6845.6 |
| Median | 2803.5 | 2821.0 | 2816.0 |
| (Q1, Q3) | (1572.0, 5380.0) | (1548.0, 5206.0) | (1556.0, 5314.0) |
| Range | 10.0 to 175000.0 | 70.0 to 86155.0 | 10.0 to 175000.0 |
| **Subjects randomized during index event of heart failure hospitalization** | | | |
| Subjects with Data | 115 | 114 | 229 |
| Mean | 8066.1 | 6476.0 | 7274.5 |
| SD | 11331.7 | 7104.6 | 9479.2 |
| Median | 4330.0 | 3662.0 | 4056.0 |
| (Q1, Q3) | (1847.0, 8194.0) | (1602.0, 8653.0) | (1725.0, 8194.0) |
| Range | 177.0 to 75415.0 | 300.0 to 35144.0 | 177.0 to 75415.0 |
| **Subjects discharged within 10 days prior to randomization** | | | |
| Subjects with Data | 381 | 377 | 758 |
| Mean | 4773.9 | 4753.7 | 4763.9 |
| SD | 4783.2 | 5397.4 | 5094.5 |
| Median | 3307.0 | 2958.0 | 3210.0 |
| (Q1, Q3) | (1769.0, 5992.0) | (1474.0, 5630.0) | (1588.0, 5880.0) |
| Range | 99.0 to 34025.0 | 190.0 to 36857.0 | 99.0 to 36857.0 |
| **Subjects discharged between 10-30 days prior to randomization** | | | |
| Subjects with Data | 579 | 598 | 1177 |
| Mean | 5054.0 | 4686.8 | 4867.4 |
| SD | 8871.5 | 6381.4 | 7706.4 |
| Median | 3028.0 | 2854.5 | 2913.0 |
| (Q1, Q3) | (1592.0, 5852.0) | (1502.0, 5039.0) | (1561.0, 5405.0) |
| Range | 29.0 to 175000.0 | 161.0 to 80561.0 | 29.0 to 175000.0 |
| **Subjects discharged between 30-60 days prior to randomization** | | | |
| Subjects with Data | 333 | 348 | 681 |
| Mean | 5441.6 | 4985.5 | 5208.5 |
| SD | 11093.0 | 5520.2 | 8699.5 |
| Median | 3102.0 | 3433.5 | 3248.0 |
| (Q1, Q3) | (1628.0, 5680.0) | (1988.0, 6075.0) | (1811.0, 5847.0) |
| Range | 10.0 to 175000.0 | 70.0 to 50920.0 | 10.0 to 175000.0 |

As one would expect from the above findings, patients who entered the study with a short delay after HF hospitalisation (within 1 months) showed no reduction in the composite primary endpoint (HR [95% CI] of 1.01 [0.88, 1.16]). Considering all the evidence discussed, one can assume that this group included a substantial proportion of patients who were not stabilised adequately. In contrast, patients entering the study with a longer delay from HF hospitalisation showed a reduction in the composite primary endpoint (HR [95% CI] of 0.79 [0.64, 0.97], 0.94 [0.71, 1.24], and 0.85 [0.67, 1.07] in patients enrolled within 1 - 2, 2 - 3, and 3 - 6 months from HF hospitalisation).

The results for the secondary outcomes were generally consistent with those for the primary endpoint. The HRs [95% CI] for CV mortality and first hHF amounted to 0.93 [0.81; 1.06] (p=0.269) and 0.90 [0.81; 1.00] (p=0.048), respectively.

The treatment with vericiguat resulted in a 9% relative risk reduction in the overall events (first and recurrent) of hospitalisation for HF (compared with PLB (HR [95% CI]: 0.91 [0.84-0.99]; p=0.023). There was a minor numerical reduction in all-cause mortality in patients treated with vericiguat (HRs

[95% CI]: 0.95 [0.84-1.07]; p=0.377). Finally, the risk reduction for the exploratory endpoint of CV hospitalisation further supports a potential clinical benefit of vericiguat (HR [95% CI]: 0.88 [0.81-0.96]).

| Outcome | Vericiguat (N=2526) | | Placebo (N=2524) | | Hazard Ratio (95% CI)‡ |
|---|---|---|---|---|---|
| | *no. (%)* | *events/100 patient-yr* | *no. (%)* | *events/100 patient-yr* | |
| **Secondary outcomes** | | | | | |
| Death from cardiovascular causes | 414 (16.4) | 12.9 | 441 (17.5) | 13.9 | 0.93 (0.81–1.06) |
| Hospitalization for heart failure | 691 (27.4) | 25.9 | 747 (29.6) | 29.1 | 0.90 (0.81–1.00) |
| Total hospitalizations for heart failure¶ | 1223 | 38.3 | 1336 | 42.4 | 0.91 (0.84–0.99) |
| Secondary composite outcome and components | | | | | |
| Death from any cause or first hospitalization for heart failure | 957 (37.9) | 35.9 | 1032 (40.9) | 40.1 | 0.90 (0.83–0.98) |
| Death from any cause§ | 266 (10.5) | | 285 (11.3) | | |
| Hospitalization for heart failure | 691 (27.4) | | 747 (29.6) | | |
| Death from any cause | 512 (20.3) | 16.0 | 534 (21.2) | 16.9 | 0.95 (0.84–1.07) |

Taken from Ref. [7]

## 6.4 Safety

The safety profile of vericiguat in subjects with symptomatic CHF and LVEF < 45% is based on the pivotal phase 3 study VICTORIA. In addition, the phase 2b dose-finding study and 28 phase 1 studies contributed to the safety profile of vericiguat.
The most frequently reported adverse events with a higher rate in the vericiguat treatment group vs placebo were hypotension (15.4% vs. 14.1%), followed by anaemia (7.6% vs. 5.7%), syncope (4.0% vs. 3.5%), nausea (3.8% vs. 2.7%), headache (3.4% vs. 2.4%), dyspepsia (2.7% vs. 1.1%), vomiting (2.2% vs. 1.8%), gastroesophageal reflux disease (1.7% vs. 0.7%) and iron deficiency anaemia (1.1% vs. 0.8%).
The proportions of subjects with serious adverse events (SAEs) were similar between the treatment groups. The only SAE preferred terms reported with an incidence ≥2% in either treatment group were pneumonia, cardiac failure, and acute kidney injury.
Fatal events were chosen as “Efficacy Endpoints” in the VICTORIA trial, hence deaths were not routinely reported as SAEs. Therefore, the number of adverse events resulting in a fatal outcome differs from the number of CEC reported deaths in the efficacy analyses.
The proportions of subjects with non-CV death were similar between treatment groups. There were 98 (3.9%) vericiguat subjects and 93 (3.7%) placebo subjects with death due to a non-CV event.

## 6.5 Final Clinical and Clinical Pharmacology Benefit Risk Assessment

Heart failure (HF) is a major concern in public health and associated with considerable morbidity and mortality. The 1-year and 5-year mortality rates in patients with chronic HF are ~7% and ~33%, respectively, and acute decompensation of HF has become the leading cause of CV hospitalisations in people over 60 years of age. The prognosis gets even worse in patients who have had a hospitalisation for HFrEF (5-year mortality rate >75%). The recent addition of SGLT2 inhibitors (e.g., dapagliflozin) to SOC has improved the treatment of patients with HFrEF. Nevertheless, there is a medical need for further treatment options, preferably for those affecting the pathogenesis of HF in a manner different from the currently available treatments.

*Beneficial effects*
The pharmacokinetic and pharmacodynamic characteristics of vericiguat have been thoroughly studied in healthy subjects as well as in the intended patient population. Vericiguat has a low potential for



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pharmacokinetic drug-drug interactions. No dose adjustments in subjects with impaired renal (mild to severe) or hepatic function (mild and moderate), or based on demographic factors are required.

Vericiguat reduced (relative risk reduction: 10%) the composite primary endpoint consisting of CV death and hospitalisation for HF (time to 1st event). The hazard ratio (HR[95% CI]) of the vericiguat group versus placebo control was 0.90 [0.82; 0.98] (p=0.019). The absolute risk reduction in the primary endpoint was 4.2 events per 100 patient-years. This effect was primarily driven by the reduction of HF hospitalisation events (hHF). The HRs [95% CI] for the two components of the primary endpoint were 0.93 [0.81; 1.06] (CV mortality; p=0.269) and 0.90 [0.81; 1.00] (hHF; p=0.048). Vericiguat also reduced the total HF hospitalisations (first and recurrent events) compared with placebo (HR [95% CI]: 0.91 [0.84-0.99]; p=0.023). There was a minor numerical reduction in all-cause mortality (HRs [95% CI]: 0.95 [0.84; 1.07]; p=0.377). Finally, there was a risk reduction for the exploratory endpoint CV hospitalisation in vericiguat-treated patients (HR [95% CI]: 0.88 [0.81-0.96]).

There is heterogeneity of the treatment benefit depending on baseline NT-proBNP and LVEF with implications for the definition of the target population.

*Uncertainty in the knowledge about the beneficial effects*
Lack of data in subjects with end-stage renal disease (ESRD) or severe hepatic impairment limits the use of vericiguat in these patients. The risk of effects on the QT interval at supratherapeutic exposures is unclear due to lack of data. It remains unclear whether vericiguat doses higher than 10 mg could have yielded more favourable efficacy outcomes.

The effect on the primary endpoint was observed for a mean treatment duration of just ~1 year. None of the individual components of the primary endpoint showed a statistically significant reduction in the vericiguat group of VICTORIA powered for CV mortality.

Currently, the additivity of the clinical benefits of vericiguat and SGLT2 inhibitors for patients with HFrEF remains unclear.

*Unfavourable effects (risks)*
Vericiguat belongs to the relatively new therapeutic group of sGC stimulators. Therefore, knowledge on its safety profile is still limited. Although its safety profile might be expected to be in line with other sGC stimulating agents, the interaction with other therapies used in a CHF population with reduced ejection fraction and the disease characteristics may complicate the interpretation of the safety profile.

Conclusion

In summary, vericiguat treatment resulted in a statistically significant reduction in the primary endpoint as compared with placebo control. The robustness of this effect in the overall study population of the VICTORIA trial is uncertain (e.g. lack of efficacy in patients with very high NT-proBNP levels and LVEF ≥40%). This has been addressed in the revised indication restricted to patients who have been stabilised after a HF decompensation event (with the aim of excluding patients with very high NT-proBNP levels from treatment) and to patients with reduced ejection fraction (LVEF <40%).

Various safety concerns are related to sGC stimulators such as vericiguat, primarily hypotension, episodes of syncope, and anaemia. None of these concerns is considered prohibitive for an approval of vericiguat in the revised indication.

Taken together, the benefit-risk ratio for vericiguat in the target population defined by the adapted indication (i.e., patients stabilised adequately after a prior HF decompensation event) can be considered positive.

## 6.6 Approved Indication and Dosage

See information for healthcare professionals in the Appendix.



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# 7 Risk Management Plan Summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken in order to further investigate and monitor the risks as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorisations.

**References**


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# 8 Appendix

## 8.1 Approved Information for Healthcare Professionals

Please be aware that the following version of the information for healthcare professionals relating to Verquvo was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the reference document, which is valid and relevant for the effective and safe use of medicinal products in Switzerland, is the information for healthcare professionals approved and authorised by Swissmedic (see www.swissmedicinfo.ch).

**Note:**
The following information for healthcare professionals has been translated by the MAH. The Authorisation Holder is responsible for the correct translation of the text. Only the information for healthcare professionals approved in one of the official Swiss languages is binding and legally valid.



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▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the “Undesirable effects” section for advice on the reporting of adverse reactions.

**Verquvo®**

**Composition**

*Active substances*

Vericiguat.

*Excipients*

Verquvo 2.5 mg coated tablets contain: microcrystalline cellulose, croscarmellose sodium, hypromellose, lactose monohydrate (61.2 mg), magnesium stearate, sodium laurylsulfate, coating: hypromellose, talc, titanium dioxide (E171). Sodium per coated tablet: 0.80 mg.
Verquvo 5 mg coated tablets contain: microcrystalline cellulose, croscarmellose sodium, hypromellose, lactose monohydrate (58.5 mg), magnesium stearate, sodium laurylsulfate, coating: hypromellose, talc, titanium dioxide (E171), ferroc oxide red (E172). Sodium per coated tablet: 0.81 mg.
Verquvo 10 mg coated tablets contain: microcrystalline cellulose, croscarmellose sodium, hypromellose, lactose monohydrate (117.0 mg), magnesium stearate, sodium laurylsulfate, coating: hypromellose, talc, titanium dioxide (E171), ferroc oxide yellow (E172). Sodium per coated tablet: 1.65 mg.

**Pharmaceutical form and active substance quantity per unit**

Film-coated tablets each containing 2.5 mg, 5 mg, or 10 mg vericiguat.

*Appearance*
2.5 mg: white, round, biconvex film-coated tablet with a diameter of 7 mm, debossed with “2.5” on one side and “VC” on the other side.
5 mg: brown-red, round, biconvex film-coated tablet with a diameter of 7 mm, debossed with “5” on one side and “VC” on the other side.
10 mg: yellow-orange, round, biconvex film-coated tablet with a diameter of 9 mm, debossed with “10” on one side and “VC” on the other side.

## Indications/Uses

Verquvo is indicated for the treatment of symptomatic, chronic heart failure in adult patients with reduced ejection fraction who have been stabilized after a recent decompensation requiring iv therapy.
Vericiguat is used in combination with other treatments for heart failure (see «Dosage/Administration» and «Properties/Effects»).

## Dosage/Administration

Prior to initiation of treatment with Verquvo, adequate stabilisation after a recent decompensation event must be ensured, particularly in patients with greatly elevated NT-proBNP levels. Clinical stabilization should include addressing volume overload by intensified (IV) diuretic therapy and treatment with other standard therapies for heart failure (see “Warnings and precautions” section).

The recommended starting dose of Verquvo is 2.5 mg once daily, taken with food. Double the dose of Verquvo approximately every 2 weeks to reach the target maintenance dose of 10 mg once daily, as tolerated by the patient.

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

*Delayed administration*

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

*Special patient groups*

*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 for this patient group (see “Pharmacokinetics” section).

*Renal impairment*

No dose adjustment of Verquvo is required in patients with estimated glomerular filtration rate (eGFR) ≥15 mL/min/1.73 $m^2$ (without dialysis) (see “Pharmacokinetics” section). Verquvo has not been studied in patients with eGFR <15 mL/min/1.73 $m^2$ at treatment initiation or on dialysis and is therefore not recommended for these patient groups (see “Pharmacokinetics” section).

*Elderly patients (≥65 years)*

No dosage adjustment of Verquvo is required for elderly patients (see “Pharmacokinetics” section.)
No overall differences in safety or efficacy of vericiguat were observed between patients aged 65 years and older and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

*Children and adolescents*

Efficacy and safety of Verquvo have not been studied in children and adolescents less than 18 years of age (see “Pharmacokinetics” section).

**Contraindications**

- Verquvo is contraindicated in patients with concomitant use of other soluble guanylate cyclase (sGC) stimulators, such as riociguat (see “Interactions” section).
- Hypersensitivity to any of the excipients (see “Warnings and precautions” section).
- Verquvo is contraindicated in patients with concomitant use of phosphodiesterase-5-inhibitors, such as sildenafil (see «Interactions» section).

**Warnings and precautions**

*Patients with markedly elevated NT-proBNP*

Predefined subgroup analyzes and post-hoc analyzes of the VICTORIA study suggest that treatment with Verquvo increases cardiovascular mortality and the risk of hospitalization for heart failure in patients with markedly elevated NT-proBNP levels (see «Clinical efficacy» section). Additional post-hoc analyses indicate insufficient stabilization of these patients after previous decompensation. Before starting treatment with Verquvo, it should be ensured that the patients concerned are adequately stabilized (see section «Dosage /Administration»).

*Symptomatic hypotension*

Treatment with Verquvo may be associated with symptomatic hypotension. In the VICTORIA study, adverse events assessed 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 considered to be serious in 1.2% of patients treated with Verquvo and 1.5% of patients treated with placebo (see "Undesirable effects" section).
Verquvo has not been studied in patients with systolic blood pressure less than 100 mmHg or with symptomatic hypotension at treatment initiation.
The potential for symptomatic hypotension must be considered 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 “Interactions” section). If symptomatic hypotension occurs, consider dose adjustment of diuretics and treatment of other causes of hypotension (e.g., hypovolemia). If symptomatic hypotension persists despite these measures, temporary reduction in dose or interruption of Verquvo should be considered.

*Excipients*

Verquvo contains 55.59 – 111.15 mg of lactose (as lactose monohydrate), depending on the dose strength. Patients with rare hereditary galactose intolerance, total lactase deficiency, or glucose-galactose malabsorption should therefore not use Verquvo.
The tablets contain less than 1 mmol sodium (23 mg) per dose and can be classified essentially “sodium-free”.

**Interactions**

Pharmacokinetic interactions
*Influence of other substances on the pharmacokinetics of Verquvo*
Drugs increasing gastric pH (e.g., proton pump inhibitors, H2-receptor antagonists, antacids)
Vericiguat is less soluble at neutral than at acidic pH. pre- and co-treatment with drugs that increase gastric pH, such as proton pump inhibitors or antacids, decrease vericiguat exposure (AUC) by about 30% following fasted administration. However, co-treatment with drugs that increase gastric pH did not affect vericiguat exposure in patients with heart failure when vericiguat was taken as directed with food (see “Dosage and Administration” section).

Vericiguat is a substrate of UGT1A9 and UGT1A1 and transporter P glycoprotein (P gp) and breast cancer resistance protein (BCRP).

No clinically relevant effect on vericiguat exposure was observed when vericiguat was coadministered with ketoconazole (multi-pathway CYP and transporter inhibitor), mefenamic acid (UGT1A9 inhibitor), rifampicin (multi-pathway UGT, CYP, and transporter inducer), digoxin, warfarin, aspirin, sildenafil or the sacubitril/valsartan combination in in vivo studies.

No clinically relevant effect on vericiguat exposure is expected when vericiguat is coadministered with atazanavir (UGT1A1 inhibitor).
Based on *in vitro* data, vericiguat is not a substrate of organic cation transporter (OCT1) or organic anion transporting polypeptides (OATP1B1 and OATP1B3).

*Influence of Verquvo on the pharmacokinetics of other substances*
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.
*In-vitro*-studies indicate that 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.

In in vivo studies coadministration of vericiguat with midazolam (CYP3A substrate) or digoxin (P-gp substrate) showed no clinically relevant effect on midazolam or digoxin exposure.

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.

*Pharmacodynamic interactions*

*Coadministration contraindicated*

Other soluble guanylate cyclase stimulators

Verquvo is contraindicated in patients with concomitant use of other soluble guanylate cyclase (sGC) stimulators, such as riociguat (see “Contraindications” section).

PDE-5 inhibitors

The simultaneous use of Verquvo and phosphodiesterase - 5 (PDE - 5) inhibitors such as sildenafil has not been studied in patients with heart failure and is contraindicated due to the potentially increased risk of symptomatic hypotension (see “Contraindications”).
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 reduction of ≤5.4 mmHg (systolic/diastolic blood pressure, mean arterial pressure) compared to administration of vericiguat alone.
Coadministration was not associated with a clinically relevant effect on the exposure (AUC and $C_{max}$) of either drug.

*Other interactions*

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.

Coadministration of acetylsalicylic acid was not associated with a clinically relevant effect on vericiguat exposure (AUC and $C_{max}$).

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 activity of Factors II, VII, and X.

Coadministration was not associated with a clinically relevant effect on the exposure (AUC and $C_{max}$) of either drug.

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.

Coadministration was not associated with a clinically relevant effect on the exposure (AUC and $C_{max}$) of either drug.

Organic nitrates

Coadministration 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” section).

**Pregnancy, lactation**

*Women of child bearing potential*

Women of child bearing potential should use effective forms of contraception during treatment.

*Pregnancy*

There are no data from the use of Verquvo in pregnant women**.**

A study in pregnant rats showed that vericiguat is transferred to the fetus through the placenta**.**

Studies in animals have shown reproductive toxicity in presence of maternal toxicity *(*see section *“Preclinical Data”).*

Verquvo should not be used during pregnancy.

*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 (see “Preclinical data” section). A decision must be made whether to discontinue breast-feeding or to discontinue or abstain from Verquvo therapy, taking into account the benefit of breastfeeding 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 fertility study with male and female rats, vericiguat showed no impairment of fertility or early embryonic development (see “Preclinical data” section).

**Effects on ability to drive and use machines**

No corresponding studies have been performed.
The occurrence of symptomatic hypotension has been reported (see section “Warning and precautions”); this could affect the ability to drive or use machines.

**Undesirable effects**

The safety of Verquvo in patients with symptomatic chronic heart failure and LVEF ≤45%, was evaluated in the pivotal Phase 3 VICTORIA study, in which patients were treated with Verquvo (up to 10 mg once daily; n=2519) or placebo (n=2515) (see "Properties/Effects” section).
The mean duration of Verquvo exposure was 1 year, and the maximum duration was 2.6 years.

Discontinuation of therapy due to an undesirable effect during the double-blind period of the VICTORIA study was reported in 167 patients treated with Verquvo (6.6%) and in 158 patients treated with placebo (6.3%).

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

The overall incidence of adverse drug reactions (ADRs) was similar between Verquvo and placebo. The individual ADRs in the various system organ classes do not differ significantly between Verquvo and placebo.

Adverse drug reactions are listed by system organ class and then by frequency – the most common ADRs first – according to the following convention: Very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000); frequency not known: these undesirable effects were observed in clinical studies other than the above-mentioned study, or the reports are from post-marketing surveillance. The undesirable effects are shown in decreasing order of severity within each frequency group.
Table 1 lists adverse drug reactions occurring in patients treated with Verquvo and greater than placebo in VICTORIA.

**Table 1: Adverse drug reactions occurring in patients treated with Verquvo and greater than placebo in VICTORIA by system organ class (SOC)**

| Adverse drug reaction | Verquvo N=2519 n (%) | Placebo N=2515 n (%) |
|---|---|---|
| **Blood and lymphatic system disorders** | | |
| Anemia* | 243 (9.6) | 185 (7.4) |
| **Gastrointestinal tract 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: anaemia, anaemia macrocytic, anaemia of chronic disease, autoimmune haemolytic anaemia, blood loss anaemia, haemolytic anaemia, hypochromic anaemia, iron deficiency anaemia, microcytic anaemia, nephrogenic anaemia, normochromic anaemia, normochromic normocytic

anaemia, normocytic anaemia, pancytopenia, pernicious anaemia, haematocrit decreased, haemoglobin decreased, and red blood cell count decreased
†Includes: blood pressure decreased, blood pressure diastolic decreased, blood pressure systolic decreased, hypotension, and orthostatic hypotension

Cardiac electrophysiology
In a dedicated QT study in patients with stable coronary artery disease, administration of 10 mg 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).
No supratherapeutic exposures were tested. The integrated risk assessment of nonclinical and clinical data supports that administration of vericiguat 10 mg is not associated with clinically meaningful QTc prolongation.

Reporting suspected adverse reactions after authorization 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 new or serious adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

**Overdose**

*Symptoms*

Limited data are available with regard to overdosage in patients treated with vericiguat. In VICTORIA, doses up to 10 mg have been studied. In a study in HF patients with preserved ejection fraction (LVEF ≥45%), multiple doses of vericiguat 15 mg have been studied and were generally well tolerated. In the event of an overdose, hypotension may result.

*Treatment*

Symptomatic treatment should be provided. Vericiguat is unlikely to be removed by dialysis because of its high protein binding.

**Properties/Effects**

*ATC code*

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 important 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 signaling 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 reduction in systolic blood pressure was approximately 1 to 2 mmHg greater in patients who received vericiguat compared with the placebo group.

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 the placebo group.

*Clinical efficacy*

*VICTORIA*

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 (NYHA Class II-IV) and left ventricular ejection fraction ≤45% following a worsening heart failure event (heart failure hospitalization within 6 months before randomization or use of outpatient IV diuretics for the treatment of heart failure within 3 months before randomization).

The primary endpoint was the composite of cardiovascular (CV) death or hospitalization for heart failure (HF) (time to first event).

Treatment 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. Ninety percent of patients in the vericiguat group were treated with the 10 mg target dose by the end of the study.

The median follow-up for the primary endpoint was 11 months.
The mean age was 67 years. 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 (LVEF) was 29%. At the time of randomization, the mean eGFR was 62 mL/min/1.73 $m^2$; 10% of patients had an eGFR ≤30 mL/min/1.73 $m^2$. 67% 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 concentration was 2,816 pg/mL at the time of randomization.

Before enrolling in the study, patients were managed with standard-of-care therapy, including ACE inhibitors/ARBs (73%), beta-blockers (93%), mineralocorticoid receptor antagonists (70%), and a combination of an angiotensin receptor blocker and a neprilysin inhibitor (ARNI; 15%). 28% had an implantable cardiac defibrillator, and 15% had a biventricular pacemaker. 91% of patients were treated with 2 or more heart failure medications (beta-blocker, renin-angiotensin system (RAS) inhibitor, or MRA) and 60% of patients were treated with all 3.

Compared with placebo, Verquvo significantly reduced the risk of CV death or hospitalization (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 vericiguat compared with placebo (NNT=24 for 1 year); see Table 2.

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

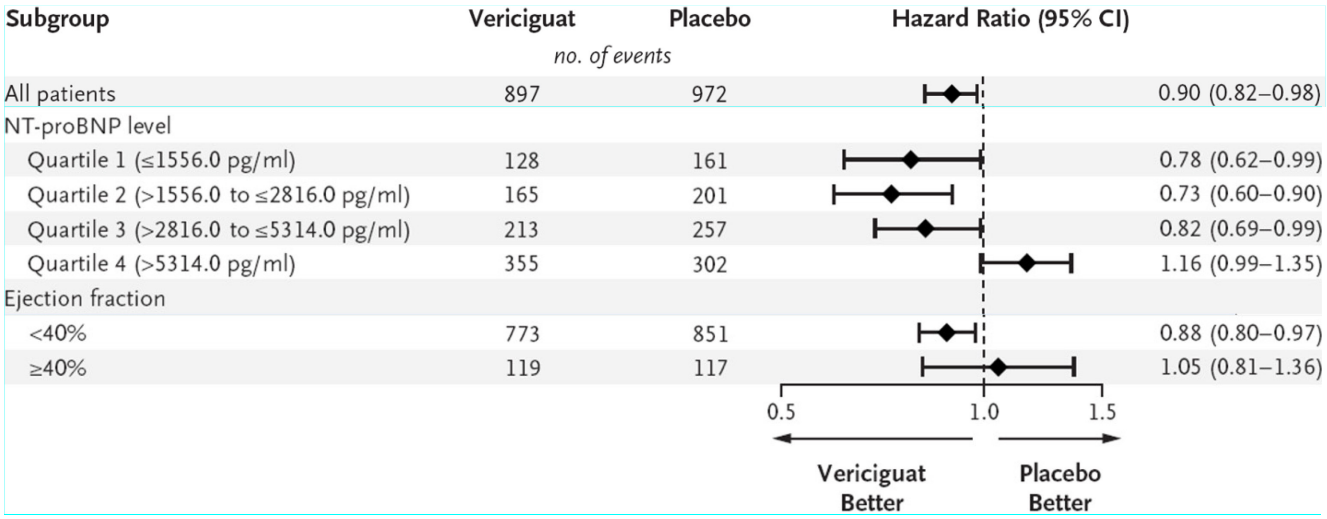
| | **Verquvo N=2526** | | **Placebo N=2524** | | **Treatment comparison** | | |
|---|---|---|---|---|---|---|---|
| | **n (%)** | **Annual event rate (%)*** | **n (%)** | **Annual event rate (%)*** | **Hazard ratio (95% CI)†** | **p-value‡** | **Annualized ARR (%)§** |
| **Primary endpoint** | | | | | | | |
| Composite of CV 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 | | 12.9 | | 13.9 | 0.93 | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | 414 (16.4) | | 441 (17.5) | | (0.81, 1.06) | | |
| Heart failure hospitalization | 691 (27.4) | 25.9 | 747 (29.6) | 29.1 | 0.90 (0.81, 1.00) | | |

*Total number of subjects with an event per 100 subject years at risk.
†Hazard ratio (vericiguat over placebo) and confidence interval from a Cox proportional hazards model.
‡From the log-rank test.
§ Annualized absolute risk reduction, calculated as difference (placebo-vericiguat) in percent per year.
¶For patients with multiple events, only the first event contributing to the composite endpoint is counted.
N: number of subjects in intent-to-treat (ITT) population. n: number of patients with an event.

The effect on the primary composite endpoint was largely consistent for the predefined subgroups with the exception of those dependent on the NT-proBNP level and the left ventricular ejection fraction at baseline (Figure 1). In patients with a markedly increased NT-proBNP (fourth quartile), the risk of CV death or heart failure hospitalization was increased in the vericiguat group compared to the placebo group. The subgroup analyzes support the efficacy of Verquvo without restrictions only for heart failure patients with reduced left ventricular ejection fraction (<40%).

Figure 1: Subgroup analysis for the primary endpoint depending on the baseline NT-proBNP level and ejection fraction



**Pharmacokinetics**

*Absorption*

Vericiguat shows slightly less than dose proportional, time-independent pharmacokinetics, with low to moderate intra and interindividual variability when administered with food. Vericiguat accumulates in plasma up to 151-171% and reaches pharmacokinetic steady state after approximately 6 days. Population pharmacokinetic (PK) model-based steady-state geometric mean PK parameters of vericiguat in heart failure patients are as follows: $C_{max}$ of doses 2.5 mg, 5 mg, and 10 mg: 120, 201, and 350 µg/L, respectively; and AUC of doses 2.5 mg, 5 mg, and 10 mg: 2,300, 3,850, and 6,680 µg•h/L, respectively.

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 those of a whole tablet (see “Dosage/administration” section).
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, vericiguat should be taken with food (see “Dosage/administration” section).

*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.

*Metabolism*

Glucuronidation is the major biotransformation pathway of vericiguat to form an N-glucuronide, which is pharmacologically inactive and the major metabolite in plasma. N-glucuronidation is catalyzed predominantly by UGT1A9 located in the kidney and in the liver, as well as UGT1A1 located in the intestine and the liver. The 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]-labeled 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).

*Kinetics in specific patient groups*

*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 “Dosage/administration” section, use in Specific Populations).

In a 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 normalized for body weight) after a single dose compared to healthy controls.

Plasma protein binding of vericiguat was not altered by renal impairment (eGFR >15 ml/min/1.73 $m^2$) (see “Dosage/administration” section).

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

*Hepatic impairment*

In subjects with mild hepatic impairment (Child-Pugh A), mean exposure to vericiguat (AUC of unbound drug) was 21% higher compared to healthy subjects with normal hepatic function. In subjects with moderate hepatic impairment (Child-Pugh B), mean exposure to vericiguat was 47% higher compared to healthy subjects with normal hepatic function. Plasma protein binding of vericiguat was unchanged in patients with hepatic impairment (Child-Pugh A and B) The pharmacokinetics of vericiguat have not been studied in patients with severe hepatic impairment (Child-Pugh C) (see “Dosage/administration” section).

*Elderly patients (≥65 years)*

In VICTORIA, 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. The population pharmacokinetic analysis showed no clinically significant effect of age on the pharmacokinetics of vericiguat

*Children and adolescents*
No studies with vericiguat have been performed in children and adolescents.

*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 relevant.

*Effects of gender, ethnicity, race, and baseline NT-proBNP*
Based on a population pharmacokinetic analysis, no clinically relevant effect on the pharmacokinetics of vericiguat was observed for gender, ethnicity, race, and baseline NT-proBNP concentration.

**Preclinical 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.

*Mutagenicity and carcinogenicity*

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 assays.
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 maximum recommended human dose (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-statistically insignificant numerical increase of benign pheochromocytomas and Leydig cell tumors 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 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 of vericiguat.

*Reproduction toxicity*

When administered to rats at doses of 5, 15, or 50 mg/kg/day, vericiguat showed 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 MRHD of 10 mg/day, AUC of unbound drug).
A development toxicity study 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 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 (49 times the MHRD) during the preweaning period.

*Other preclinical findings*

In adolescent rapidly-growing rats, reversible bone formation effects (hypertrophy of growth plate and hyperostosis and remodeling of metaphyseal and diaphyseal bone) were seen at exposures of approximately ≥20 times the human exposure at the MRHD (unbound AUC) that were mediated by a mechanism of action-related intracellular cGMP increase. These effects were not observed after long-term administration of vericiguat to adult rats up to exposures of approximately 50 times the human exposure at the MRHD (unbound AUC). In addition, no comparable findings were seen in dogs which were almost full-grown at start of treatment up to exposures of 15 times the human exposure at the MRHD (unbound AUC).

**Other information**

*Shelf life*

Do not use this medicine after the expiry date ("EXP") stated on the container.

*Special precautions for storage*

Do not store above 30 °C.
Keep out of the reach of children.

**Authorisation number**

68001 (Swissmedic)

**Packs**

*2.5 mg film-coated tablets:* Packs of 14 film-coated tablets and hospital packs of 1 x 100 film-coated tablets (B)
*5 mg film-coated tablets:* Packs of 14, 28, or 98 film-coated tablets and hospital packs of 1 x 100 film-coated tablets (B)
*10 mg film-coated tablets:* Packs of 14, 28, or 98 film-coated tablets and hospital packs of 1 x 100 film-coated tablets (B)

**Marketing authorisation holder**

Bayer (Schweiz) AG, Zurich.

**Date of revision of the text**

September 2021