Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Verquvo

Active ingredients: Vericiguat

Sponsor: Bayer Australia Ltd

July 2022

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating therapeutic goods, including medicines, medical devices, and biologicals.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety, and efficacy.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to the Australian public outweigh any risks associated with the use of therapeutic goods.
- The TGA relies on the public, healthcare professionals and industry to report problems with therapeutic goods. The TGA investigates reports received to determine any necessary regulatory action.
- To report a problem with a therapeutic good, please see the information on the TGA website.

About AusPARs

- The Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission. Further information can be found in Australian Public Assessment Report (AusPAR) guidance.
- AusPARs are prepared and published by the TGA.
- AusPARs are static documents that provide information that relates to a submission at a particular point in time. The publication of an AusPAR is an important part of the transparency of the TGA's decision-making process.
- A new AusPAR may be provided to reflect changes to indications or major variations to a prescription medicine subject to evaluation by the TGA.

Copyright
© Commonwealth of Australia 2022
This work is copyright. You may reproduce the whole or part of this work in unaltered form for your own personal use or, if you are part of an organisation, for internal use within your organisation, but only if you or your organisation do not use the reproduction for any commercial purpose and retain this copyright notice and all disclaimer notices as part of that reproduction. Apart from rights to use as permitted by the *Copyright Act 1968* or allowed by this copyright notice, all other rights are reserved, and you are not allowed to reproduce the whole or any part of this work in any way (electronic or otherwise) without first being given specific written permission from the Commonwealth to do so. Requests and inquiries concerning reproduction and rights are to be sent to the TGA Copyright Officer, Therapeutic Goods Administration, PO Box 100, Woden ACT 2606 or emailed to <tga.copyright@tga.gov.au>.

Contents

List of abbreviations

Abbreviation	Meaning
ACE	Angiotensin converting enzyme
ACM	Advisory Committee on Medicines
AESI	Adverse event of special interest
ARB	Angiotensin II receptor blocker
ARNI	Angiotensin receptor neprilysin inhibitor
ARR	Absolute risk reduction
ARTG	Australian Register of Therapeutic Goods
ASA	Australia specific annex
AUC	Area under the concentration time curve
AUC_{0-24}	Area under the concentration time curve during 24 hours
BNP	Brain (B-type) natriuretic peptide
CI	Confidence interval
CL/F	Oral clearance
C_{max}	Maximum concentration
CMI	Consumer Medicines Information
DLP	Data lock point
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency (European Union)
ERAUC	Exposure ratio based on area under concentration time curve
EU	European Union
GVP	Good Pharmacovigilance Practices
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HR	Hazard ratio
ITT	Intent to treat

Abbreviation	Meaning
LVEF	Left ventricular ejection fraction
M1	Metabolite 1 (vericiguat N-glucuronide)
NONMEM	Nonlinear mixed effects modelling
NT-proBNP	N-terminal-pro-hormone brain (B-type) natriuretic peptide
NYHA	New York Heart Association
PI	Product Information
PK	Pharmacokinetic(s)
PopPK	Population pharmacokinetic(s)
PRISM	Patient response identifiers for stratified medicine
PSUR	Periodic safety update reports
PT	Preferred Term
RMP	Risk management plan
RV	Residual variability
SAE	Serious adverse event
sGC	Soluble guanylyl cyclase
SGLT2	Sodium glucose co-transporter 2
SOC	System Organ Class
T2DM	Type 2 diabetes mellitus
TEAE	Treatment emergent adverse event
TGA	Therapeutic Goods Administration
T_{max}	Time of maximum concentration
UGT1A	UDP-glucuronosyltransferase
USA	United States of America
Vc/F	Apparent central volume of distribution

Product submission

Submission details

Type of submission:	New chemical entity
Product name:	Verquvo
Active ingredient:	Vericiguat
Decision:	Approved
Date of decision:	10 November 2021
Date of entry onto ARTG:	15 November 2021
ARTG numbers:	339992, 339993, 339994
, *Black Triangle Scheme:*	Yes This product will remain in the scheme for 5 years, starting on the date the product is first supplied in Australia
Sponsor's name and address:	Bayer Australia Ltd 875 Pacific Highway Pymble NSW 2073
Dose form:	Film-coated tablet
Strengths:	2.5 mg, 5 mg, and 10 mg
Container:	Blister pack
Pack sizes:	Available for all strengths (2.5 mg, 5 mg, and 10 mg): 14 film-coated tablets 14 film-coated tablets (starter pack) 28 film-coated tablets 100 film-coated tablets (hospital dispensing pack)
Approved therapeutic use:	*Verquvo is indicated in addition to standard of care therapy for the treatment of symptomatic chronic heart failure in adult patients with reduced ejection fraction less than 45% who are stabilised after a recent heart failure decompensation event requiring admission and/or IV diuretic therapy (see Section 5.1 Pharmacodynamic properties - Clinical trials).*
Route of administration:	Oral
Dosage:	Verquvo should be initiated under the supervision of a cardiologist. The recommended starting dose of Verquvo is 2.5 mg once daily. The dose should be doubled

approximately every 2 weeks to reach the target maintenance dose of 10 mg once daily, as tolerated by the patient.

Before starting Verquvo, care should be taken to optimise volume status and diuretic therapy to stabilise patients after the decompensation event, particularly in patients with very high NT-proBNP levels (see Section 5.1 Pharmacodynamic properties, Clinical trials). If patients experience symptomatic hypotension, dose adjustment of concomitant diuretics and treatment of other causes of hypotension (for example. hypovolaemia) should be considered. If symptomatic hypotension persists despite such measures, temporary reduction in dose or interruption of Verquvo should be considered (see Section 4.4 Special warnings and precautions for use).

Treatment should not be initiated in patients with systolic blood pressure less than 100 mmHg (see Section 4.4 Special warnings and precautions for use of the Product Information).

Safety and efficacy of Verquvo have not been established in patients less than 18 years of age (see Section 4.4 Special warnings and precautions for use, paediatric use; and Section 5.2 Pharmacokinetic properties - special populations of the Product Information).

Verquvoo is contraindicated in patients with concomitant use of other soluble guanylate cyclase stimulators, such as riociguat (see Section 4.5 Interactions with other medicines and other forms of interactions).

For further information refer to the Product Information.

Pregnancy category: D

Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. This must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your State or Territory

Product background

This AusPAR describes the submission by Bayer Australia Ltd (the sponsor) to register Verquvo (vericiguat) 2.5 mg, 5 mg, and 10 mg, film coated tablets, for the following proposed indication:

> *Verquvo is indicated for the treatment of symptomatic chronic heart failure in adult patients with reduced ejection fraction less than 45% who had a previous worsening heart failure event (see Section 5.1 Pharmacodynamic properties – Clinical trials).*

Vericiguat is described as a novel stimulator of soluble guanylyl cyclase (sGC), which itself is a key enzyme in the nitric oxide signalling pathway. When nitric oxide binds to sGC, cyclic guanosine monophosphate is synthesised, triggering vasorelaxation, and indirectly inhibiting smooth muscle proliferation, leukocyte recruitment and platelet aggregation.[1]

At the time of this submission only one other sGC stimulator is approved for use. Riociguat (Adempas) was approved in 2014 in Australia;[2] and is indicated for the treatment of multiple forms of pulmonary arterial hypertension, and chronic thromboembolic pulmonary hypertension.

Heart failure is a clinical syndrome that presents with typical signs and symptoms reflecting the inability of the heart to fill with blood at normal pressure or to eject sufficient blood to supply the organs of the body. The most frequent symptom, which is common to a wide range of diseases not just affecting the heart, is breathlessness on exertion. As the disease progresses, breathlessness may develop on lying down, bending forward, and at rest, and be accompanied by other non-specific symptoms such as fatigue and ankle swelling. A range of conditions that affect the structure or function of the heart may trigger heart failure and researchers and clinicians have used a number of different approaches to classify and define both the syndrome and the potential causes. Heart failure is estimated to affect over 38 million people worldwide and about 480,000 people in Australia, is more common among the elderly and has a significantly greater prevalence in the indigenous Australian population.[3] Between 2015 and 2016, there were about 173,000 hospitalisations in Australia where heart failure and cardiomyopathy were recorded as the main or additional diagnosis, representing 1.6% of all hospitalisations.[4] In the New South Wales and Australian Capital Territory, the NSW HF SNAPSHOT study prospectively audited patients hospitalised with heart failure over one month in 2013 and found the median length of stay was six days and 58% were categorised as heart failure with reduced ejection fraction.[5]

[1] Stasch JP et al. (2011) Soluble guanylate cyclase as an emerging therapeutic target in cardiopulmonary disease. *Circulation* 123(20):2263-73
[2] AusPAR for Adempas (riociguat) Bayer Australia Ltd PM-2013-00307-1-3. Available at: https://www.tga.gov.au/auspar/auspar-riociguat
[33] Atherton JJ et al., for NHFA CSANZ Heart Failure Guidelines Working Group (2018) National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand: Guidelines for the Prevention, Detection, and Management of Heart Failure in Australia 2018 *Heart Lung and Circulation* 27:1123-1208
[4] Australian Institute of Health and Welfare (2017) Admitted patient care 2015–16: Australian hospital statistics, AIHW, Australian Government. Available at: https://www.aihw.gov.au/reports/hospitals/ahs-2015-16-admitted-patient-care
[5] Newton PJ, Davidson PM, Reid CM, et al. Acute heart failure admissions in New South Wales and the Australian Capital Territory: the NSW HF Snapshot Study. Med J Aust. 2016;204(3):113.e1-113.e1138.

According to the National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand Australian clinical guidelines for the management of heart failure;[6] the syndrome is commonly classified into two categories based on the left ventricular ejection fraction (LVEF) and other objective evidence of failure, along with the presence of symptoms with or without clinical signs of heart failure. Patients with symptoms with or without signs of heart failure who have a left ventricular ejection fraction of less than 50% are classified as having heart failure with reduced ejection fraction (HFrEF). Those patients experiencing symptoms with or without signs of heart failure where the ejection fraction is 50% or more may require additional objective evidence to confirm a diagnosis of heart failure with preserved ejection fraction (HFpEF). This evidence frequently is provided by echocardiography but depending on the underlying cause of the symptoms, may require alternative diagnostic testing. Most research to date has reported reduced mortality and morbidity in response to new therapies in heart failure patients with reduced ejection fraction, with less evidence of efficacy among patients with preserved ejection fraction.

International guidelines include a third category, heart failure with mid-range ejection fraction, where the LVEF ranges between 40% and 49%. It shares features with heart failure with both preserved, and reduced ejection fraction.[7,8]

The New York Heart Association (NYHA) criteria categorise heart failure into four classes based on patient symptoms and function.[9,10] Class I describes an asymptomatic cohort that does not appear to satisfy the definitions of heart failure with reduced or preserved ejection fraction..

Australian and international guidelines regarding the optimal treatment of heart failure (after addressing any underlying preventable or treatable cause of the syndrome) agree that the initial management of heart failure with reduced ejection fraction should include angiotensin converting enzyme (ACE) inhibitors (or otherwise angiotensin II receptor blockers (ARB)), beta blockers and low-dose mineralocorticoid receptor agonists, to improve survival and decrease hospitalisations for heart failure. Additional therapies, depending on the patient and the contributing pathology, may include diuretics, ivabradine, or change from prescribing an ACE inhibitor/ARB to an angiotensin receptor neprilysin inhibitor (ARNI), for example sacubitril-valsartan. Heart failure patients with preserved ejection fraction may be adequately treated with diuretics and management of hypertension if present; patients with valvular, pericardial or congenital heart disease may benefit from a surgical intervention, including implanted electronic devices. A multidisciplinary approach that involves physiotherapy, exercise interventions, dietitians, psychologists and heart failure nurses may also improve survival and decrease re-hospitalisations.

[6] NHFA CSANZ Heart Failure Guidelines Working Group, Atherton JJ, Sindone A, et al. National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand: Guidelines for the Prevention, Detection, and Management of Heart Failure in Australia 2018. Heart Lung Circ. 2018;27(10):1123-1208.
[7] Ponikowski P et al., for Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) (2016) 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure *European Heart Journal* 37:2129-2200
[8] Yancy CW et al., for the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guideliens (2013) 2013 ACCF/AHA Guideline for the Management of Heart Failure *Journal if the American College of Cardiology* 62(16):e147-239
[9] The New York Heart Association (NYHA) criteria categorise heart failure into four classes based on patient symptoms and function.
Class I: No limitation of ordinary physical activity.
Class II: Slight limitation of ordinary physical activity. No symptoms at rest.
Class III: Marked limitation of ordinary physical activity. No symptoms at rest.
Class IV: Symptoms on any physical activity or at rest.
[10] The Criteria Committee of the New York Heart Association. (1994). Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels (9th ed.). Boston: Little, Brown & Co. pp. 253–256.

More recently, sodium glucose co-transporter 2 (SGLT2) inhibitors have shown improved outcomes in patients with heart failure. Among those, dapagliflozin is a selective competitive SGLT2 inhibitor that was first approved in Australia in 2012 as a treatment for type 2 diabetes mellitus (T2DM), based on its glucuretic properties.[11] More recent research (the DECLARE trial);[12] reported that dapagliflozin can reduce the risk of hospitalisation for heart failure in adults with diabetes together with established cardiovascular disease or with risk factors for cardiovascular disease, and the dapagliflozin heart failure clinical trial established the efficacy of dapagliflozin in treating heart failure with reduced ejection fraction in both the presence or absence of T2DM.

This submission was evaluated as part of the Australia-Canada-Singapore-Switzerland-United Kingdom (ACCESS) Consortium with work-sharing between the TGA, Health Sciences Authority Singapore, and Swissmedic. Each regulator made independent decisions regarding approval (market authorisation) of the new medicine.

Regulatory status

This product is considered a new chemical medicine for Australian regulatory purposes.

At the time the TGA considered this submission, a similar submission had been approved in European Union (EU) on 20 July 2021, United States of America (USA) on 19 January 2021 and in Japan on 23 June 2021. A similar submission was under consideration in Singapore and Switzerland.

The following table summarises these submissions and provides the indications where approved.

Table 1: International regulatory status

Region	Submission date	Status	Approved indications
European Union	27 May 2020	Approved on 16 July 2021	*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)*
United States of America	20 May 2020	Approved on 19 January 2021	*Verquvo is indicated to reduce the risk of cardiovascular death and heart failure (HF) hospitalization following a hospitalization for heart failure or need for outpatient IV diuretics, in adults with symptomatic chronic HF and ejection fraction less than 45% [see Clinical Studies (14)].*

[11] AusPAR for Forxiga (dapagliflozin) Bristol-Myers Squibb Australia / AstraZeneca PM-2010-03812-35. Available at: https://www.tga.gov.au/auspar/auspar-dapagliflozin-propanediol-monohydrate-4
[12] Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events (DECLARE-TIMI58); ClinicalTrials.gov Identifier: NCT01730534. Available at: https://clinicaltrials.gov/ct2/show/NCT01730534

Region	Submission date	Status	Approved indications
Japan	5 June 2020	Approved on 23 June 2021	*Chronic heart failure; however, only patients receiving standard treatment for chronic heart failure.* *5.1: Since the efficacy and safety of Verquvo has not been established in patients with chronic heart failure and preserved left ventricular ejection fraction (LVEF), Verquvo should be administered to patients with chronic heart failure and reduced LVEF.* *5.2: Eligible patients should be selected based on a thorough understanding of the results provided in the 'clinical studies' section and the demographic characteristics (e.g., standard therapy, left ventricular ejection fraction; LVEF, systolic blood pressure) of the patients enrolled in the clinical trial.*

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA PI/CMI search facility.

Registration timeline

The following table captures the key steps and dates for this submission.

Table 2: Timeline for Submission PM-2020-03566-1-3

Description	Date
Submission dossier accepted and first round evaluation commenced	13 August 2020
First round evaluation completed	14 December 2020
Sponsor provides responses on questions raised in first round evaluation	11 March 2021
Second round evaluation completed	6 October 2021
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	31 August 2021
Sponsor's pre-Advisory Committee response	13 September 2021

Description	Date
Advisory Committee meeting	30 September and 1 October 2021
Registration decision (Outcome)	10 November 2021
Completion of administrative activities and registration on the ARTG	15 November 2021
Number of working days from submission dossier acceptance to registration decision*	199

*Statutory timeframe for standard submissions is 255 working days

Submission overview and risk/benefit assessment

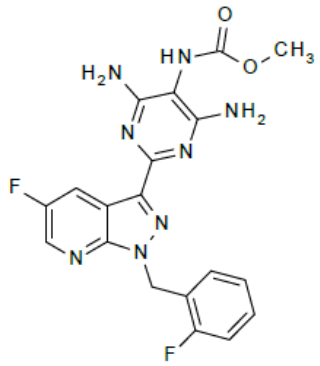
This section is a TGA summary of wording used in TGA's evaluation report, which discussed numerous aspects of overseas evaluation reports and included some information that was commercial-in-confidence.

Quality

The quality evaluator confirmed that the product satisfies Australian legislative, pharmacopoeial monograph and relevant technical requirements.

Vericiguat is a chemically synthesised molecule with molecular formula $C_{19}H_{16}F_2N_8O_2$, and the pictured structure is shown in Figure 1.

Figure 1: Chemical structure of vericiguat



The drug substance is a white to yellowish micronised powder with five forms (modifications) and also several solvates, a monohydrate, dihydrate and amorphous form identified. Vericiguat is considered a low-soluble, highly permeable and weakly basic biopharmaceutics classification system class II drug. Particle size is controlled to achieve the desired dissolution profile.

The sponsor proposes to register immediate release tablets as follows

- 10 mg: yellow-orange film coated tablet, round biconvex, markings on top side '10' and bottom side 'VC'.
- 5 mg: brown-red film coated tablet, round biconvex, markings on top side '5' and bottom side 'VC'.

- 2.5 mg: white film coated tablet, round biconvex, markings on top side '2.5' and bottom side 'VC'.

The tablets are packaged in foil blister packs each containing 14 tablets, one or two blister packs in each cardboard box, depending on pack size (14 or 28 tablets) and hospital dispensing packs of 100 tablets.

Proposed conditions of registration

Laboratory testing & compliance with Certified Product Details (CPD)

i. All batches of Verquvo supplied in Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).

ii. When requested by the TGA, the Sponsor should be prepared to provide product samples, specified reference materials and documentary evidence to enable the TGA to conduct laboratory testing on the Product. Outcomes of laboratory testing are published biannually in the TGA Database of Laboratory Testing Results http://www.tga.gov.au/ws-labs-index and periodically in testing reports on the TGA website.

Nonclinical

The nonclinical evaluator reported that the overall quality of nonclinical module was high and compliant with the relevant guideline.[13] All pivotal toxicity studies were conducted under Good Laboratory Practice conditions using the proposed clinical route and dosing regimen, and the major human metabolite of vericiguat (vericiguat N-glucuronide, also referred as M1 (metabolite 1)) was well characterised.

In vitro, vericiguat (0.01 to 100 μM) stimulated soluble guanylyl cyclase (sGC) in a concentration dependent manner, both alone and synergistically with nitric oxide. It exhibited vasorelaxant activity at clinically relevant concentrations in vascular tissues *in vitro* (including under conditions of nitrate tolerance). *In vivo*, vericiguat had systemic and pulmonary antihypertensive activity in healthy rats and in dogs and was active in rat, dog and pig models of systemic and pulmonary hypertension and heart failure, supporting the proposed clinical indication. The major human circulating metabolite (M1) was not pharmacologically active.

Off-target activity for vericiguat and its major metabolite (M1) is not predicted based on the results of standard screening assays for activity at a broad panel of receptors, ion channels, transporters and enzymes, including a panel of cyclic guanosine monophosphate (cGMP) metabolising phosphodiesterases. Vericiguat did not have any clinically relevant effect on platelet aggregation induced by adenosine diphosphate, the thrombin receptor activator peptide 6 (TRAP-6) or collagen.

Safety pharmacology studies assessed effects on the cardiovascular, respiratory, gastrointestinal and central nervous systems. No clinically relevant effect on inhibition of hERG-related gene potassium ion tail current was observed *in vitro*. Vericiguat is not predicted to prolong the QT interval;[14] in patients. Decreased systolic and diastolic blood pressure accompanied by increased heart rate in dogs treated with ≥ 0.6 mg/kg oral vericiguat, about four times the unbound clinical maximum concentration (C_{max}) are consistent with the pharmacological activity of vericiguat. Intestinal motility was inhibited

[13] ICH M3 (R2) on non-clinical safety studies for the conduct of human clinical trials for pharmaceuticals. CPMP/ICH/286/95

[14] The **QT interval** is the time from the start of the QRS wave complex to the end of the corresponding T wave. It approximates to the time taken for ventricular depolarisation and repolarisation, that is to say, the period of ventricular systole from ventricular isovolumetric contraction to isovolumetric relaxation.

in male rats dosed orally at 5 mg/kg, about six times the unbound clinical C_{max}. Central nervous system effects in male rats dosed orally at 15 mg/kg (approximately 37 times the unbound clinical C_{max}) included ptosis, splayed hindlimbs, slow deliberate gait and minor delays in righting reflex, together with reduced body temperature. Further studies in rats at the same dose level found no impairment of motor coordination in the rotarod test and no effect on chemoconvulsion. Vericiguat shows very limited penetration across the blood brain barrier and a direct effect on central nervous system function is unlikely.

Overall, the pharmacokinetic profile in animals was qualitatively similar to that of humans, but important quantitative differences existed. Vericiguat was readily and rapidly absorbed with a similar time after administration of a drug when the maximum plasma concentration is reached (T_{max}) in all species. Half-life values were similar in rats and dogs but longer in humans. Plasma protein binding of vericiguat was highly species specific, being approximately 98% in humans, compared with only 92% in mice, 95% in rats, 96% in rabbits, 90% in dogs and 95% in monkeys. Tissue distribution of vericiguat was wide but penetration into brain and spinal cord was very limited. The M1 was not a significant metabolite in animals, but, given its chemical nature, this is not considered to be of toxicological concern. Drug related material was excreted approximately equally via urine and faeces in humans while faeces predominated for animal species.

Pharmacokinetic drug interactions involving cytochrome P450 enzymes;[15] or transporters are not anticipated. While nonclinical data suggests inhibitors of UDP-glucuronosyltransferase (UGT1A)1-9 may increase vericiguat exposures, this did not appear to translate to effects on exposures in patients.

Vericiguat had low to moderate acute toxicity by the clinical route in mice, rats and dogs.

Repeat dose toxicity studies by the oral route were conducted in mice (13 weeks), rats (up to 6 months) and Beagle dogs (up to 9 months). Maximum exposures (unbound area under concentration time curve (AUC)) were high to very high in mice, high in rats (low in the juvenile rat study) and moderate in dogs. The metabolite M1 was adequately covered in the mouse carcinogenicity assay, but M1 exposures were subclinical in rats. Target organs for toxicity were the cardiovascular and renin angiotensin system, including the heart and vasculature (decreased arterial blood pressure, tachycardia, hypertrophy of myocardial arteries and plexiform changes in mesenteric veins), adrenal glands (hypertrophy or hyperplasia, medullary changes consistent with chromaffin cell activation), gastrointestinal tract (evidence of motility disturbance leading to increased Paneth cells and inflammatory changes in rats, and rectal prolapse in dogs) and bone (hypertrophy of growth plates, hyperostosis and remodelling of metaphyseal and diaphyseal bone).

Vericiguat was not mutagenic in the bacterial mutation assays or clastogenic *in vitro* (mouse lymphoma thymidine kinase assay) or *in vivo* (in the mouse and rat micronucleus tests). A weight of evidence approach suggests vericiguat is not genotoxic. The development of ovarian tubulostromal adenomas in female mice at > 20 mg/kg/day orally (unbound exposure ratio based on the AUC of 33) and adrenal pheochromocytomas and Leydig cell tumours in male rats at > 6 mg/kg/day orally (unbound exposure ration by

[15] **Cytochrome P450 (CYP) enzymes:** CYPs are the major enzymes involved in drug metabolism, accounting for large part of the total metabolism. Most drugs undergo deactivation by CYPs, either directly or by facilitated excretion from the body. Also, many substances are bioactivated by CYPs to form their active compounds.
Many drugs may increase or decrease the activity of various CYP isozymes either by inducing the biosynthesis of an isozyme (enzyme induction) or by directly inhibiting the activity of the CYP (enzyme inhibition). This is a major source of adverse drug interactions, since changes in CYP enzyme activity may affect the metabolism and clearance of various drugs. Such drug interactions are especially important to take into account when using drugs of vital importance to the patient, drugs with important side-effects and drugs with small therapeutic windows, but any drug may be subject to an altered plasma concentration due to altered drug metabolism.

AUC of 12) in the 2 year carcinogenicity assays are of unlikely clinical relevance. Fertility was unaffected in male and female rats treated with vericiguat at exposure levels > 50 times the unbound clinical AUC. Vericiguat was not teratogenic in rats. Late abortions and resorptions in rabbits due to pharmacological activity on dams resulted in reduced numbers of viable fetuses at clinically relevant concentrations (unbound exposure ratio based on AUC of 1), and a teratogenic effect on the developing heart and major vessels could not be completely ruled out due to data limitations. Pre/postnatal toxicity in rats following maternal doses of ≥ 7.5 mg/kg/day orally (the lowest tested dose) included increased incidence of stillbirths and pup mortality or total litter loss, reduced body weight gain and delayed onset of developmental markers including sexual maturation.

The nonclinical evaluator did not object to the registration of vericiguat as a new chemical entity.

Clinical

Summary of clinical studies

In support of this submission the sponsor submitted the following:

- one Phase III study:
  - the VICTORIA trial (Study 16493; the pivotal clinical study for this submission);[16] was a randomised parallel-group, placebo-controlled, double-blind, event-driven, multi-center pivotal phase iii clinical outcome trial of efficacy and safety of the oral sGC stimulator vericiguat in subjects with heart failure with reduced ejection fraction (HFrEF).
- three Phase II studies, one using the target population (heart failure with reduced ejection fraction (HRrEF)) for this submission:
  - the SOCRATES-REDUCED trial (Study 15371);[17] and the SOCRATES-PRESERVED trial (Study 15829);[18] were dose-finding studies and the first studies for vericiguat in patients with heart failure. Both studies followed the same design principally based on the design of the Phase I multiple-dose escalation studies in healthy volunteers.
    - § the SOCRATES-REDUCED trial was a randomised parallel-group, placebo-controlled, double-blind, multi-centre dose finding phase II trial exploring the pharmacodynamic effects, safety and tolerability, and pharmacokinetics of four dose regimens of the oral sGC stimulator vericiguat (BAY 1021189) over 12 weeks in patients with worsening heart failure and reduced ejection fraction (HFrEF).
    - § the SOCRATES-PRESERVED trial was a similar study but in patients with heart failure with preserved ejection fraction (HFpEF).

[16] Armstrong PW, et al. for the VICTORIA study group. Vericiguat in Patients with Heart Failure and Reduced Ejection Fraction *N Engl J Med* 2020;382:1883-93.
[17] Gheorghiade M, et al. for the SOCRATES REDUCED study group. Effect of Vericiguat, a Soluble Guanylate Cyclase Stimulator, on Natriuretic Peptide Levels in Patients With Worsening Chronic Heart Failure and Reduced Ejection Fraction. The SOCRATES-REDUCED Randomized Trial. *JAMA*. 2015 Dec 1;314(21):2251-62.
[18] Pieske B, et al. for the SOCRATES-PRESERVED study group. Vericiguat in patients with worsening chronic heart failure and preserved ejection fraction: results of the SOluble guanylate Cyclase stimulatoR in heArT failurE patientS with PRESERVED EF (SOCRATES-PRESERVED) study. *European Heart Journal* (2017) 38, 1119–1127

  - the VITALITY trial (Study 19334), in patients with heart failure with preserved ejection fraction (HFpEF).
- multiple pharmacokinetic (PK) and pharmacodynamic (PD) Phase I studies, and PK-PD analyses.

Pharmacology

Pharmacokinetics

The pharmacokinetic (PK) and pharmacodynamic characteristics of vericiguat were studied in a dose range of 0.5 to 15 mg in healthy subjects and in the intended patient population.

Absorption

Following oral administration of a solution at single doses of 0.5 to 15 mg, vericiguat was rapidly absorbed with median T_{max} ranging between 0.73 to 1.75 hours. Plasma levels declined in a bi-exponential manner. The absolute bioavailability of vericiguat following oral administration of a 10 mg dose, in combination with a high fat, high calorie breakfast, was 93%. AUC and C_{max} in healthy volunteers increased in a dose proportional manner following single and multiple doses in the dose range from 1.25 to 10 mg. Steady state levels were reached by Day 3 to 4 with administration of multiple doses (twice daily and four times daily). Mild accumulation was identified following four times daily dosing with accumulation ratios for AUC ranging from 155 to 171%.

Administration of vericiguat with a high calorie high fat meal delayed median T_{max} from 2 hours to 4.5 hours and increased vericiguat bioavailability (increase of 44% for AUC and increase of 41% for C_{max}). C_{max} was slightly elevated (increase of 19%) and the median T_{max} was about 1 hour earlier when vericiguat was taken with a continental breakfast compared to a high fat breakfast. The slightly elevated C_{max} is not considered to be likely clinically relevant. Administration in combination with food is the proposed dosing recommendation.

Distribution

The volume of distribution of vericiguat following intravenous administration was determined to be approximate 44 L. Vericiguat is highly bound to plasma proteins (97.6 to 97.9%), primarily to albumin. Protein binding was not affected by mild or moderate hepatic or renal impairment. However, the pharmacokinetics of vericiguat in patients with severe hepatic impairment or with end stage renal disease have not been studied.

Metabolism

Vericiguat is primarily cleared by UGT1A1- and UGT1A9-mediated metabolism to a pharmacologically inactive N-glucuronide metabolite (M1). Since UGT1A9 is expressed in liver and kidney, metabolism in the kidneys may contribute to vericiguat metabolic clearance.

Preclinical data indicated that several cytochrome P450 enzymes are capable of metabolising vericiguat, however, with a low turnover. A mild increase in vericiguat was observed in a clinical drug-drug interaction study with ketoconazole.

Elimination and excretion

In healthy volunteers vericiguat had a mean systemic plasma clearance of 1.62 L/h and a terminal half-life of about 20 hours after intravenous administration. In a mass balance study, 53.1% (range: 49.9 to 56.1%) of a radioactive vericiguat dose was recovered in urine and 45.2% (range: 40.1 to 49.9%) in faeces, respectively. Metabolite M1 was the predominant substance in the urine of all study participants, accounting for 40.8% of the administered radioactive dose and about 77% of the radioactivity in urine. Unchanged

vericiguat was the major radioactive species in the faeces, accounting for 42.6% of the administered dose and 94% of the radioactivity in faeces.

In vitro experiments indicated that gut microbiota were able to convert metabolite M1 back to vericiguat, indicating that (part) of the unchanged vericiguat in faeces may have been secreted as M1 and the potential for enterohepatic recycling, however this does not appear to have a significant effect on pharmacokinetics (PK).

Pharmacokinetics in patients with heart failure with reduced ejection fraction

The exposure to vericiguat in patients with HFrEF appears to be slightly higher (about 18%) than in healthy volunteers. The sponsor indicated that this variation is likely associated with differences in weight and age distributions between the two populations. There was no apparent association between higher pharmacokinetics and clinical responses.

Special populations

No dose adjustment is proposed for mild or moderate hepatic impairment. Vericiguat is not recommended for use in patients with severe hepatic impairment.

Impaired renal function appears to increase exposure to vericiguat in a dose dependent manner. No dose adjustment is proposed for mild or moderate renal impairment. Vericiguat is not recommended for use in patients with an estimated glomerular filtration rate (eGFR) < 15 mL/min/1.73m^2 or on dialysis.

Interactions with other drugs

While *in vivo* and *in vitro* studies demonstrated small effects on the PK of vericiguat with some drugs, no studies indicated interactions that may have a clinically relevant effect. Similarly, vericiguat did not have clinically important effects on a range of drug transporters. There is some uncertainty regarding the possibility that vericiguat may be a mild inducer of CYP3A4 enzymes.

Population pharmacokinetics data

Several population pharmacokinetic (popPK) models were developed during the clinical development program. Study 20964 (also described as Study 05D7T5) was considered the 'Final integrated population pharmacokinetics (PopPK) analysis', where PK data from VICTORIA and SOCRATES-REDUCED trials were used to:

- Develop a PopPK model that characterises the vericiguat plasma concentration profile over time and describes the variability in vericiguat PK in subjects with heart failure with reduced ejection fraction.
- Characterise the impact of intrinsic and extrinsic factors on vericiguat exposures.
- Generate empirical Bayes estimates of verciguat exposures to support exposure-response (E-R) analyses for clinical efficacy and safety.

Analysis applied a nonlinear mixed effects modelling approach (NONMEM, version 7), and stepwise covariate analysis both for forward selection and backward elimination of covariates.

A base structural model consisting of a one compartment model with first order absorption and linear elimination described the plasma concentration time data well. An exponential variance model was used to describe inter-individual variability (IIV) in first order absorption rate constant (ka), apparent clearance (CL/F), and apparent central volume of distribution (Vc/F) and a combined additive and proportional variance model was used to describe residual variability (RV). Since apparent PK parameters were estimated, a covariance between CL/F and Vc/F was included in the model to account for IIV in bioavailability (F1). Bioavailability in study participants taking 5 mg doses or 10 mg

doses was approximately 16% and 27% lower than in participants taking 2.5 mg doses, respectively. The effect of baseline body weight as a power function on CL/F was statistically significant, as was the effect of time varying body weight as a power function on Vc/F. In general, fixed and random effect parameters were estimated with good precision.

The steady state area under the concentration time curve during 24 hours ($AUC_{0\text{-}24h}$), calculated using a fixed 10 mg dose, was approximately 27% higher for the < 60 kg groups, and 19.6% lower in the > 90 kg body weight groups, respectively, compared to the reference group (60 to 90 kg body weight group). This is consistent with the fact that body weight was a statistically significant covariate on CL/F. Changes in the steady state $AUC_{0\text{-}24h}$ and C_{max} associated with other covariates were not statistically significant. The sponsor suggests that these changes may have primarily been due to differences in body weight within the covariate categories. Age, bilirubin, eGFR, sex, albumin, use of proton pump inhibitor, use of any drugs affecting gastric pH, and N-terminal-pro hormone brain (B-type) natriuretic peptide (NT-proBNP) were not significant predictors of vericiguat PK.

Pharmacodynamics

The pharmacodynamics effects of vericiguat were evaluated after single and multiple dose administrations in healthy subjects and evaluated in a pooled analysis. Overall, vericiguat administration led to vasodilation manifested by an exposure dependent lowering of systemic blood pressure and a reflex increase in heart rate.

At therapeutic doses, there is no apparent effect of vericiguat on QTcF interval.[19] However, studies have not been performed with supratherapeutic exposures.

Potential pharmacodynamic effects of combination of vericiguat with (in separate studies) acetyl salicylic acid, Warfarin, glyceryl trinitrate, or sacubitril/valsartan had no significant pharmacodynamic effect. There is a recommendation that the use of vericiguat in combination with isosorbide mononitrate, or with sildenafil may be contraindicated because of an unpredictable risk of adverse events.

Dose finding

To establish the optimal dose of vericiguat, three Phase II studies were conducted in patients with reduced (SOCRATES-REDUCED trial) and preserved (SOCRATES-PRESERVED and VITALITY trials) left ventricular ejection fraction (LVEF), respectively. The focus of this evaluation is on the SOCRATES-REDUCED trial using a target population which was most relevant to the proposed indication.

The 12-week SOCRATES-REDUCED trial investigated the effect of four vericiguat regimens (1.25 mg, 2.5 mg, 5 mg, and 10 mg) as compared with placebo control in patients with worsening chronic heart failure and reduced LVEF. The study showed no significant difference for the primary endpoint (change NT-proBNP) from Baseline to Week 12) from placebo in the per-protocol set of pooled (2.5 mg to 10 mg) vericiguat data.

[19] The **corrected QT interval** (**QTc**) estimates the QT interval at a standard heart rate. This allows comparison of QT values over time at different heart rates and improves detection of patients at increased risk of arrhythmias. The **QTcF** is the QT interval corrected for heart rate according to Fridericia's formula.

Table 3: SOCRATES-REDUCED trial; Primary endpoint change in N-terminal pro-hormone B-type natriuretic peptide from Baseline to Week 12 (per-protocol analysis set)

Treatment comparison	Difference of means vs. placebo - log scale	90% CI of difference	Ratio of geometric means vs. placebo - back transformed	90% CI of ratio	p-value
Pooled 2.5 mg up to 10 mg	-0.1220	-0.32, 0.07	0.885	0.73 - 1.08	0.1506

Abbreviations: CI = confidence interval; vs. = versus.

A prespecified exploratory secondary analysis suggested a dose response relationship between increasing vericiguat dose and NT-proBNP reduction (p = 0.0174). In an exploratory exposure-response analysis, reduction of NT-proBNP was observed to be dependent on vericiguat exposure and on baseline NT-proBNP. No plateau of the exposure-response relationship was observed in the investigated exposure range. The evaluation questioned whether the 10 mg dose was ultimately optimal, but no other study data was requested.

Efficacy

Victoria trial (Study 16493)

Study overview

The pivotal efficacy study (the VICTORIA trial, Study 16493) was an international, multicentre, randomised two arm, placebo controlled, double blind Phase III study in patients with chronic heart failure and reduced left ventricular ejection fraction (LVEF). Study participants were titrated from a starting dose of 2.5 mg vericiguat (or matching placebo) to a maximum of 10 mg vericiguat (or matching placebo) daily, based on maintaining a minimum systolic blood pressure. Vericiguat was additional to standard of care treatment.

Adults, aged ≥ 18 years, with a history of chronic heart failure (NYHA Class II to IV);[9] on standard therapy, with LVEF < 45% within 12 months prior to randomisation, who had experienced a 'qualifying decompensation event' were enrolled. The most common qualifying event (> 65% of enrolled patients) was hospitalisation for heart failure within three months prior to randomisation. Other qualifying events included hospitalisation for heart failure within three to six months prior to randomisation (restricted to no more than 20% of the total population) and requirement for intravenous diuretic treatment for heart failure (without hospitalisation) within three months prior to randomisation. In addition, patients had to have documented elevated B-type natriuretic peptide (BNP) or NT-proBNP levels within 30 days prior to randomisation (NT-proBNP ≥ 1000 pg/mL (180 pmol/L); or BNP ≥ 300 pg/mL if in sinus rhythm, NT-proBNP ≥ 1600 pg/mL (189 pmol/L); or BNP ≥ 500 pg/mL if in atrial fibrillation).

Patients with unstable heart failure as defined by any intravenous treatment within 24 hours prior to randomisation, and/or systolic blood pressure < 100 mmHg or symptomatic hypotension, concurrent or anticipated use of long acting nitrates or nitric oxide donors, concurrent or anticipated use of phosphodiesterase type 5 (PDE5) inhibitors, concurrent or anticipated use of an sGC stimulator such as riociguat, allergy or sensitivity to any sGC stimulator, patients awaiting heart transplantation, receiving continuous intravenous infusion of an inotrope, or having/anticipating receiving an implanted ventricular assist device were excluded, as were patients with other severe or uncontrolled concomitant conditions.

The primary endpoint was the time to the first occurrence of the composite outcome of cardiovascular death and hospitalisation with heart failure. Secondary outcomes were the individual components of the composite primary endpoint (time to cardiovascular death, time to hospitalisation for heart failure), time to total heart failure hospitalisations (first and recurrent), time to first occurrence of the composite of all-cause mortality and hospitalisation with heart failure, and all-cause mortality. Sample size was powered for the cardiovascular death component of the composite primary endpoint. A minimum follow-up time of ten months was planned in the event that the cardiovascular death event rate was higher than anticipated. Stratified log rank tests were applied to the intent-to-treat (ITT) population for all primary and secondary endpoints except time to total heart failure hospitalisations.

Cardiovascular death and heart failure hospitalisation were to be tested only if the primary composite endpoint was significant and tested in parallel with multiplicity adjusted solely for the interim analysis. However, no interim analysis was performed as the cardiovascular death event rate was higher than anticipated. The secondary end points were tested using a hierarchical testing approach without adjustment for multiplicity. Sub-group analyses planned a priori included by age (< 65 years versus ≥ 65 years), sex, geographic region, type of index event, eGFR (> 15 to ≤ 30 mL/min/1.73 m^2 versus > 30 mL/min/1.73 m^2), NYHA class, use of sacubitril/valsartan at Baseline, baseline NT-proBNP (by quartiles), baseline LVEF (< 35% versus ≥ 35%), and race.

Overall, 5050 patients (3842 (76%) males and 1208 (24%) females) were randomised (1:1) in the VICTORIA trial of which about 77% completed the study. All patients randomised were included in the efficacy analysis. The discontinuation rate of 23% was accounted for nearly completely by cases of death during the study (alternative reasons cumulatively made up < 1.5% in each treatment arm). Patient demographics (sex, age, representation of regions, race and ethnicity) and important baseline characteristics (for example, NYHA class, qualifying event, renal function, NT-proBNP level, medical disorders in addition to heart failure, and concomitant medication for heart failure and other co-morbidities) appeared to be well balanced between treatment arms. The study participants had a mean age of 67 years who were mostly in NYHA class II;[9] (about 59%) or class III (about 40%). The mean LVEF was about 29%. The mean eGFR at Baseline was about 62 mL/min/1.73 m^2 (about 10% had an eGFR ≤ 30 mL/min/1.73 m^2). The mean (median) baseline NT-proBNP levels were 4803.7 pg/mL (2803.5 pg/mL) in the vericiguat arm, and 4679.6 pg/mL (2821 pg/mL) in the placebo arm. Over 90% of the patients in both arms received a combination of at least two heart failure medications. The proportion of patients treated with a combination of three classes of medicines: mineralocorticoid receptor antagonists; any renin-angiotensin-aldosterone system inhibitor (ACE inhibitor, ARB, ARNI); and beta-blocker was about 60%. The median time from an index event to randomisation was 32 days.

Results

Treatment with vericiguat resulted in a 10% relative risk reduction for the composite endpoint of cardiovascular death and hospitalisation with heart failure compared to treatment with placebo (hazard ratio (HR) (95% confidence interval (CI)) 0.90 (0.82, 0.98), p = 0.019). The result would statistically appear to be driven by the hospitalisation with heart failure component, as time to cardiovascular death was not significantly different between vericiguat and placebo.

Table 4: VICTORIA trial (Study 16493); Absolute risk reduction and number needed to treat

	Vericiguat (N=2526)			Placebo (N=2524)			Treatment Comparison (Placebo-Vericiguat)			
	n	(%)	Annual %†	n	(%)	Annual %†	HR (95% CI)‡	p-Value‖	Annualized Absolute Risk Reduction %‖	Number Needed to Treat¶
Primary Composite Endpoint	897	(35.5)	33.6	972	(38.5)	37.8	0.90 (0.82, 0.98)	0.019	4.18	23.9
CV Death	414	(16.4)	12.9	441	(17.5)	13.9	0.93 (0.81, 1.06)	0.269	1.02	97.9
1st Heart Failure Hospitalization	691	(27.4)	25.9	747	(29.6)	29.1	0.90 (0.81, 1.00)	0.048	3.16	31.6

† Total subjects with an event per 100 subject years at risk.

‡ Hazard ratio (vericiguat over placebo) and confidence interval from Cox proportional hazard model controlling for stratification factors.

‖ From log-rank test stratified by the stratification factors defined by region and race.

‖ Difference (placebo – vericiguat) in annual even rate calculated as the number of subjects with an event per 100 subject years at risk.

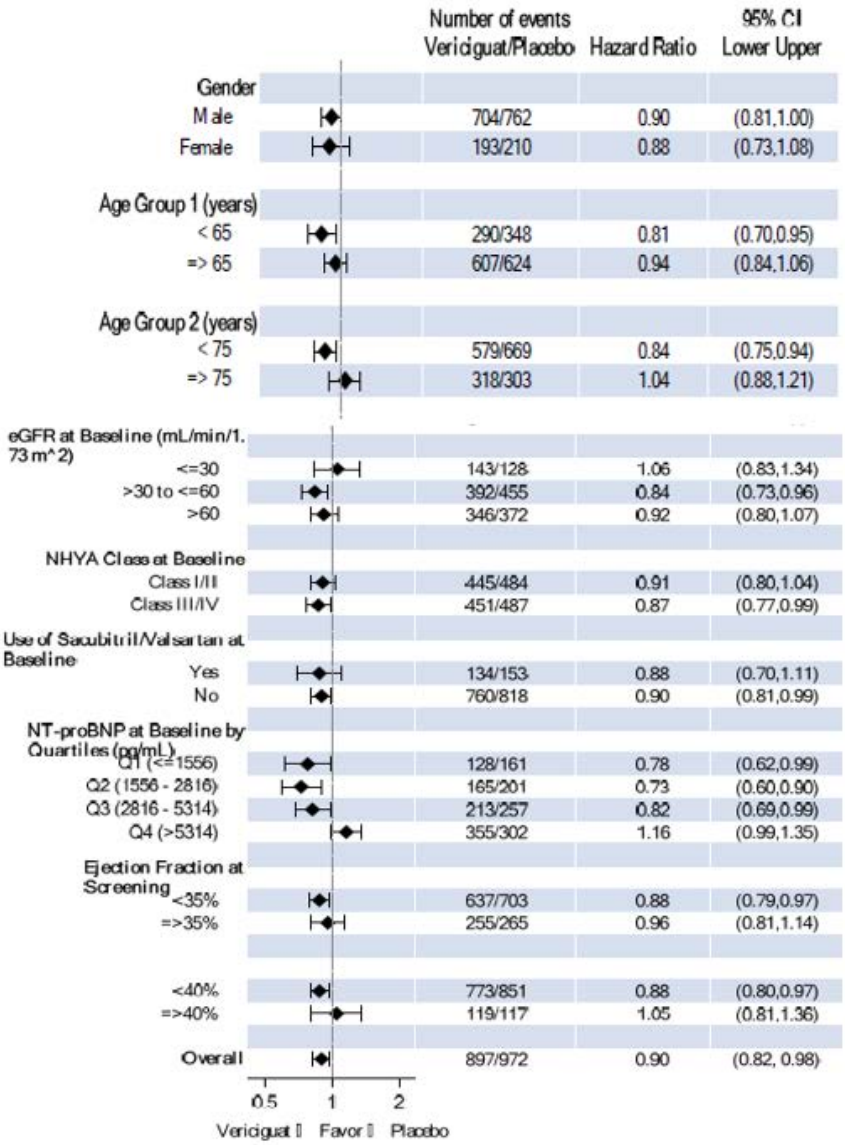
Calculated as 100 divided by the difference in annual event rates (placebo – vericiguat) numbers needed to treat is the number of patients who would need to be trated over an average of one year to prevent one endpoint event.

Based on data up to the primary completion date of 18 June 2019.

Abbreviations: CI = confidence interval; CV = cardiovascular; HR = hazard ratio; N=Number of subjects in ITT population. n=Number of subjects with an event.

The absolute risk reduction (ARR) was 3%. Applying the reported ARR of 4.2 events per 100 patient-years corresponds to a number needed to treat to prevent one additional outcome of 34. The applicant reported that the positive benefit appeared to be maintained up to at least two years post randomisation. Forest plots (both pre-specified and *post hoc*) indicated that the beneficial effects of vericiguat may be influenced by age (younger patients benefited more than older patients) and by NT-proBNP concentrations at randomisation (patients in the quartile with the highest concentration of NT-proBNP may potentially be harmed by vericiguat), see Figure 2.

Figure 2: VICTORIA trial (Study 16493) Forest plot, primary composite endpoint by subgroups



Abbreviations: CI = confidence interval; eGFR = estimated glomerular filtration rate; NHYA = New York Heart Association criteria; Q = quartile.

The secondary endpoints all showed numerical trends to better outcomes with vericiguat, although not all achieved statistical significance (Table 5)

Table 5: VICTORIA trial (Study 16493) Primary and secondary outcomes

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)		
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)

* Data shown are through the primary analysis cut-off date (18 June 2019). For patients with multiple events, only the first event that contributed to the composite outcome is counted. CI denotes confidence interval.

† Hazard ratios (vericiguat as compared with placebo) and confidence intervals were calculated with the use of Cox proportional-hazards models controlling for stratification factors (defined according to geographic region and race).

‡ P values were calculated by means of a stratified log-rank test with stratification factors defined according to geographic region and race.

§ Deaths included in the primary and secondary composite outcomes were not preceded by a hospitalisation for heart failure.

¶ Patients could have been hospitalised more than once.

Source: Armstrong PW, et al. for the VICTORIA study group. Vericiguat in Patients with Heart Failure and Reduced Ejection Fraction. *N Engl J Med* 2020; 382:1883-93.

Questioning the clinical relevance of the small, but statistically significant effect on the primary endpoint (a difference of less than one month between time to first event in vericiguat and placebo treated groups), the sponsor was asked to justify the statement that clinically relevant improvement persisted beyond two years. Additional analyses supported claims that efficacy may persist beyond two years, but that the question of clinical relevance had not been resolved. Comparisons were drawn between the results of VICTORIA trial, compared to the pivotal studies for valsartan/sacubitril (the PARADIGM-HF trial);[20] and dapagliflozin (DAPA-HF trial).[21] The sponsor defended the outcomes of VICTORIA trial, identifying that the baseline risk profile in the enrolled patients in the study, including eGFR, NT-proBNP levels, the presence of atrial fibrillation

[20] McMurray J et al., for the PARADIGM-HF Study group. Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure. *N Engl J Med* 2014; 371:993-1004

[21] McMurray J et al., for the DAPA-HF Study group. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. *N Engl J Med* 2019; 381:1995-2008

and the diagnosis of NYHA Class III to IV,[9] was worse than in either PARADIGM-HF and DAPA-HF trials. Around 14% of patients enrolled in VICTORIA trial were receiving co-treatment with sacubitril/valsartan and there remained a need for new therapies acting via different mechanisms. The sponsor also highlighted that the ARR for the primary outcome measure was similar in DAPA-HF and VICTORIA trials.

Safety

The safety profile of vericiguat is based on the results of the pivotal VICTORIA trial (Study 16493). Supportive safety data was collected in SOCRATES-REDUCED trial (Study 15371) and the Phase I studies. The mean duration of exposure was 375.5 days (maximum of 964 days) to any dose of vericiguat and 362 days (maximum of 935 days) to 10 mg vericiguat. The mean duration of exposure to placebo was 374.7 days (maximum of 966 days).

Treatment-emergent adverse events

The most frequently reported treatment-emergent adverse events (TEAE) with a higher rate in the vericiguat treatment group compared to placebo were hypotension (15.4% versus 14.1%), followed by anaemia (7.6% versus 5.7%), syncope (4% versus 3.5%), nausea (3.8% versus 2.7%), headache (3.4% versus 2.4%), dyspepsia (2.7% versus 1.1%), vomiting (2.2% versus 1.8%), gastroesophageal reflux disease (1.7% versus 0.7%) and iron deficiency anaemia (1.1% versus 0.8%)

Related treatment-emergent adverse events

By System Organ Class (SOC), TEAEs reported to be probably related to the study drug included gastrointestinal disorders (2.5%, including by Preferred Yerm (PT) nausea and dyspepsia), nervous system disorders (2.5%) and vascular disorders (7.2%), but by PT was hypotension (6.8%, compared to 5.9% in the placebo group).

Deaths, serious adverse events, discontinuations

In the VICTORIA trial, all-cause mortality was included as an efficacy outcome, as was cardiovascular death. Based on concordant adjudication by the trial's clinical events committee and clinical investigators, 98 deaths in the vericiguat group and 93 deaths in the placebo group were non-cardiovascular and presumably not related to study medication. One death following acute kidney injury was considered unlikely to be related to study medication.

Serious adverse events (SAE) occurred with similar frequency in vericiguat and placebo treatment groups, the most frequently reported SAE by SOC included infections and infestations (10.7% in both groups, by PT pneumonia was reported by 4% and 4.5% in vericiguat and placebo groups, respectively), cardiac disorders (vericiguat 8.1%, placebo 10.7%, by PT cardiac failure in 3.2% and 4.4% respectively) and renal and urinary disorders (vericiguat 5.6%, placebo 5.3%; acute kidney injury 2.5% and 2%, respectively). A range of safety issues were identified that appeared to be more frequent in the vericiguat group and requested additional information from the sponsor. The sponsor's response that the reported conditions were all likely to occur in the study population and there was no plausible evidence that they were likely to be related to vericiguat was acceped. It was requested that infections, hyperthyroidism and nephropathy should be nominated in the risk management plan (RMP) as potential risks that require post-market monitoring. It is the opinion of the Delegate that routine pharmacovigilance should be sufficient to capture further events of this nature should they occur.

Adverse events of special interest

Symptomatic hypotension with or without syncope was classified as an adverse event of special interest (AESI) based on the mechanism of action of vericiguat. Hypotension

adverse events were reported in 9.1% of subjects treated with vericiguat and 7.9% of subjects treated with placebo and were considered serious in 1.2% of subjects treated with vericiguat and 1.5% of subjects treated with placebo. This did not appear to be related to time since commencing treatment or to the Canadian Cardiovascular Society grading of Angina class, NYHA class or use of angiotensin receptor neprilysin inhibitor (ARNI) at Baseline.

Syncope was also reported more frequently by patients in the vericiguat group (4%) compared with the placebo group (3.5%). The applicant argued that serious events were 'low and similar between the treatment groups', noting that no events resulted in treatment discontinuation.

Hepatic events (including increases or abnormalities in serum transaminases, alkaline phosphatase and bilirubin, acute hepatic failure and other terms encompassing liver injury) were considered AESI. The rates of hepatic events were noted to be low in both vericiguat and placebo treated groups but higher in the vericiguat group (0.9%) than in the placebo group (0.5%). Hepatic events were considered not related to study medication by the clinical investigators, usually considering congestive heart failure decompensation itself as an alternative explanation.

Renal events were also considered AESI. While reports of acute kidney injury were balanced in vericiguat and placebo groups, it was noted that serum creatinine > 1 mg/dL was reported roughly three times more frequently with vericiguat as compared to placebo. Each report was associated with a complex clinical situation. There did not appear to be a significant contribution of low eGFR to the frequency of adverse events.

Anaemia occurred more frequently in patients treated with vericiguat than patients treated with placebo. The mechanism underlying this effect is not known, but has also been reported with another sGC stimulator, riociguat, implying that a class effect may be possible. While anaemia events were usually considered non-serious and manageable, anaemia is known to contribute to the worsening of heart failure. Despite low frequency reports in the study, it is recommended that anaemia should be considered an adverse drug reaction to vericiguat.

In general, the reported adverse event profile in the VICTORIA trial aligns with the proposed vasodilatory effect of vericiguat and does not appear to present significant safety concerns that cannot be adequately managed through the Product Information (PI) and risk management plan (RMP).

Risk management plan

The sponsor has submitted EU-risk management plan (RMP) version 0.1 (27 April 2020; data lock point (DLP) 31 October 2019) and Australia specific annex (ASA) version 1.0 (19 June 2020) in support of this application. At fifth round of evaluation, the sponsor has submitted EU-RMP version 0.4 (dated 21 May 2021; DLP 31 October 2019) and ASA version 1.1 (dated 28 September 2021) in support of this application.

This is second in class and the only other member of this class that is currently approved is riociguat (Adempas), which has been on the ARTG since 2014.[2]

The summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised in Table 6. Further information regarding the TGA's risk management approach can be found in risk management plans for medicines and biologicals and the TGA's risk management approach.

Table 6: Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	None	–	–	–	–
Important potential risks	None	–	–	–	–
Missing information	Use in patients with severe renal impairment (eGFR < 15 mL/min/1.73 m^2)	ü*	–	ü	–
	Use in patients with severe hepatic impairment	ü*		ü	

*Follow-up Questionnaire

The summary of safety concerns is considered satisfactory.

Only routine pharmacovigilance activities, which includes an Australian adverse event follow-up form, have been proposed for this submission. The pharmacovigilance plan is adequate as routine pharmacovigilance should capture any untoward or severe safety issue which may or may not be already known.

Routine risk minimisation only, through the draft PI and Consumer Medicines Information (CMI), has been proposed. This approach is acceptable provided any updates to the safety specification is adequately reflected in updated advice in the PI and CMI.

Wording for conditions of registration

Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.

The suggested wording is:

> *The Verquvo EU-Risk Management Plan (RMP) (version 0.4, dated 21 May 2021, data lock point 31 October 2019), with Australian Specific Annex (version 1.1, dated 28 September 2021), included with submission PM-2020-03566-1-3, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.*

The following wording is recommended for the PSUR requirement:

> *An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).*
>
> *Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of the approval letter.*

The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration.

As Verquvo is a new chemical entity it should be included in the Black Triangle Scheme as a condition of registration. The following wording is recommended for the condition of registration:

Verquvo (vericiguat) is to be included in the Black Triangle Scheme. The PI and CMI for Verquvo must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.

Risk-benefit analysis

Delegate's considerations

Clinical relevance and heterogeneity of clinical effect

The sponsor has provided a well-designed study that supported a small, but statistically significant benefit of vericiguat over placebo, in addition to standard of care therapies, on the primary efficacy outcome of time to death from cardiovascular causes or first hospitalisation for heart failure. The observation appears to be driven by the second component, hospitalisations for heart failure. In absolute terms, applying an analysis of the restricted mean survival time difference for 24 months, this amounted to a delay in the time to first occurrence of the primary endpoint in the vericiguat arm of around 18 days, for the time to cardiac death of around 5 days, and time to first hospitalisations for heart failure of around 15 days, compared to placebo. The clinical importance of the statistical difference is uncertain.

A second point of uncertainty is the apparent heterogeneity of the clinical effect. Older patients did not appear to benefit to the same extent as younger patients, regardless of whether cut-off ages of 65 years or 75 years were applied. Patients with ejection fraction greater than or equal to 40% did not appear to benefit, patients with NYHA category better than III;[9] also experienced no apparent benefit, and patients with very high NT-proBNP at Baseline may actually do worse with the addition of vericiguat to therapy. The sponsor defended the study to the European Medicines Agency (EMA) by applying a patient response identifiers for stratified medicine (PRISM) analysis;[22], examining 64 baseline variables (demographics, vital signs, baseline standard of care, baseline laboratory measurements, medical histories and index events) in a model to identify the co-variates with the strongest interactions with the treatment effect. The sponsor stated that NT-proBNP was identified as the most influential predictor of different treatment response, with serum chloride concentrations a second modifier. NT-proBNP concentrations, which may be associated with poor control of heart failure, are known to be labile and therefore, in spite of the potentially negative association with clinical response, should not be used to distinguish between patients who may benefit from vericiguat and those who may not.

Comparing the VICTORIA trial population with those enrolled in other clinical trials for heart failure medicines (sacubitril/valsartan (Entresto) in PARADIGM trial;[20] and dapagliflozin in DAPA-HF trial);[21] the most obvious difference in the inclusion criteria was

[22] PRISM (Patient Response Identifiers for Stratified Medicine) is a general-purpose subgroup identification approach described by Jemielita and Mehrotra (submitted for publication).

that VICTORIA trial enrolled patients while still under treatment for a qualifying event, and a sizable proportion within the first 30 days following that event. While the *post hoc* PRISM analysis did not identify time after index event to enrolment as a major risk factor on the response to vericiguat, it is worth noting that patients enrolled at times closer to the index event substantially overlapped with patients with higher NT-proBNP at randomisation, and that median baseline NT-proBNP in VICTORIA trial was higher than in the other two studies. The median baseline NT-proBNP levels were 2803.5 pg/mL in the vericiguat arm, and 2821 pg/mL in the placebo arm. The median NT-proBNP level at study enrolment in PARADIGM trial was 1629 pg/mL for Entresto treated patients, and 1593 pg/mL for enalapril treated patients. Median NT-proBNP level at Baseline in DAPA-HF trial was 1428 pg/mL in dapagliflozin treated patients, and 1446 pg/mL in placebo patients. Interestingly, the mean baseline NT-proBNP levels in VICTORIA trial were over 4000 pg/mL, indicating that NT-proBNP levels at Baseline, at least in this study, were not normally distributed, with several individuals contributing very high levels to the calculation.

Finally, the sponsor argues that a greater proportion of patients in VICTORIA trial had NYHA Class III;[9] heart failure than in either of the other studies. In combination, the sponsor argues that the results of VICTORIA trial are not directly comparable to the other studies as patients enrolled in VICTORIA trial were arguably at higher risk of heart failure decompensation. This statement was supported by the higher number of events reported in a shorter time frame in VICTORIA trial than in either of the other two studies, with median time on treatment of 10.8 months, compared to 18 months as anticipated. *Post hoc* analyses supported assessments that patients enrolled early into VICTORIA trial were potentially clinically unstable and required further optimisation of other heart failure therapies and volume status.

Therapeutic indication

The (at best) moderate effect of vericiguat on the primary efficacy outcome, and evidence of heterogeneity of the effect among certain sub-groups, should be weighed against the continuing need for new medications, with different mechanisms of action, for the treatment of patients with chronic heart failure. Various adverse events (for example, hypotension, syncope, and anemia) have been associated with the use of vericiguat, but these events are generally mild to moderate and can be adequately managed with precautions in the Product Information. In addition, there were some other weaknesses with the clinical studies submitted for vericiguat. However, these concerns are not considered sufficient to preclude registration of vericiguat for a restricted population. Among those, limited data in patients with end stage renal failure or severe hepatic impairment, which may be addressed in the Product Information. Limited experience in patients with NYHA Class IV heart failure;[9] is a study weakness applicable to many recent clinical trials. In VICTORIA trial, patients with Class I/II were arguably less responsive to vericiguat than patients with Class III/IV heart failure. Most concerning, the potential for harm in patients with very high NT-proBNP, arguably less clinically stable with regard to heart failure treatment, needs to be mitigated.

The sponsors for dapagliflozin and sacubitril/valsartan have both had limitations applied to therapeutic use in Australia, either by inclusion in the approved indication, or by additional advice in the dosage and method of administration section, as reproduced here:

Dapagliflozin:

> *Forxiga is indicated in adults for the treatment of symptomatic heart failure with reduced ejection fraction, as an adjunct to standard of care therapy (see section 5.1 Pharmacodynamic properties)*

Sacubitril/valsartan:

> *Entresto is indicated in adult patients for the treatment of chronic heart failure (NYHA Class II-IV) with reduced ejection fraction.*
>
> *Entresto is usually administered in conjunction with other heart failure therapies, in place of an ACE inhibitor or other ARB.*
>
> *Entresto should be initiated, and up-titration conducted, by a physician experienced with the treatment of heart failure.*

Notably, both indications are silent on the value ascribed to 'reduced ejection fraction', however in both of these large clinical trials, efficacy was confirmed at all levels of ejection fraction studied. This may be more of an issue for vericiguat, which did not appear to have a significant effect in patients with ejection fraction over 35%. The definition of heart failure with reduced ejection fraction (HFrEF) in Australian guidelines;[6] differs from other international guidelines.

Comparable international regulators have attempted to identify a sub-population within VICTORIA trial for which vericiguat is most likely to be effective. These attempts have included refining the description of the index event and its subsequent treatment in the approved indication. The EMA has included the phrase *'who are stabilised after a recent decompensation event requiring IV therapy'*, in the indication, whereas the sponsor negotiated with SwissMedic to include an additional warning:

'Before starting vericiguat, care should be taken to optimise volume status and diuretic therapy, as well as other guideline-directed heart failure therapies, particularly in patients with very high NT-proBNP levels'.

Proposed action

The VICTORIA trial in patients with HFrEF has demonstrated a statistically significant clinical benefit in a population of patients with heart failure who have experienced an acute decompensation event while on standard of care therapies. The relative risk reduction of 10% was associated with an absolute risk reduction of the primary endpoint 0f 4.2 events per 100 patient-years and primarily driven by the reduction of heart failure hospitalisation events. The hazard ratios (with 95% confidence intervals) for the two components of the primary endpoint were 0.93 (0.81; 1.06) (cardiovascular mortality; p = 0.269) and 0.90 (0.81; 1) (heart failure hospitalisation; p = 0.048). Vericiguat also reduced the total heart failure hospitalisations (first and recurrent events) compared with placebo (hazard ratio (95% CI): 0.91 (0.84 to 0.99); p = 0.023). There are a number of uncertainties with regard to clinical effect in a range of subgroups which need to be addressed. This is most likely best achieved by restrictions imposed in the indication, as have been applied by the EMA and SwissMedic.

Advisory Committee considerations

The Advisory Committee on Medicines (ACM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following.

Specific advice to the Delegate

The ACM advised the following in response to the Delegate's specific request for advice:

1. ***What is the opinion of the Committee with regard to the clinical importance of the statistically significant improvement in the primary endpoint (time to first event of cardiovascular death and hospitalisation for heart failure) and components of less than one month?***

The ACM was of the view that the statistically significant improvement in the primary endpoint is of marginal clinical significance. The ACM commented that there was a modest (10% relative; 4.2% absolute) reduction in the primary composite endpoint of cardiovascular death and heart failure hospitalisation with no reduction in cardiovascular or all-cause deaths at a cost of symptomatic hypotension, a 77% increase in hepatic abnormalities, and a slight increase in mild anaemia. Furthermore, the ACM noted that the quality of life data was not significant.

However, on balance, the ACM advised that the application was approvable due to the generally acceptable safety profile and the statistically significant improvement in heart failure hospitalisation. The ACM was of the view that Verquvo is unlikely to be widely adopted in Australia given the wide range of heart failure medicines currently available and the level of evidence accorded in the recent ESC guidelines.[23]

To ensure that Verquvo is only used in the most appropriate circumstances, the ACM advised that prescription (initiation of therapy) should be limited to cardiologists.

2. Given the different classifications of heart failure with reduced ejection fraction (HFrEF) in Australia and internationally, how might a restriction to treatment of patients with HFrEF < 40% be presented in the Australian Product Information?

The ACM advised that, based on the trial data, an ejection fraction of less than 40%, or less than 45% would be acceptable. The ACM noted that the error margins were quite large for the ≥ 40% ejection fraction subgroup analysis and on balance, they advised that it would be preferable to specify '< 45%' as this would align with the trial protocol and with other regulators.

3. What is the opinion of the Committee on commencing treatment with vericiguat on patients with very high NT-proBNP levels?

The ACM advised that, while patients with high NT proBNP levels should not be excluded from using Verquvo, a statement similar to the following should be added to the PI to highlight that patients with high NT proBNP levels are at high risk for deterioration and death:

'*in patients with the highest quartile of nt-pro BNP in the study (> 5314 pg/mL) patients receiving placebo did better than those given vericiguat. This nt-pro BNP level identifies patients with HFrEF at the highest risk for poor outcomes, including death. The trial did not demonstrate benefit of vericiguat in this subgroup of the cohort (pre-specified analysis)*'.

4. What is the opinion of the Committee regarding limiting the indication for vericiguat to use:

a. in combination with other registered heart failure medications/standard of care?

The ACM agreed that it was important for Verquvo to be used in combination with other registered heart failure medications/standard of care, as this aligns with the trial data.

b. in patients who are stabilised after a recent decompensation event requiring intravenous therapy?

The ACM advised that, in line with the trial criteria, the indication should be restricted to patients who are stabilised after a recent decompensation event requiring intravenous (IV) diuretic therapy, emphasising that 'diuretic' should be specified as general IV therapy is too broad.

[23] Visseren FLJ, Mach F, Smulders YM, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J. 2021;42(34):3227-3337. Available at: https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/Acute-and-Chronic-Heart-Failure

c. in patients with NYHA Class III heart failure?

The ACM noted that the trial included NYHA Class I to IV heart failure patients, with a large portion being Class III. The ACM was of the view that the indication does not need to be restricted to NHYA Class III heart failure patients, allowing prescribing cardiologists to use their clinical judgement. The ACM reiterated the importance of restricting initiation of prescribing to cardiologists.

5. Other advice

The ACM recommended the following modified indication wording to improve clarity:

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

The ACM advised the following changes (additions shown in bold) to wording in the Consumer Medicines Information (CMI) would improve clarity:

- 'Do not take Verquvo if you are taking riociguat **(for high pressures in the lung)**, or medicine for erectile dysfunction.'
- 'It is not known whether it passes into **human** breast milk and may harm your baby.' The ACM noted that the nonclinical studies show that vericiguat passes into animal milk.

The ACM advised the following change to wording in the Product Information (PI) would improve clarity:

- 'Decompensation event requiring IVT' should be changed to 'decompensation requiring IV diuretic therapy' to make it clear that those on IV inotropic therapy are not included, as they were excluded from the clinical trial.

Conclusion

The ACM considered this product to have an overall positive benefit-risk profile for the indication

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

Outcome

Based on a review of quality, safety, and efficacy, the TGA approved the registration of Verquvo (vericiguat) 2.5 mg, 5 mg, and 10 mg, film coated tablets, blister pack, indicated for:

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

Specific conditions of registration applying to these goods

- Verquvo (vericiguat) is to be included in the Black Triangle Scheme. The PI and CMI for Verquvo must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.
- The Verquvo EU-Risk Management Plan (RMP) (version 0.4, dated 21 May 2021, data lock point 31 October 2019), with Australian specific annex (version 1.1, dated 28 September 2021), included with submission PM-2020-03566-1-3, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

  An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs). Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of the approval letter.

  The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration.

Attachment 1. Product Information

The PI for Verquvo approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA PI/CMI search facility.

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
https://www.tga.gov.au