Taiwan Food and Drug Administration

Assessment Report

Trade Name： Verquvo 2.5/5/10 mg film-coated tablets

Active Ingredient：Vericiguat

License Number： MOHW-PI 028107, 028108, 028109

Applicant：台灣拜耳股份有限公司

Approval Date： 2021/7/5

Indication：

For the treatment of symptomatic chronic heart failure in adult patients with ejection fraction less than 45% who are stabilized after a worsening heart failure event which is a hospitalization for heart failure or need for outpatient IV diuretics.

Background Information

Trade Name	Verquvo 2.5, 5, 10 mg film-coated tablets
Active Ingredient(s)	Vericiguat
Applicant	台灣拜耳股份有限公司
Dosage Form & Strengths	Film-coated tablets 2.5, 5, 10 mg
Indication	適用於心衰竭惡化事件後病情穩定且射出分率小於 45%之症狀性慢性心衰竭成年病

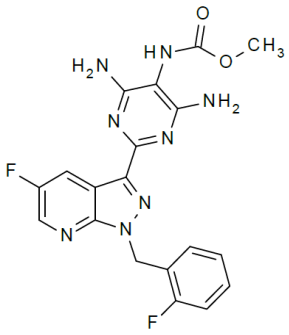
	人。心衰竭惡化事件係指需住院或門診靜脈利尿劑治療。 For the treatment of symptomatic chronic heart failure in adult patients with ejection fraction less than 45% who are stabilized after a worsening heart failure event which is a hospitalization for heart failure or need for outpatient IV diuretics.
Posology	建議 Verquvo 起始劑量為每日一次 2.5 毫克。約每 2 週加倍劑量，在病人可耐受的情形下達到每日一次 10 毫克的目標維持劑量。 The recommended starting dose of VERQUVO is 2.5 mg orally once daily. 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.
Pharmacological Category **ATC Code**	C01DX22

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug substance

The drug substance, vericiguat, is chemically designated as methyl {4,6-diamino-2-[5-fluoro-1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]pyrimidin-5-yl}carbamate and has the following structure:



It is a white to yellowish powder. The molecular formula and the molecular weight are $C_{19}H_{16}F_2N_8O_2$ and 426.39 g/mol, respectively.

Adequate information of characterization of the drug substance has been provided. The

structure of vericiguat is confirmed by UV/VIS spectrum, IR spectrum, Raman spectrum, nuclear magnetic resonance (NMR) spectroscopy, mass spectrometry and elemental analysis. The specification for the drug substance includes tests for appearance, identity, impurities, water content, particle size and assay.

2.1.2 Drug product

The drug product is supplied for oral use as film-coated tablets containing 2.5 mg of vericiguat, 5 mg of vericiguat or 10 mg of vericiguat. The excipients used in the drug product comply with compendial monographs or in-house.

The specification for the drug product includes appearance, identity, assay, degradation products, dissolution, uniformity of dosage units and microbial purity. Analytical methods are described well and validated.

Stability studies of drug product under long term condition (25°C/60% RH and 30°C/75% RH) and accelerated condition (40°C/75% RH) have been carried out.

2.2 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

In in vitro pharmacological studies, vericiguat potently stimulated sGC, leading to increased cGMP production, which was shown with isolated recombinant sGC, sGC applying luminometric GTP consumption, a sGC-overexpressing cell line, and vascular endothelial cells assays. Vericiguat inhibited the phenylephrine and U46619-induced pre-constricted contractions of isolated vessels in rabbit, canine, or porcine concentration-dependently. In the isolated rat heart Langendorff preparation, vericiguat reduced the coronary perfusion pressure and did not affect HR, LVDP, and +dp/dt. In nitrate tolerance assay, vericiguat potently inhibited phenylephrine-induced contractions in normal and nitrate-tolerant saphenous artery rings.

In in vivo studies, vericiguat produced a dose-dependent and long-lasting decrease in blood pressure with a reflex increase in heart rate in normotensive rats and spontaneously hypertensive rats. Besides, in the renin transgenic rat model, vericiguat reduced the relative heart weights, urinary protein excretion, and mortality. In anesthetized dogs with or without hypoxic conditions, vericiguat caused a dose-dependent decrease in mean aortic blood pressure, a long-lasting decrease in pulmonary artery pressure, and a dose-dependent increase in cardiac output, coronary blood flow, and oxygen saturation in the coronary sinus, indicating a positive shift in the myocardial oxygen balance. In a rapid pacing-induced heart failure and pulmonary hypertension model, vericiguat exerted a pronounced pressure-lowering effect on the pulmonary artery side with a balanced reduction of afterload.

2.2.2 Toxicological Studies

In a mouse repeated-dose toxicity study, gastrointestinal motility disturbance due to smooth muscle cell relaxation was observed. Secondary to vasodilation and hemodynamic effects, a non-adverse increase in water intake and associated decrease in serum creatinine and urea as well as slight hemodilution were observed. In rat studies, the toxicity profile was characterized by hemodynamic and gastrointestinal effects and sequelae thereof and changes in bone metabolism and morphology in adolescent rats. All effects were shown to be at least partially reversible in a 4-week study with 2-week recovery. No histopathologic findings in bones or changes in bone biomarkers were seen in full-grown rats and dogs. In dog studies, the toxicity profile was characterized by gastrointestinal and hemodynamic effects, similar to that observed in mice and rats.

In the rat fertility and early embryonic development study, there was no indication of an effect of vericiguat up to the highest dose. In the rat embryo-fetal developmental toxicity study, maternal toxicity secondary to the hemodynamic effects and gastrointestinal effects of vericiguat was observed. Up to the highest toxic dose, no meaningful effects on embryo-fetal development were observed. In rabbits, vericiguat increased the abortion rate in late gestation and increased post-implantation loss at clearly maternally toxic dose levels. An increased incidence of cardiac ventricular septal defect along with truncus arteriosus communis was observed.

In the pre- and postnatal development study, effects on rat body weight and food consumption were observed at all doses. Increased incidences of stillbirths and pup mortality were noted, resulting in lower pup viability indices at the highest dose. Delayed sexual maturation was also visible in the F1 generation. Juvenile rats were indirectly exposed to vericiguat during lactation. Repeated exposure of vericiguat to juvenile rats caused severe intestinal inflammation with necrotizing enteritis at the highest dose.

Vericiguat was negative for genotoxicity and considered no carcinogenic risk. No potential antigenicity, immunotoxicity, and phototoxicity were observed.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

Vericiguat was a poorly soluble, highly permeable drug and classified as BCS Class 2. It was rapidly absorbed with T_{max} of 1-1.5 hr and increased in a slightly less than dose-proportional manner. Given once daily, accumulation of vericiguat was approximately 155% to 171% in healthy subjects under fasted condition.

The absolute bioavailability is 93% when taken with food. Administration of vericiguat with a high fat, high calorie meal prolonged T_{max} to about 4 hours and increased C_{max} and AUC by 40% and 44%, respectively. The bioavailability of vericiguat with respect to AUC and C_{max} was comparable when given as 10 mg intact IR tablet or crushed tablet.

Vericiguat is highly bound to plasma proteins (97.8%). The mean steady-state volume of distribution of vericiguat is approximately 44 L. Vericiguat primarily undergoes glucuronidation by UGT1A9 and to a lesser extent, by UGT1A1 to form an inactive N-glucuronide metabolite. CYP-mediated metabolism is a minor clearance pathway. Following oral administration of radiolabeled vericiguat, 53% and 45% of the dose were excreted in urine and feces, respectively.

In general, the vericiguat PK is generally consistent between healthy subjects and HFrEF patients.

2.3.2 Interaction Studies

Vericiguat and its N-glucuronide M-1 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. Though vericiguat is a substrate of P-gp and BCRP, the impact is limited for the high oral bioavailability (93%). Vericiguat is not a substrate of OCT1, OATP1B1, OATP1B3.

It is contraindicated in patients with concomitant use of other soluble guanylate cyclase (sGC) stimulators. Concomitant use with PDE5 inhibitor hasn't been studies in HFrEF patients and is therefore not recommended due to potential risk of symptomatic hypotension.

2.3.3 Special Populations

The effect of age, gender, body weight, and baseline NT proBNP on PK was not considered clinically relevant and not required dose adjustment.

No dose adjustment of vericiguat is required in patients with mild or moderate hepatic impairment. It is not recommended to use in patients with severe hepatic impairment due to insufficient information in clinical. For renal impairment, there is no dose adjustment for HFrEF patients with eGFR $\geqq$ 15 mL/min/1.73m^2. But it is not recommended to use vericiguat in patients with eGFR<15 mL/min/1.73m^2 or on dialysis.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

One phase III study VICTORIA was evaluated for the efficacy of vericiguat for the treatment of symptomatic chronic heart failure in adult patients with ejection fraction less than 45% who

had a previous worsening heart failure event. Treatment with vericiguat resulted in a 10% relative hazard reduction in the first event of clinical events committee (CEC) confirmed cardiovascular death or heart failure hospitalization compared with placebo (HR 0.90 [95% CI, 0.82-0.98]; p=0.019).

Vericiguat was also superior to placebo in the secondary endpoints of total events (first and recurrent) of CEC confirmed heart failure hospitalization (HR 0.91 [95% CI, 0.84-0.99]; p=0.023) and all-cause mortality or heart failure hospitalization (HR 0.90 [95% CI, 0.83-0.98]; p=0.021).

2.4.2 Safety Results

Main TEAEs include anemia, dyspepsia, hypotension, nausea, headache and dizziness. Hypotension would be of most concern. The proportion of subjects who did not reach the 10 mg dose of vericiguat or did not stay at 10 mg for > 80% of the study period was 38.4% (968/2519), indicating the impact of BP reduction on maintenance of target dose 10 mg.

2.5 Bridging Study Evaluation

In population PK analysis, body weight was identified as the only intrinsic factor with significant effect on both CL and VL. As compared to patients with heart failure (HF) and weighted 60-90 kg, AUC_{ss} was ↑27% in HF patients weighting <60 kg.

Overall, vericiguat exposure in Asian healthy subjects was about 50~80% higher, especially with respect to C_{max}, when compared to White subjects. Evaluation of PK in Asian patients with heart failure using PopPK analysis indicated a slightly higher exposure at steady state of approximately 20%. Half-life was comparable between Asian patients and all other patients.

Pharmacokinetic information is only available from 58 Taiwanese patients (2450 patients included in the evaluation worldwide). The PK profiile in this limited Taiwanese dataset, such as AUC, C_{max}, C_{trough} and $t_{1/2}$, were slightly different than that in the global population.

The ethnic difference caused by the body weight effect was within the observed pharmacokinetic inter-subject variability, 33%. Therefore, the ethnic sensitivity was not concerned from PK perspective.

There were a total of 865 East Asian subjects, out of overall 5050 subjects, enrolled to the pivotal VICTORIA trial. The trend of efficacy of East Asians was consistent with overall population, the safety profile was similar between East Asian and overall population. Higher incidence of hypotension (27.3% vs. 15.4%) was found in 102 Taiwan subjects.

2.6 Conclusion

The benefit/risk ratio of vericiguat was marginally positive but considered to be clinically meaningful. The approval of Verquvo was recommended. The indication should be revised, in line with the target population of VICTORIA, as following.

「For the treatment of symptomatic chronic heart failure in adult patients with ejection fraction less than 45% who are stabilized after a worsening heart failure event which is a hospitalization for heart failure or need for outpatient IV diuretics.」

Efficacy was diminished in patients with eGFR < 30 mL/1.73 m2 or with high serum NT-proBNP (> 5300 pg/mL), this information should be well described in label.

3. Post-Marketing Requirements

The Applicant will provide data from post-marketing-research (PMR) that collects prospective and retrospective data in women exposed to vericiguat during pregnancy to assess risk to the pregnancy and maternal complications, adverse effects on the developing fetus and neonate, and adverse effects on the infant.