Public Assessment Report
VERQUVO

INFORMASI PRODUK

Nama obat	:	VERQUVO
Bentuk sediaan	:	Tablet salut selaput
Zat aktif	:	Vericiguat 2,5 mg, 5 mg & 10 mg
Kemasan	:	Dus, 1 blister @ 14 tablet salut selaput Dus, 2 blister @ 14 tablet salut selaput
Pendaftar	:	PT. Bayer Indonesia
Produsen	:	Bayer AG, Leverkusen, Jerman
Kategori Registrasi	:	Registrasi obat baru dengan Zat aktif baru
Indikasi yang diajukan:	:	*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).*
Posologi yang diajukan	:	*Adults:* - *The recommended starting dose of VERQUVO is 2,5 mg once daily, taken with food* - *Double the dose of VERQUVO approximately every 2 weeks to reach maintenance dose of 10 mg once daily, as tolerated by the patient* - *For patient who are unable to swallow whole tablets, VERQUVO may be crushed and mixed with water immediately before administration* - *Verquvo is administered in conjunction with other HF therapies*

PENGANTAR

Verquvo merupakan obat dengan zat aktif baru vericiguat merupakan obat yang masuk ke dalam kelas senyawa baru, yaitu *the soluble guanylate cyclase (sGC) stimulator* yang digunakan untuk mengobati *chronic heart failure with reduce ejection*. *Heart failure* berhubungan dengan kerusakan sintesis nitric oxide (NO) dan penurunan aktivitas pada resetornya *Soluble guanylyl cyclase (sGC)*. Defisiensi *sGC-derived cyclic guanosine monophosphate (cGMP)* berkontribusi terhadap disfungsi miokard dan pembuluh darah. Vericiguat bekerja dalam mengembalikan defisiensi relatif pada sinyal NO-sGC-cGMP dengan secara langsung menstimulasi sGC, secara independen dan sinergis dengan NO, untuk meningkatkan kadar cGMP intraseluler, yang dapat meningkatkan fungsi miokard dan pembuluh darah.

Mengingat vericiguat merupakan zat aktif baru, saat ini evaluasi difokuskan pada data uji non klinik, klinik, dan mutu obat untuk pembuktian efikasi, keamanan, dan mutu obat lebih lanjut.

ASPEK MUTU

Verquvo (vericiguat) tersedia dalam bentuk tablet salut selaput, mengandung vericiguat 2,5 mg, 5 mg, dan 10 mg. Obat jadi terbagi menjadi dua bagian, yaitu bagian tablet inti yang mengandung eksipien *microcrystalline cellulose, croscarmellose sodium, hypromellose, lactose monohydrate, magnesium stearate, serta sodium laurilsulfate*, dan bagian salut selaput yang mengandung iron oxide red (5 mg tablet), iron oxide yellow (10 mg), hypromellose, talc dan titanium dioxide. Obat jadi dikemas dalam PVC/PVDC/Aluminium foil blisters transparan.

Zat Aktif

Zat aktif vericiguat merupakan serbuk putih hingga putih kekuningan dan telah dilakukan karakterisasi, diantaranya pemerian, kelarutan, pH larutan, pKa, koefisien partisi, higroskopisitas, densitas, *Polymorphism, Pseudo-polymorphism* dan *melting Points*. Berdasarkan hasil karakterisasi tersebut diketahui bahwa veriguat merupakan serbuk putih hingga putih kekuningan, praktis tidak larut pada aird dan sangat tidak laut pada ethanol, tidak bersifat higroskopis, vericiguat muncul dalam 5 modifikasi, dan Modifikasi I merupakan bentuk yang digunakan.

Struktur kimia vericiguat telah ditunjukkan berdasarkan uji *by elemental analysis, IR spectroscopy, NMR spectroscopy, mass spectrometry* dan *UV/Vis spectroscopy*.

Spesifikasi zat aktif telah ditetapkan terdiri dari *pemerian (visual), identification (IR, HPLC), particle size, palladium, water, residual solvent (ethanol, isopropyl acetate, benzene, toluene, dimethysulfoxide/ GC) unspecified impurity, sum of all impurity (HPLC), assay (HPLC).*

Metode analisis yang digunakan dalam pengujian zat aktif merupakan metode non kompendial yang tervalidasi.

Uji stabilitas zat aktif telah dilakukan dan menunjukkan obat stabil ketika disimpan pada suhu 25°C dan 30°Cselama 24 bulan. Uji stabilitas stress test (*thermal stress, hydrolytic stress, dan oxidative stress*) teramati munculnya impurities dan degradasi produk. Uji photostability dalam bentuk solid substances dan solution menunjukkan bahwa dalam bentuk solid substances tidak ada degradasi dan vericiguat dalam bentuk solid teramati stabil terhadap cahaya, sedangkan dalam bentuk larutan termatai muncul degradasi dua senyawa unknown sehingga vericiguat dalam bentuk larutan teramati sensitif terhadap cahaya.

Obat jadi

Obat jadi diproduksi dalam bentuk tablet salut selaput berbentuk bulat , biconvex, berwarna putih diameter 7 mm dengan marking “2,5” dan “VC” pada masing-masing sisi (2,5 mg), berwarna coklat-merah diameter 7 mm dengan marking “5” dan “VC” pada masing-masing sisi (5 mg), dan berwarna kuning-orange diameter 9 mm dengan marking “10” dan “VC” pada masing-masing sisi (10 mg).

Proses pembuatannya dilakukan dengan granulasi basah, dan juga dilakukan identifikasi terhadap tahapan kritikal, dilakukan pada tahap granulasi, penyalutan dan pengemasan, sedangkan *in-process controls* dilakukan pada tahap pengeringan (*loss on drying*) dan tahap kompresi (*uniformity of mass; resistance to crushing, Friability and Disintegration*) saja. Validasi proses telah dilakukan terhadap 3 bets skala produksi untuk masing-masing kekuatan. Hasil validasi proses menunjukan kemampuan proses menghasilkan obat jadi yang memenuhi kriteria penerimaan yang ditetapkan.

Spesifikasi obat telah ditetapkan yaitu pemerian (visual), identifikasi (HPLC, UV spectrum), keseragaman kandungan (HPLC), disolusi, produk degradasi (HPLC), Assay (HPLC), *dan mirobial purity*Parameter dalam spesifikasi dipilih berdasarkan karakterisitik fisikokima dan sifat kritikal zat aktif, serta *guideline* yang berlaku dengan mempertimbangkan antara lain hasil uji bets yang digunakan dalam uji klinik, data stabilitas jangka panjang. Metode analisa yang digunakan telah divalidasi. Hasil analisa bets memberikan hasil yang memenuhi spesifikasi yang dipersyaratkan.

Data stabilitas dari 3 bets obat skala produksi telah dilakukan pada zona IVB, yaitu pada suhu 30°C/75% RH selama 24 bulan dan suhu 40°C/75% RH selama 6 bulan dengan hasil yang memenuhi spesifikasi yang dipersyaratkan. Pada uji thermal dan hidrolisis pada suhu 80°C teramati adanya peningkatan degradan Fluorodihydropurinone, sedangkan hasil uji photostability menunjukan hasil memenuhi spesifikasi (tidak ada peningkatan *impurity*).

Kesimpulan
Dari aspek mutu, Verquvo tablet salut selaput dapat dipertimbangkan untuk diterima.

ASPEK KHASIAT DAN KEAMANAN

Studi Non Klinik
Farmakologi
- Vericiguat menunjukan pengaruh dosis terhadap penurunan tekanan darah jangka panjang, peningkatan detak jantung, cardiac output (CO),), coronary blood flow (CBF), and oxygen saturation in the coronary sinus (SVO2) pada tikus dan anjing dibius.
- Uji in vitro pada sGC rekombinan terisolasi, garis sel berlebih sGC dan sel endotel vaskular, vericiguat menstimulasi sGC pada konsentrasi dari 0,01 hingga 100 µM. Vericiguat menstimulasi sGC tanpa nitric oxide (NO) tetapi memiliki efek sinergis ketika NO ditambahkan.

Farmakokinetik
- Vericiguat sangat permeabel pada sel Caco-2. Setelah pemberian vericiguat oral yang diformulasikan dalam etanol:polietilen glikol 400 (PEG400):air (10:60:30; v:v:v) diberikan pada tikus dan anjing, penyerapannya cukup cepat, dengan Tmax berkisar antara 0,5 – 3 jam. Bioavailabilitas oral vericiguat pada tikus dan anjing adalah ~40-50% dan ~70%.
- Pengikatan protein plasma vericiguat dan metabolit M-1 (N-glukuronida vericiguat) bergantung pada spesies. Nilai persentase *unbound plasma* pada mencit, tikus, anjing dan manusia adalah 7,99%, 4,55%, 10,2%, 2,18%, untuk vericiguat, dan 15,2%, 3,13%, 15,2%, 1,63%, untuk M-1.Volume distribusi vericiguat padatikus dan anjing adalah 0,8 - 1,1 L/kg.
- Setelah pemberian per-oral vericiguat [14C], senyawa induk merupakan komponen dominan dalam plasma tikus, mencit, dan anjing (>97% dari total AUC), dengan metabolit M-1 sebagai komponen kecil yang bersirkulasi. Sebaliknya, metabolit M-1 merupakan komponen utama dalam plasma manusia, menyumbang 72% dari total radioaktivitas AUC, dibandingkan dengan 27% senyawa induknya. M-1 tidak aktif secara farmakologis terhadap sGC dan tidak memiliki aktivitas di luar target.
- Vericiguat menunjukkan *plasma clearance* yang rendah (0,15 – 0,21 L/jam/kg), dan waktu paruh terminal 3 – 5 jam pada tikus dan anjing. Setelah pemberian PO vericiguat [14C] pada tikus dan anjing, obat diekskresikan melalui jalur feses/bilier pada tikus dan anjing (tikus: 81,2%; anjing: 89,2% dari dosis). Ekskresi yang seimbang diamati pada manusia (urin: 53,1%, feses: 45,2% dari dosis). Vericiguat diekskresikan ke dalam susu tikus menyusui.

Toksisitas
- Tidak ada toksisitas akut yang teramati pada studi pivotal pengulang dosis toksistas oral pada tikus hingga 60 mg/kg/hari dan anjing hingga 25 mg/kg/hari (sekitar 75 atau 12 kali paparan pada manusia (unbound AUC)

pada dosis rekomendasi maksimum pada manusia 10 mg/hari).

- Toksistitas oral berulang dilakukan pada tikus dan Anjing hingga 26 dan 39 minggu dengan NOAEL adalah 30 mg/kg/hari (± 50 kali paparan manusia) dan 5 mg/kg/hari (±8 kali paparan manusia).
- Karsinogenisitas dinilai dalam studi 2 tahun yang dilakukan pada tikus CD1 dan tikus Wistar. Vericiguat tidak menunjukkan efek karsinogenik pada tikus yang diberi dosis hingga 150 mg/kg/hari (jantan) atau hingga 250 mg/kg/hari (betina). Dosis ini dikaitkan dengan paparan 149 (laki-laki) atau 286 (perempuan) kali paparan manusia (AUC tidak terikat) pada MRHD 10 mg/hari. Dalam studi karsinogenisitas pada tikus, tidak ada temuan tumor atau hiperplastik terkait vericiguat yang terlihat hingga paparan 12 kali lipat paparan manusia pada MRHD. Peningkatan numerik non-statistik dari *pheochromocytomas* jinak dan tumor sel Leydig serta hiperplasia masing-masing diamati pada pria setelah pemberian dosis tinggi 20 mg/kg/hari yang menyebabkan paparan 41 kali lipat paparan manusia pada MRHD yang dianggap sebagai tidak relevan untuk pasien. Data non-klinis menunjukkan tidak ada risiko karsinogenik pada manusia pada dosis klinis.
- Vericiguat tidak bersifat genotoksik dalam uji mutagenisitas mikroba in vitro (Ames), uji limfoma tikus in vitro, dan uji mikronukleus tikus dan tikus in vivo.
- Dalam studi dosis berulang pada fertilitas dan perkembangan embrio awal selama 4 minggu pada tikus jantan dan betina, vericiguat tidak berpengaruh pada kesuburan atau kinerja reproduksi hingga dosis tertinggi 50 mg/kg/hari (66 kali paparan manusia pada MRHD 10 mg/hari, AUC tidak terikat).

Studi Klinik

Data yang diserahkan untuk mendukung indikasi yang diajukan terdiri dari 1 studi klinik fase II dan 1 studi klinik fase III.

1. SOCRATES REDUCED (Phase II)
   Hasil studi klinik fase II *dose-ranging* (SOCRATES REDUCED) yang membandingkan 5 kelompok *treatment* vericiguat 1.25 mg (n=91) vs vericiguat 2.5 mg (n=90) vs vericiguat 2.5-5 mg (n=91) vs vericiguat 2.5-10 mg (n=91) dan placebo (n=92) pada pasien dengan *worsening heart failure and reduced ejection fraction* (HFrEF) selama 12 minggu, menunjukkan:
   a. Tidak terdapat perbedaan yang signifikan pada *geometric mean ratio* (GMR) dari *baseline* pada *N-terminal pro-brain natriuretic peptide* (NT-proBNP) pada minggu ke-12 antara nilai *pool* 3 dosis tertinggi vericiguat (2.5 mg, 2.5-5 mg, dan 2.5-10 mg) dengan kelompok plasebo (GMR 0.885 [95% CI, 0.73-1.08]; p=0.1506).
   b. Hasil *dose ranging study* ini menunjukkan dosis Vericiguat 2.5-10 mg menurunkan NTproBNP yang terbaik dibanding plasebo pada minggu ke-12 (GMR 0.779 [90% CI, 0.61-1.00]; p=0.0483).
2. Studi VICTORIA (Fase III)
   a. Studi ini membandingkan 2 kelompok treatment vericiguat 2.5-10 mg (n=2515 completed follow-up for the primary endpoint) vs placebo (n=2511 completed follow-up for the primary endpoint) pada pasien HFrEF selama 3 tahun.
   b. Kriteria inklusi Studi VICTORIA antara lain memiliki riwayat HF kronis (NYHA kelas II sampai IV) pada terapi standar sebelum memenuhi syarat dekompensasi HF, dan memiliki riwayat rawat inap HF sebelumnya dalam waktu 6 bulan sebelum randomisasi atau pengobatan diuretik IV untuk HF (tanpa rawat inap) dalam waktu 3 bulan sebelum randomisasi.
   c. *Standard of care HF medications* yang digunakan pada *baseline* antara lain terapi individu *beta-blocker* (93.1%), *renin-angiotensin system inhibitor* (87.4%), *mineralocorticoid receptor antagonist* (70.3%), *sacubitril/valsartan* (14.5%), dan terapi kombinasi dari 2 atau 3 *standard of care HF medications*.
   d. Pada hasil efikasi primer, vericiguat menunjukkan 10% *relative hazard reduction* pada *first event confirmed cardiovascular (CV) death* atau *HF hospitalization* dibanding plasebo (HR 0.90 [95% CI, 0.82-0.98]; p=0.019).
   e. Untuk parameter efikasi sekunder vericiguat menunjukkan *relative hazard reduction* dari setiap parameter yang dievaluasi sebagai berikut:
      - *First HF hospitalization* (HR 0.90 [95% CI, 0.81-1.00]; p=0.048) *CV death* (HR 0.93 [95% CI, 0.81-1.06]; p=0.269)
      - *Total HF hospitalizations (first and recurrent)* (HR 0.91 [95% CI, 0.84-0.99];p=0.023)
      - *Composite of all-cause mortality or HF hospitalization* (HR 0.90 [95% CI, 0.83-0.98]; p=0.021)
      - *All-cause mortality* (HR 0.95 [95% CI, 0.84-1.07]; p=0.377).
   f. Analisis *Number Needed to Treat* (NNT) vericiguat menunjukkan nilai NNT untuk *primary composite end point* sebesar 23,98; untuk *CV death* sebesar 97,9; dan untuk *1st heart failure hospitalization* sebesar 31,6.
3. Data keamanan menunjukkan *primary drug related adverse event* vericiguat adalah simptomatik hipotensi (4.3% vericiguat vs 3.7% plasebo), *syncope* (0.3% vericiguat vs 0.4% placebo) dan *gastrointestinal disorders* (2,5% vs 1,4% placebo).
4. Berdasarkan hasil evaluasi studi non klinik dan klinik di atas disimpulkan bahwa obat diterima dengan perbaikan indikasi sebagai berikut:

   Verquvo is indicated for the treatment of symptomatic chronic heart failure in adult patients with reduced ejection fraction less than 45% who are stabilised after a recent decompensation event requiring IV therapy and have recently been hospitalized and stabilized with IV diuretic therapy or patients at high risk despite

guideline-based medical therapy, including angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARB), betablockers, mineralocorticoid receptor antagonists (MRA), and a combination of an angiotensin receptor and neprilysin inhibitor (ARNI).

Pendaftar mengajukan revisi indikasi dengan didukung studi fase III VICTORIA disertai justifikasi dan hasil evaluasi nya sebagai berikut:

1. Salah satu kriteria inklusi pasien sebagai data penunjang yaitu "*Have a previous HF hospitalization within 6 months prior to randomization or IV diuretic treatment for HF (without hospitalization) within 3 months prior to randomization*". Sesuai Pedoman AHA/ACC/HFSA (American College of Cardiology/American Heart Association/Heart Failure Society of America) Guideline for the Management of Heart Failure dan implementasi secara klinis, untuk pasien gagal *jantung yang dirawat di rumah sakit, umumnya diberikan diuretik sebagai decongestion strategy.*
2. Hasil studi diketahui bahwa terdapat lebih dari 70% pasien yang dirawat di RS dan sekitar 15% pasien yang tidak dirawat di RS.
    a. Hasil studi untuk seluruh populasi menunjukkan bahwa vericiguat memberikan efikasi yang lebih baik dibanding plasebo dalam menurunkan risiko first event confirmed cardiovascular (CV) death atau HF hospitalization, dengan nilai hazard ratio (HR) 0,90 [95% CI, 0,82-0,98]; p=0,019.
    b. Sedangkan hasil analisis subgroup pada kelompok pasien yang mendapat terapi diuretik tanpa dirawat di RS (n=399/2526), vericiguat menunjukkan hasil yang tidak berbeda bermakna dibanding plasebo dengan nilai HR 0,78 [95% CI, 0,60-1,02); p=0,412.

KEPUTUSAN

Mempertimbangkan data khasiat dan keamanan tersebut di atas, diputuskan registrasi zat aktif baru Verquvo tablet salut selaput diterima dengan perbaikan indikasi sebagai berikut:

Indikasi

Verquvo is indicated for the treatment of symptomatic chronic heart failure in adult patients with reduced ejection fraction less than 45% who are stabilized with IV diuretic therapy after hospitalization for heart failure, occurring on guideline-based medical therapy, including angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARB), betablockers, mineralocorticoid receptor antagonists (MRA), and a combination of an angiotensin receptor and neprilysin inhibitor (ARNI).

Public Assessment Report
VERQUVO

PRODUCT INFORMATION

Name of drug	:	VERQUVO
Dosage forms	:	Film coated tablet
Active ingredient	:	Vericiguat 2.5 mg, 5 mg & 10 mg
Packaging	:	Box, 1 blister @ 14 film coated tablets Box, 2 blisters @ 14 film coated tablets
Applicant	:	PT. Bayer Indonesia
Manufacturer	:	Bayer AG, Leverkusen, Germany
Registration Category	:	New drug registration with new Active ingredient
Proposed indications:	:	*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).*
Proposed posology	:	*Adults:* - *The recommended starting dose of VERQUVO is 2,5 mg once daily, taken with food* - *Double the dose of VERQUVO approximately every 2 weeks to reach maintenance dose of 10 mg once daily, as tolerated by the patient* - *For patient who are unable to swallow whole tablets, VERQUVO may be crushed and mixed with water immediately before administration* - *Verquvo is administered in conjunction with other HF therapies*

INTRODUCTION

Verquvo is a drug with the new active ingredient vericiguat, a drug that belongs to a new class of compounds, namely *the soluble guanylate cyclase (sGC) stimulator* used to treat *chronic heart failure with reduced ejection fraction*. *Heart failure* is associated with impaired synthesis of nitric oxide (NO) and decreased activity of the receptor, *Soluble guanylyl cyclase (sGC)*. Deficiency of *sGC-derived cyclic guanosine monophosphate (cGMP)* contributes to myocardial and vascular dysfunction. Vericiguat works to reverse the relative deficiency in NO-sGC-cGMP signaling by directly stimulating sGC, independently and synergistically with NO, to increase intracellular cGMP levels, which may improve myocardial and vascular function.

Considering that vericiguat is a new active ingredient, the current evaluation is focused on non-clinical, clinical, and drug quality test data to obtain further evidence of the efficacy, safety and quality of the drug.

QUALITY ASPECTS

Verquvo (vericiguat) is available in film-coated tablet dosage form, containing 2.5 mg, 5 mg, and 10 mg of vericiguat. Finished drug product consists of two parts, namely the core tablet part which contains the excipients *microcrystalline cellulose, croscarmellose sodium, hypromellose, lactose monohydrate, magnesium stearate, and sodium laurilsulfate*, and the film coating part which contains iron oxide red (5 mg tablet), iron oxide yellow (10 mg), hypromellose, talc and titanium dioxide. Finished drug product is packed in transparent PVC/PVDC/Aluminum foil blisters.

Active Ingredient

Active ingredient vericiguat is a white to yellowish powder and characterization has been carried out on it, including description, solubility, solution pH, pKa, partition coefficient, hygroscopicity, density, *Polymorphism, Pseudo-polymorphism* and *melting Points*. Based on these characterization procedures, vericiguat was identified as a white to yellowish powder, practically insoluble in water and very slightly soluble in ethanol, not hygroscopic. Vericiguat appears in 5 modifications, and Modification I is the form used.

The chemical structure of vericiguat has been confirmed by *elemental analysis, IR spectroscopy, NMR spectroscopy, mass spectrometry* and *UV/Vis spectroscopy*.

The specification for the active ingredient has been provided as its *description (visual), identification (IR, HPLC), particle size, palladium, water, residual solvent (ethanol, isopropyl acetate, benzene, toluene, dimethysulfoxide/ GC) unspecified impurity, sum of all impurity (HPLC), assay (HPLC).*

The analytical method used in testing the active ingredient is a validated non-compendial method.

The stability test of the active substance has been carried out and showed that the drug is stable when stored at 25°C

and 30°C for 24 months. Stress stability tests (*thermal stress, hydrolytic stress, and oxidative stress*) showed the presence of impurities and product degradation. Photostability tests on samples in the form of solid substances and solutions showed that in the form of solid substances no degradation occurred and that vericiguat in solid form was stable to light. Meanwhile, in the sample in solution form there was degradation of two unknown compounds, therefore it was concluded that vericiguat in solution form was sensitive to light.

Finished drug product

Finished drug products are available as round, biconvex, white film-coated tablets, 7 mm in diameter and debossed with “2.5” and “VC” markings on either side (2.5 mg), brown-red tablets 7 mm in diameter with “5” and “VC” markings on either side (5 mg), and yellow-orange tablets 9 mm in diameter with “10” and “VC” markings on either side (10 mg

The manufacturing process is carried out using wet granulation, involving an identification process at critical stages, carried out at the granulation, coating and packaging stages, while *in-process controls is carried out* at Drying stage (loss on drying) and compression step (uniformity of mass; resistance to crushing, Friability and Disintegration) only. Process validation has been carried out on 3 production scale batches for each dosage strength. Process validation results showed the ability of the process to produce finished drugs that meet the specified acceptance criteria.

Drug specifications have been determined, consisting of description (visual), identification (HPLC, UV spectrum), content uniformity (HPLC), dissolution, degradation products (HPLC), assay (HPLC), and microbial purity. The parameters in the specifications are selected based on the physicochemical characteristics and critical properties of the active ingredient, as well as the applicable guidelines taking into account, among other things, the results of batch tests used in clinical trials and the long-term stability data. The analytical method employed has been validated. Batch analysis provided results that fulfilled the required specifications.

Stability data testing of 3 batches of drugs on a production scale was carried out in zone IVB, namely at a temperature of 30°C/75% RH for 24 months and at a temperature of 40°C/75% RH for 6 months, with results that fulfilled the required specifications. In the thermal and hydrolysis tests at a temperature of 80°C, an increase in Fluorodihydropurinone degradant was observed, while the photostability test results showed that the sample fulfilled the required specifications (no increase in impurity).

Conclusion
Based on the quality aspects, Verquvo film coated tablets can be considered for acceptance.

EFFICACY AND SAFETY ASPECTS

Non-Clinical Studies
Pharmacology
- Vericiguat produced a dose-dependent and long-lasting decrease in blood pressure, increase in heart rate, cardiac output (CO), coronary blood flow (CBF), and oxygen saturation in the coronary sinus (SVO2) when tested on anesthetized rats and dogs.
- In an in vitro study on isolated recombinant sGC, sGC-overexpressing cell line, and vascular endothelial cells, vericiguat stimulated sGC at a concentration of 0.01 to 100 μM. Vericiguat stimulated sGC without nitric oxide (NO) but exhibited a synergistic effect when NO is added.

Pharmacokinetics
- Vericiguat was highly permeable in Caco-2 cells. After oral administration of vericiguat formulated in ethanol:polyethylene glycol 400 (PEG400):water (10:60:30; v:v:v) to rats and dogs, absorption was observed to be quite rapid, with a Tmax ranging from 0.5 – 3 hours. The oral bioavailability of vericiguat in rats and dogs was ~40-50% and ~70%, respectively.
- Plasma protein binding of vericiguat and metabolite M-1 (N-glucuronide of vericiguat) is species-dependent. The percentage of unbound plasma in mice, rats, dogs and humans was 7.99%, 4.55%, 10.2%, 2.18%, for vericiguat, and 15.2%, 3.13%, 15.2%, 1.63%, for M-1. The distribution volume of vericiguat in rats and dogs was 0.8 - 1.1 L/kg.
- Following oral administration of vericiguat [14C], the parent compound was observed to be the dominant component in rat, mice, and dog plasma (>97% of total AUC), with the M-1 metabolite appearing as a minor circulating component. In contrast, the M-1 metabolite was the major component in human plasma, accounting for 72% of the total AUC radioactivity, compared with 27% from the parent compound. M-1 was pharmacologically inactive against sGC and has no off-target activity.
- Vericiguat exhibited low *plasma clearance* (0.15 – 0.21 L/hour/kg), and a terminal half-life of 3 – 5 hours in rats and dogs. Following oral administration of vericiguat [14C] to rats and dogs, the drug was excreted via the fecal/biliary route in rats and dogs (rats: 81.2%; dogs: 89.2% of the dose). Balanced excretion was observed in humans (urine: 53.1%, feces: 45.2% of the dose). Vericiguat is excreted into the milk of lactating mice.

Toxicity
- No acute toxicity was observed in in pivotal repeat-dose oral toxicity studies in rats at up to 60 mg/kg/day and dogs at up to 25 mg/kg/day (approximately 75 or 12 times the human exposure (unbound AUC) at the maximum recommended dose for human of 10 mg/day).
- Repeated oral toxicity tests were performed on rats and dogs for up to 26 and 39 weeks with NOAEL of 30

mg/kg/day (±50 times human exposure) and 5 mg/kg/day (±8 times human exposure).

- Carcinogenicity was assessed in 2-year studies conducted on CD1 mouse and Wistar rats. Vericiguat did not show carcinogenic effects in mice administered doses of up to 150 mg/kg/day (male) or up to 250 mg/kg/day (female). This dose was associated with an exposure of 149 (men) or 286 (women) times the human exposure (unbound AUC) at an MRHD of 10 mg/day. In the carcinogenicity study in rats, no vericiguat-related tumor or hyperplastic findings were seen up to exposures of 12 times the human exposure at the MRHD. A non-statistical numerical increase of benign pheochromocytomas and Leydig cell tumors as well as respective hyperplasias were observed in males after administration of the high dose of 20 mg/kg/day leading to exposure of 41 times the human exposure at the MRHD which are considered not relevant for patients. Non-clinical data indicates no carcinogenic risk to humans at clinical doses.
- Vericiguat was non-genotoxic in the in vitro microbial mutagenicity test (Ames), in vitro mouse lymphoma test, as well as in the in vivo rat and mouse micronucleus test.
- In a study of the effects of repeated doses on fertility and early embryonic development conducted over 4 weeks in male and female rats, vericiguat had no effect on fertility or reproductive performance up to the highest dose of 50 mg/kg/day (66 times the human exposure at an MRHD of 10 mg/day days, unbound AUC).

Clinical Study

The data submitted to support the proposed indication consists of 1 phase II clinical study and 1 phase III clinical study.

1. SOCRATES REDUCED (Phase II)
   Results from a dose-ranging phase II clinical study (SOCRATES REDUCED) comparing 5 treatment groups of vericiguat 1.25 mg (n=91) vs vericiguat 2.5 mg (n=90) vs vericiguat 2.5-5 mg (n=91) vs vericiguat 2.5-10 mg (n=91) and placebo (n=92) in patients with worsening heart failure and reduced ejection fraction (HFrEF) for 12 weeks showed:
   a. No significant difference in the geometric mean ratio (GMR) of the baseline in N-terminal pro-brain natriuretic peptide (NT-proBNP) at week 12 between the pooled values of the 3 highest doses of vericiguat (2.5 mg, 2.5-5 mg, and 2.5-10 mg) and the placebo group (GMR 0.885 [95% CI, 0.73-1.08]; p=0.1506).
   b. The results of this dose ranging study showed that a Vericiguat dose of 2.5-10 mg produced the best reduction in NTproBNP compared to placebo at week 12 (GMR 0.779 [90% CI, 0.61-1.00]; p=0.0483).
2. VICTORIA Study (Phase III)
   a. This study compared 2 vericiguat treatment groups with a dose of 2.5-10 mg (n=2515 completed follow-up for the primary endpoint) vs placebo (n=2511 completed follow-up for the primary endpoint) in HFrEF patients for 3 years.
   b. Inclusion criteria for the VICTORIA Study including a history of chronic HF (NYHA class II to IV) on standard therapy before qualifying for HF decompensation, and a history of previous HF hospitalization within 6 months prior to randomization or IV diuretic treatment for HF (without hospitalization) within 3 months prior to randomization.
   c. *Standard of care HF medications* applied on the *baseline* are, among others, individual *beta-blocker* therapy (93.1%), *renin-angiotensin system inhibitor* (87.4%), *mineralocorticoid receptor antagonist* (70.3%), *sacubitril/valsartan* (14.5%), and a combination therapy of 2 or 3 *standard of care HF medications*.
   d. In the primary efficacy results, vericiguat demonstrated a 10% *relative hazard reduction* in *first event confirmed cardiovascular (CV) death* or *HF hospitalization* compared to placebo (HR 0.90 [95% CI, 0.82-0.98]; p=0.019).
   e. Meanwhile for secondary efficacy parameters, vericiguat showed *relative hazard reduction* for each parameter evaluated as follows:
      - *First HF hospitalization* (HR 0.90 [95% CI, 0.81-1.00]; p=0.048) *CV death* (HR 0.93 [95% CI, 0.81-1.06]; p=0.269)
      - *Total HF hospitalizations (first and recurrent)* (HR 0.91 [95% CI, 0.84-0.99];p=0.023)
      - *Composite of all-cause mortality or HF hospitalization* (HR 0.90 [95% CI, 0.83-0.98]; p=0.021)
      - *All-cause mortality* (HR 0.95 [95% CI, 0.84-1.07]; p=0.377).
   f. The analysis of *Number Needed to Treat* (NNT) of vericiguat resulted in a NNT value of 23.98 for *primary composite end point*; 97.9 for *CV death*; and 31.6 for *1st heart failure hospitalization*.
3. Safety data showed primary drug related adverse events of vericiguat were symptomatic hypotension (4.3% vericiguat vs 3.7% placebo), syncope (0.3% vericiguat vs 0.4% placebo) and gastrointestinal disorders (2.5% vs 1.4% placebo).
4. Based on the results of the non-clinical and clinical studies above, it was concluded that the drug is accepted with revised indications as follows:
   Verquvo is indicated for the treatment of symptomatic chronic heart failure in adult patients with reduced ejection fraction less than 45% who are stabilised after a recent decompensation event requiring IV therapy and have recently been hospitalized and stabilized with IV diuretic therapy or patients at high risk despite guideline-based medical therapy, including angiotensin-converting enzyme (ACE) inhibitors or angiotensin

II receptor blockers (ARB), betablockers, mineralocorticoid receptor antagonists (MRA), and a combination of an angiotensin receptor and neprilysin inhibitor (ARNI).

The Applicant submits revised indications supported by the results of the VICTORIA phase III study completed with the justification and evaluation of the results as follows:

1. One of the inclusion criteria for patients as supporting data is "*Have a previous HF hospitalization within 6 months prior to randomization or IV diuretic treatment for HF (without hospitalization) within 3 months prior to randomization*". In accordance with the AHA/ACC/HFSA (American College of Cardiology/American Heart Association/Heart Failure Society of America) Guideline for the Management of Heart Failure and clinical implementation, *patients with heart failure who are hospitalized are generally given diuretics as a decongestion strategy.*
2. From the study results, it is known that more than 70% of patients were hospitalized and around 15% of patients were not hospitalized.
    a. The results of the entire population study showed that vericiguat provided better efficacy than placebo in reducing the risk of first event confirmed cardiovascular (CV) death or HF hospitalization, with a hazard ratio (HR) of 0.90 [95% CI, 0.82-0.98]; p=0.019.
    b. Meanwhile, based on subgroup analysis in the group of patients who received diuretic therapy without being hospitalized (n=399/2526), vericiguat showed results that were not significantly different compared to placebo with an HR value of 0.78 [95% CI, 0.60-1.02); p=0.412.

CONCLUSION

Considering the efficacy and safety data as described above, it was decided that the registration of the new active ingredient Verquvo film-coated tablets is accepted with the following revisions to the indications:

Indications

Verquvo is indicated for the treatment of symptomatic chronic heart failure in adult patients with reduced ejection fraction less than 45% who are stabilized with IV diuretic therapy after hospitalization for heart failure, occurring on guideline-based medical therapy, including angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARB), betablockers, mineralocorticoid receptor antagonists (MRA), and a combination of an angiotensin receptor and neprilysin inhibitor (ARNI).