Taiwan Food and Drug Administration

Assessment Report

Trade Name：泰時維膜衣錠 100 毫克/
AYVAKIT film-coated tablets 100 mg

Active Ingredient：Avapritinib

License Number：MOHW-PI 028029

Applicant：裕利股份有限公司

Approval Date：2021/02/09

Indication：
治療具有血小板衍生生長因子α受體 (PDGFRA) D842V 突變，無法切除或轉移性腸胃道間質瘤的成年病人

For the treatment of adult patients with unresectable or metastatic gastrointestinal stromal tumor (GIST) harboring PDGFRA D842V mutations.

Background Information

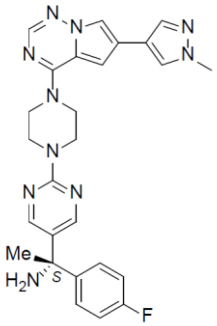
Trade Name	泰時維膜衣錠 / AYVAKIT TM film-coated tablets
Active Ingredient(s)	avapritinib
Applicant	裕利股份有限公司
Dosage Form & Strengths	膜衣錠 100 mg
Indication	治療具有血小板衍生生長因子α受體 (PDGFRA) D842V 突變，無法切除或轉移性腸胃道間質瘤的成年病人 For the treatment of adult patients with unresectable or metastatic gastrointestinal stromal tumor (GIST) harboring PDGFRA D842V mutations.
Posology	詳見仿單
Pharmacological Category **ATC Code**	L01EX18

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug substance

The drug substance, avapritinib, is chemically designated as (*S*)-1-(4-fluorophenyl)-1-(2-(4-(6-(1-methyl-1*H*-pyrazol-4-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yl)piperazin-yl)pyrimidin-5-yl)ethan-1-amine and has the following structure:



It is a white to off-white to yellow solid. The molecular formula and the molecular weight are $C_{26}H_{27}FN_{10}$ and 498.57g/mol, respectively. It is non-hygroscopic. The structure of avapritinib is confirmed by IR spectrum, mass spectrum, nuclear magnetic resonance spectrum, UV, elemental analysis, and single crystal X-ray crystallography.

The specification of drug substance includes tests for description, identification, assay, impurities, solid form, and particle size distribution.

2.1.2 Drug product

Avapritinib drug product is a film-coated tablet for oral use. The tablets are supplied with three strengths, including 100 mg, 200 mg, or 300 mg of avapritinib. The excipients used in the drug product comply with the compendial monographs.

Specifications have been presented for the drug product and the test items include appearance, identification, assay, content uniformity, degradation products, dissolution, and water content. Analytical methods are described and validated.

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

2.2 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

Avapritinib (BLU-285) is a type 1 kinase inhibitor designed to potently and selectively inhibit oncogenic KIT and PDGFRα mutants by targeting the kinases' active conformation. Avapritinib showed broad inhibitory activity against a panel of GIST-relevant KIT and PDGFRα mutants. While potent on these KIT and PDGFRα mutants, avapritinib was demonstrated to be highly selective.

Avapritinib dose-dependently inhibited KIT and PDGFRα mutants in a cellular setting, and oral administration of avapritinib resulted in significant anti-tumor efficacy in KIT mutant-driven tumor models. Avapritinib was tested in a KIT exon 17 mutant P815 cell line xenograft tumor, a KIT exon 11/exon 17 mutant GIST patient-derived xenograft (PDX) tumor, and a KIT exon 11/exon 13 mutant PDX model. Avapritinib administered orally once daily (QD) as a single agent produced significant anti-tumor activity, including partial regression at higher doses, in these tumor models with inhibition of KIT mutant activity and downstream signaling markers. At active doses, avapritinib was well tolerated by the tumor-bearing animals with minimal bodyweight loss observed.

In separate studies, avapritinib demonstrated robust *in vivo* anti-tumor activity against GIST xenografts with multiple other KIT genotypes, including primary exon 9 and exon 11 mutant models and secondary exon 11/13 and exon 11/17 resistance models.

In a modified Irwin test, rats administered 45 mg/kg/day of oral avapritinib for 15 consecutive days showed an increased sensitivity to stimuli and tremors. The NOAEL was determined to be 15 mg/kg/day. Avapritinib inhibited the type 2 sodium channel with an IC_{50} of 280 nM, and the allelic variations in the type 2 sodium channel have been associated with seizure disorders. Therefore, a contributing role for avapritinib-mediated inhibition of the type 2 sodium channel in clinical neurological symptoms cannot be excluded. Avapritinib

blocked hERG channel potential with an IC_{50} of 2.4 μM; however, there were no avapritinib-related adverse effects on pulmonary function or the cardiovascular system at single doses up to 45 mg/kg. Consistent with these findings, avapritinib did not affect QT prolongation clinically or in *in vivo* nonclinical studies.

2.2.2 Toxicological Studies

Repeated dose toxicity studies were conducted in rats and dogs for up to 3 months. In the rat study, doses of ≥20 mg/kg/day avapritinib resulted in animals' death. The exact cause of death was not determined; however, toxicities included the hematopoietic and lymphoid system, adrenal gland, bone, heart, lungs, nephropathy, female reproductive organ toxicity, and hepatobiliary systems were noted. Anemia occurred clinically, as well. Avapritinib may impair female fertility. Tremors and convulsions occur in rats at doses ≥100 mg/kg/day (exposures approximately 8-fold of clinical dose).

In dogs study, almost all high-dose dogs died due to multi-focal hemorrhage in the spinal cord and brain. Edema in the choroid plexus also occurred. Intracranial hemorrhage occurred clinically as well. Dogs also displayed tremors that may be related to the type 2 sodium channel off-target pharmacological activity, as described above, or PDGFRα inhibition given that PDGFRα knockout mice have defective oligodendrocyte development and severe hypomyelination in various regions of the brain, and tremors. Additional toxicities in dogs consisted of the hematopoietic and lymphoid system, adrenal glands, gastrointestinal, male reproductive organ toxicity, and liver toxicity. Avapritinib may impair male fertility.

Avapritinib was not mutagenic in a bacterial reverse mutation (Ames) assay. Avapritinib was clastogenic in the *in vitro* chromosome aberration test in human peripheral blood lymphocytes at concentrations ≥5 μg/mL (22-hour incubation); these aberrations appeared structural rather than numerical. However, avapritinib was not clastogenic in the *in vivo* rat bone marrow micronucleus test at doses up to 150 mg/kg. Based on the weight of evidence, avapritinib may not be considered genotoxic.

Daily oral administration of avapritinib to pregnant rats resulted in decreased fetal body weights, post-implantation loss, and increases in visceral and skeletal malformations at doses ≥ 10 mg/kg/day. Because of avapritinib’s potential for embryo-fetal toxicity, half-life, and positive genotoxicity finding, the label includes a recommendation for females and males of reproductive potential to use contraception during treatment with avapritinib and 6 weeks after the final dose. Lactating women are advised not to breastfeed during treatment with avapritinib and, based on a half-life of 57 hours, 2 weeks after the final dose.

Local tolerance was assessed by reviewing the digestive track changes in rats and dogs. No

evidence of local gastrointestinal effects occurred in the rat at minimally lethal doses or lower. In the Beagle dog, diarrhea (without histologic correlate) and esophageal and stomach erosions occurred at lethal exposures. Emesis was noted in dogs at the HNSTD and the severely toxic dose levels.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

Following single 30 mg to 400 mg doses of avapritinib, T_{max} ranged from 2.0 to 4.1 hours. Avapritinib exhibited dose-proportional increases in AUC and C_{max} across the dose range of 30 mg to 400 mg following both single dose and repeated doses. Following repeated 300 mg once daily administration, steady-state was achieved after 15 days and avapritinib accumulated with a geometric mean accumulation ratio of 3.1 to 4.6. Compared to fasted conditions, the C_{max} was increased by 59% and the $AUC_{0\text{-}inf}$ was increased by 29% when avapritinib was administered after a high fat meal.

Extensive in vitro plasma protein binding of avapritinib was observed in human plasma (98.8%). The human blood-to-plasma ratio was 0.95. The mean apparent volume of distribution of avapritinib is 1200 L. In vitro studies demonstrated that avapritinib is predominantly metabolized by CYP3A4 and to a minor extent by CYP2C9.

Following a single oral dose of approximately 310 mg radiolabeled avapritinib to healthy subjects, unchanged avapritinib (49%) and metabolites M690 (hydroxy glucuronide; 35%) and M499 (oxidative deamination; 14%) were the major circulating radioactive components. Following oral administration of avapritinib 300 mg once daily in patients, the steady state AUC of BLU111207 and BLU111208, the constitutive enantiomers of the pharmacologically active metabolite M499, were approximately 35% and 42% of the AUC of avapritinib, respectively. M499 is not likely to contribute to efficacy at the recommended dose of avapritinib. After single-dose administration of avapritinib across the dose range of 30 to 400 mg in patients, the mean $t_{1/2}$ was long, ranging from 32 to 57 hours. Following a single oral dose of approximately 310 mg of radiolabeled avapritinib to healthy subjects, 70% of the radioactive dose was recovered in feces (11% unchanged) and 18% in urine (0.23% unchanged).

2.3.2 Interaction Studies

In a clinical drug-drug interaction study, co-administration of avapritinib 200 mg single dose with itraconazole increased avapritinib C_{max} 1.4-fold and $AUC_{0\text{-}inf}$ by 4.2-fold in healthy subjects. Co-administration of avapritinib 400 mg single dose with rifampin decreased avapritinib C_{max} by 74% and $AUC_{0\text{-}inf}$ by 92% in healthy subjects. Based on PBPK modeling, co-administration of avapritinib 300 mg once daily with fluconazole 200 mg once daily (a

moderate CYP3A inhibitor) is predicted to increase avapritinib AUC by 3.1-fold at steady state. Co-administration of avapritinib with cimetidine (a weak CYP3A inhibitor) is predicted to increase avapritinib AUC by 1.2-fold at steady state. Co-administration of avapritinib 300 mg once daily with efavirenz (a moderate CYP3A inducer) is predicted to decrease avapritinib C_{max} by 55% and AUC by 62% at steady-state. The effect of PPI use on relative bioavailability (F1) is estimated to be 0.77 in a population PK analysis.

2.3.3 Special Populations

Based on population PK analysis, age, race, sex, body weight, and albumin concentration have no clinically meaningful effect on the PK of avapritinib. No dedicated PK study was conducted to evaluate the impact of renal or hepatic impairment on the PK of avapritinib.

Based on population PK analysis, avapritinib exposures were similar between subjects with mild hepatic impairment (N=53), subjects with moderate hepatic impairment (N=6), and subjects with normal hepatic function (N=284). The PK of avapritinib in patients with severe hepatic impairment has not been studied.

The population PK analysis showed that avapritinib exposures were similar among subjects with mild renal impairment (N=88), subjects with moderate renal impairment (N=24), and subjects with normal renal function (N=230). The PK of avapritinib in patients with severe renal impairment or ESRD has not been studied.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

Study BLU-285-1101 was reviewed to evaluate the efficacy of avapritinib as a treatment for patients with unresectable or metastatic GIST harboring PDGFRA exon 18 mutations, including the PDGFRA D842V mutation.

Study BLU-285-1101 was an open-label, single arm, dose-escalation and expansion study. There were 43 patients in the PDGFRA exon 18 patient population consisting predominantly of patients with PDGFRA D842V mutations (38 patients, 88%) in the 300/400 mg dose group. ORR based on central radiology review by mRECIST v1.1 criteria was 84% (95% CI: 69.3%, 93.2%) with 36 of the 43 patients having CR or PR. The ORR in the 300 mg starting dose group was higher as compared to the ORR in the 400 mg group (88% vs 73%), with overlapping 95% CIs. ORR in PDGFRA D842V patients was 89.5% (34/38 patients; 95% CI: 75.2%, 97.1%).

2.4.2 Safety Results

Major TEAEs of avapritinib included nausea, fatique, anemia, periorbital edema, diarrhea, vomiting, decreased appetite, constipation, increased bilirubin, UGI bleeding, acute renal injury, decreased neutrophil count, cognitive impairment, and intracranial bleeding. Comparison of results between East Asians (30%) and Caucasian (70%) in Study BLU-285-1303 revealed apparent higher incidence of decreased neutrophil count (23.3% vs. 4.3%) and fatigue (8.3% vs. 2.9%) in East Asians. Dose reduction may be expected more frequent for East Asians.

2.5 Bridging Study Evaluation

The PK analysis of avapritinib from Study BLU-285-1101 was performed for the race comparison of PK exposure. A total of 17 East Asians patients (South Korea) and a total of 76 Caucasians patients received 300 mg of avapritinib QD and underwent intensive PK sampling. Regarding the representative exposure of avapritinib on C1D15, both $C_{max,ss}$ and $AUC_{0-\tau,ss}$ are on average 60% higher in East Asian patients compared with Caucasian patients.

The impact of ethnic factor on avapritinib PK was also assessed by cross study comparison. The PK of avapritinib from Chinese patients (Study BLU-285-1105) were compared to Caucasian patients (Study BLU-285-1101) following single dose and multiple doses of 300 mg avapritinib. After single dose administration, the C_{max} and AUC_{0-24} are 17%~25% higher in Chinese patients (N=42) compared with Caucasian patients (N=113). After multiple doses administration, the $C_{max,ss}$ and $AUC_{0-\tau,ss}$ are 27%~29% higher in Chinese patients (N=36) compared with Caucasian patients (N=110). Since avapritinib has no obvious exposure-response correlation, it was not expected to translate into a clinically meaningful impact on the efficacy and safety for the above observed exposure differences. However, attention should still be paid to the expected or unexpected AEs caused by higher exposure in East Asian.

Comparison of results between East Asians (30%) and Caucasian (70%) in Study BLU-285-1303 (indication not for this NDA) revealed apparent higher incidence of decreased neutrophil count (23.3% vs. 4.3%) and fatigue (8.3% vs. 2.9%) in East Asians. Due to rarity of disease, the number of East Asian subjects in clinical trials is limited; additional post-marketing study in this country is required.

2.6 Conclusion

There is no available treatment for unresectable or metastatic GIST harboring a PDGFRA exon 18 mutation, 34 subjects with PDGFRA D842V mutation in Study BLU-285-1101 showed promising ORR results (89.5 %) and a durable DOR; the efficacy evidence is sufficient for regular approval without further confirmatory trial. Efficacy of non-D842V

exon 18 mutations is uncertain because of the limited number of subjects (only four).

The safety profile is acceptable. Dose reduction may be expected more frequent for East Asians as compared to Caucasians.

Approval of Ayvakit is recommended, the approved indication is “the treatment of adult patients with unresectable or metastatic gastrointestinal stromal tumor (GIST) harboring PDGFRA D842V mutations”.

3. Post-Marketing Requirements

1. Post-marketing study in this country is required due to limited number of East Asian subjects in clinical trials.
2. Submit the US FDA requested report of an analysis characterizing avapritinib-associated CNS adverse reactions including but not limited to cognitive impairment and avapritinib-associated intracranial hemorrhage from completed and on-going trials.
3. Submit the final report of Study BLU-285-1101.
4. PK study to determine an appropriate dose in patients with severe hepatic impairment.