Taiwan Food and Drug Administration

Assessment Report

Trade Name：
衛復守錠劑 150 毫克/ VAFSEO Tablets 150 mg
衛復守錠劑 300 毫克/ VAFSEO Tablets 300 mg

Active Ingredient：Vadadustat

License Number：MOHW-PI-028477/ MOHW-PI-028478

Applicant：台田藥品股份有限公司

Approval Date：112.07.19

Indication：治療透析成人病人因慢性腎臟疾病導致之貧血。

Treatment of anemia associated with chronic kidney disease (CKD) in adults on dialysis.

Background Information

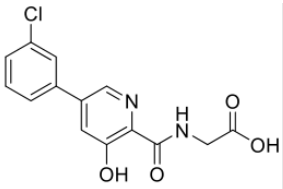
Trade Name	衛復守錠劑 150 毫克 VAFSEO Tablets 150 mg 衛復守錠劑 300 毫克 VAFSEO Tablets 300 mg
Active Ingredient(s)	Vadadustat
Applicant	台田藥品股份有限公司 Tai Tien Pharmaceutical Company
Dosage Form & Strengths	錠劑/ 150 毫克 & 300 毫克 Tablets/ 150 mg & 300 mg
Indication	治療透析成人病人因慢性腎臟疾病導致之貧血。 Treatment of anemia associated with chronic kidney disease (CKD) in adults on dialysis.
Posology	請參閱仿單。 Please refer to the approved package insert
Pharmacological Category **ATC Code**	B03XA08

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug substance

The drug substance, vadadustat, is chemically designated as [5-(3-Chlorophenyl)-3-hydroxypyridine-2-carboxamido] acetic acid. The molecular formula and the relative molecular mass for vadadustat are $C_{14}H_{11}ClN_2O_4$ and 306.70, respectively. The chemical structure of vadadustat is shown below:



It is a white to off-white solid. The structure of vadadustat is confirmed by IR spectrum, nuclear magnetic resonance (NMR) spectroscopy, (ultraviolet) UV and mass spectrum. The specification for the drug substance includes tests for appearance, identity, assay, organic impurities, physical form, water content, residual solvents, residue on ignition, elemental impurities and particle size.

2.1.2 Drug product

The drug product is supplied for oral use as film-coated tablets containing 150 mg and 300 mg vadadustat. All excipients are well known ingredients and suitable for proposed formulation. The specification for the drug product includes appearance, identification, assay, degradation, uniformity of dosage units and dissolution. Analytical methods are described well and validated. Stability studies of drug product under long term condition (25°C/60% RH) and accelerated condition (40°C/75% RH) have been carried out.

2.2 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

In vitro pharmacodynamic studies revealed that vadadustat enhance the production of endogenous EPO as well as to increase the efficiency of iron utilization by inhibiting PHD activity and stabilizing HIF-α.. *In vitro* and *in vivo* pharmacodynamic studies showed that vadadustat increased the EPO concentration, erythrocyte count, reticulocyte count, hemoglobin value, and hematocrit value in a dose-dependent manner without changes in the levels of VEGF.

Vadadustat also ameliorated CKD-associated anemia in rodent models of chronic kidney disease. Safety pharmacology study identified no significant effects on neurological systems and ECG parameters; however, increased heart rate and decreased blood pressure in rats and dogs and increased tidal volume and minute volume of ventilation in rats were observed, which can be attributed to the mechanism of HIF-prolyl-hydroxylase inhibitor.

2.2.2 Toxicological Studies

Vadadustat was evaluated in GLP-compliant toxicity studies for up to 6- and 9-month duration in rats and dogs. Toxicity findings of vadadustat were mainly related to exaggerated pharmacology associated with the stimulated erythropoiesis, which is reflected in increased blood viscosity and circulating erythrocyte mass. Increased erythropoiesis led to secondary effects such as bone marrow hypercellularity and hyperplastic changes, extramedullary hematopoiesis in the spleen or adrenal cortex, thromboembolism or hemorrhage in multiple organs, changes in iron and coagulation parameters, spleen enlargement, higher serum bilirubin, and carcass discoloration. The NOAELs were 40 mg/kg/day in the 6-month rat study and 25 mg/kg/day in the 9-month dog study, providing safety margins of 0.4 and 0.1, respectively. Toxicity findings in rats and dogs partially recovered after the recovery period.

The genotoxicity risk of Vadadustat is low, and no neoplastic findings were noted in a 2-year rat carcinogenicity study. However, in a 6-month study of rasH2 transgenic mice, vadadustat increased the incidence of splenic hemangiosarcoma at exposures lower than human exposure at the MRHD. Vadadustat had no significant effect on fertility or early embryonic development but reduced maternal body weight and increased the incidence of immure ossification in the fetal skeleton in rats and rabbits.

The NOAELs for development toxicity was 80 mg/kg/day in rats and 50 mg/kg/day in rabbits, providing safety margins of 1.7 in rats and 0.16 in rabbits based on AUC. In the PPND study in rats, vadadustat caused a decrease in the body weight of offspring during lactation and early postweaning in dams administered 80 mg/kg/day with a safety margin of 1.2 based on AUC. Of note, vadadustat was not phototoxic in rats.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

The plasma vadadustat C_{max}, $AUC_{0\text{-last}}$, and $AUC_{0\text{-}\infty}$ increased dose-dependently over the dose range of 80 to 1200 mg. The geometric mean ratios (90% CI) of C_{max} and $AUC_{0\text{-}\infty}$ of vadadustat following postprandial administration relative to administration under fasting were 73.07% (67.92%~78.61%) and 94.30% (90.30%~ 98.49%), respectively. Vadadustat may be taken under fasting conditions or after a meal. The human protein binding of vadadustat was 99.5%~99.8% and vadadustat-O-glucuronide, was 86.5%~87.8%.

The mass balance study using [^{14}C]-labeled vadadustat showed that the unchanged form and vadadustat-O-glucuronide were major circulating drug-related components observed in human plasma, accounting for 75% and 15% of the total plasma radioactivity, respectively. The vadadustat-O-glucuronide was formed by UGT1A1, UGT1A7, UGT1A8 and UGT1A9. Administered [^{14}C]-labeled vadadustat was excreted in urine and feces at 85.9%, with the urinary excretion rate of 58.9% and fecal excretion rate of 26.9%. Most of the administered radioactivity was excreted within 72 hours of administration. The urinary excretion rates of vadadustat were less than 1% of the administered dose.

2.3.2 Interaction Studies

Vadadustat, *in vitro*, was shown to be a substrate of BCRP, OAT1/OAT3, OATP1B1 and multiple UGTs. *In vitro* study results showed that vadadustat had mild inhibitory effects on CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4/5 and UGT1A1. Besides, vadadustat inhibited BCRP, OAT1, OAT3 and OATP1B1.

Co-administration with OAT1/OAT3 inhibitors may increase vadadustat plasma concentration, whereas co-administration with oral iron, iron-containing phosphate binders, or iron-free phosphate binders may decrease vadadustat plasma concentration. In addition, the pharmacokinetics (PK) of vadadustat was not likely to be greatly influenced by co-administration with BCRP/OATP1B1 inhibitors, UGT inhibitors, or proton pump inhibitors.

On the other hand, co-administration of vadadustat may increase the AUC of BCRP substrates, including rosuvastatin, simvastatin, atorvastatin and sulfasalazine (salazosulfapyridine). The AUC of furosemide (OAT3 substrate) increased about 2-fold upon co-administration with vadadustat.

2.3.3 Special Populations

Whereas no clinical studies were conducted to investigate the impact of age and gender on the PK of vadadustat. The results of the population pharmacokinetic analysis did not show that age and sex were statistically significant covariates. The results of the population pharmacokinetic analysis showed that body weight was a statistically significant covariate. An inverse correlation was shown between body weight and AUC. Overall, no dose adjustment is required by age, gender and body weight.

No major difference in the exposure to vadadustat between healthy adults and CKD patients. No noteworthy differences were observed between pre- and post-hemodialysis administration of vadadustat in the C_{max} or AUC of vadadustat or vadadustat-O-glucuronide. Therefore, no dose adjustment is required by renal impairment.

The geometric mean ratios (90% CI) of PK parameters in patients with moderate hepatic impairment compared to subjects with normal hepatic function were 105.46% (82.22~135.27%) for $AUC_{0\text{-last}}$, 105.89% (82.47~135.95%) for $AUC_{0\text{-}\infty}$, and 102.46% (79.28~132.43%) for C_{max}. These data indicated that there are no clear differences in PK parameters between subjects with moderate hepatic function and subjects with normal hepatic function. On the other hand, vadadustat has not been studied in severe hepatic impairment. Based on these results, no dose adjustments are recommended in subjects with mild and moderate hepatic impairment.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

The efficacy of vadadustat (MT-6548) was evaluated in each of non-dialysis- dependent chronic kidney disease (NDD-CKD; Study MT-6548-J01), peritoneal dialysis-dependent CKD (PD-CKD; Study MT-6548-J02), and hemodialysis- dependent CKD (HD-CKD; Studies MT-6548-J03 and J04) patients. These four studies were Phase III studies and conducted in Japan. The target Hb ranges were set to be 11.0 g/dL to <13.0 g/dL in NDD-CKD and PD-CKD patients and 10.0 g/dL to <12.0 g/dL in HD-CKD patients. The non-inferiority (NI) margin of -0.75 g/dL was used (for MT-6548 - darbepoetin alfa).

For NDD-CKD patients with anemia (MT-6548-J01), the MMRM-based LS Mean of the average Hb at Weeks 20 and 24 (primary endpoint) was 11.66 g/dL (95% CI: 11.49, 11.84 g/dL) for the MT-6548 arm, and 11.93 g/dL (95% CI: 11.76, 12.10 g/dL) for the darbepoetin arm. The 95% CIs for both arms were within the target range. The MMRM-based LS Mean difference between MT-6548 and darbepoetin alfa (MT-6548 - darbepoetin alfa) in average Hb at Week 20 and Week 24 was -0.26 g/dL (95% CI: -0.50, -0.02 g/dL). The lower limit of the 95% CI for the between-arm difference (MT-6548 - darbepoetin alfa) was above -0.75 g/dL, achieving the non-inferiority of MT-6548 to darbepoetin alfa. The same analysis was performed on data in the per protocol set (PPS) and demonstrated robustness of the primary analysis in the full analysis set (FAS).

For PD-CKD patients with anemia (MT-6548-J02), the MMRM-based LS Mean of the average Hb at Weeks 20 and 24 was 11.35 g/dL (95% CI: 10.99, 11.70 g/dL) and the LS Mean was within the target range.

For HD-CKD patients with anemia (MT-6548-J03), the MMRM-based LS Mean of the average Hb at Weeks 20 and 24 was 10.61 g/dL (95% CI: 10.45, 10.76 g/dL) for the MT-6548 arm, and 10.65 g/dL (95% CI: 10.50, 10.80 g/dL) for the darbepoetin arm. In both arms, the 95% CIs for the mean of Week 20 and Week 24 Hb measurements were within the target range. The MMRM-based LS Mean difference between MT-6548 and darbepoetin alfa in average Hb at Week 20 and Week 24 was -0.05 g/dL (95% CI: -0.26, 0.17 g/dL). The lower limit of the 95% CI for the between-arm difference was above -0.75 g/dL, achieving the non-inferiority of MT-6548 to darbepoetin alfa. The same analysis was performed on data in the PPS and demonstrated robustness of the primary analysis in the FAS.

For HD-CKD patients with anemia (MT-6548-J04), the MMRM-based LS Mean of the average Hb at Weeks 20 and 24 was 10.75 g/dL (95% CI: 10.35, 11.14 g/dL), and 95%

CI was within the target range.

Two global Phase III cardiovascular outcomes programs ($INNO_2VATE$ and PRO_2TECT) were also reviewed to evaluate the safety of MT-6548. The primary safety endpoint, assessed in a time-to-event analysis, was the first occurrence of a major adverse cardiovascular event (MACE, a composite of death from any cause, a nonfatal myocardial infarction, or a nonfatal stroke).

In $INNO_2VATE$ program, the hazard ratio (HR; MT-6548/darbepoetin alfa) for first MACE in patients with dialysis dependent (DD)-CKD was 0.96 (95% CI: 0.83, 1.13). The upper bound of the 2-sided 95% CI for the HR was lower than the prospectively defined NI margin of 1.25. In PRO_2TECT program, the HR for first MACE in patients with NDD-CKD was 1.17 (95% CI: 1.01, 1.36), which did not meet the prespecified NI margin of 1.25.

2.4.2 Safety Results

No major difference was noted in the incidence of adverse events between the treatment groups in comparative Japanese trial, MT-6548-J01 and J03. The majority of AEs were mild-intensity. There was no major difference in the incidence of severe or moderate adverse events between the treatment groups. The overall incidence rates of adverse event by dose at onset revealed no tendency of dose-dependent increase in frequency.

Overall, adverse events by PT that occurred at ≥10% in the vadadustat-treated patients at Japanese safety analysis population included Nasopharyngitis (17.0%), Diarrhea (11.4%), Catheter site infection (2.1%) and Peritonitis (1.0%). Catheter site infection and Peritonitis were observed only in subjects with PD-CKD.

Hepatobiliary AESI in Japanese safety analysis population showed no clinically meaningful concerns in vadadustat-treated patients. In the global clinical program, there were 23 vadadustat-treated subjects with hepatic events considered probably or possibly related by an unblinded hepatic adjudication committee. Only 1 subject was considered probably related and 22 considered possibly related to vadadustat. There were no reports of hepatic failure, liver transplants or deaths due to drug induced liver injury attributable to vadadustat in the global clinical program.

There is hypertension concern for HIF PHI based on molecular mechanisms. No clinically meaningful changes in BP were observed between the treatment groups in

both Japanese and global trials. The incidence of worsening hypertension was similar between the treatment groups in both Japanese and global trials.

HIF pathway also involves in the regulation of lipid and carbohydrate metabolism on molecular mechanism. Small, clinically irrelevant changes in serum glucose and lipids were observed within and between treatment groups in both Japanese and global trials.

Based on the cumulative reports from global trials, the occurrence of retinal effects due to VEGF expression and malignancies were not increased in vadadustat-treated population.

About cardiovascular risk among CKD patients on dialysis, please refer to 2.4.1.

2.5 Bridging Study Evaluation

Following a single dose and 10 daily doses of 150, 300, and 600 mg, vadadustat C_{max} and AUC parameter values increased in a dose proportional manner in healthy Japanese subjects. The metabolic ratio of major metabolite, vadadustat-O-glucuronide, was 0.08. The dose-adjusted C_{max} and $AUC_{0-\tau}$ of vadadustat after single and multiple doses of 150 mg, 300 mg, or 600 mg in Japanese and Caucasian healthy adults showed that the geometric mean values of C_{max} and $AUC_{0-\tau}$ were similar between Japanese and Caucasian healthy adults. The accumulation ratio for Cmax was 1.30 in Japanese healthy adults and 1.08 in Caucasian healthy adults, showing a slightly higher value in Japanese subjects. However, the accumulation ratio for $AUC_{0-\tau}$ was 1.18 and 1.10 in Japanese and Caucasian healthy adults, respectively, indicating little accumulation of vadadustat after repeated administration.

The PK data from four richly sampled Phase I and II studies and six sparsely sampled Phase II and III studies where a total of 60 healthy volunteers, 327 NDD-CKD patients and 291 DD-CKD patients were included in population PK analysis. Oral vadadustat PK was well characterized by a linear two-compartment model with first-order absorption and absorption lag time. Steady state was reached in patients within three days after the start of daily dosing. The accumulation ratio for a severely renally impaired patient was 1.33. Food reduced the absorption rate and increased the lag time, resulting in a delayed time to C_{max} but the bioavailability was not impacted. Moreover, in the population PK analysis, race along with age, sex, ethnicity, or Japanese descent on CL/F was not identified as a covariate influencing the AUC of vadadustat.

Moreover, the PK of vadadustat is not a steep effect-concentration curve for both efficacy and safety in the range of the recommended dosage and dose regimen. The therapeutic dose range for vadadustat is not considered to be narrow. Vadadustat is not a prodrug and the contribution of CYPs in the metabolism of vadadustat is minor. Overall, no significant difference of ethnicity is observed between Asian and non-Asian subjects. Race is not considered a sensitive factor on vadadustat PK.
From clinical perspective, the sponsor provided the Japanese phase 3 trials for BSE which is considered appropriate to represent the population in Taiwan.

In summary, bridging study was waived in consideration of the intrinsic and extrinsic factors between Japan and Taiwan.

2.6 Conclusion

In CKD patients on dialysis, vadadustat demonstrated efficacy on anemia non-inferior to ESA. CV risk in the vadadustat group was not increased and non-inferior to the ESA group in patients with dialysis dependent. The review team considered a favorable risk-benefit profile for vadadustat intended for the treatment of anemia in adults with chronic kidney disease who are on dialysis.

3. Post-Marketing Requirements

1. Please submit the post-marketing efficacy and/or safety evaluation report using registry data in Japan requested by PMDA once available.
2. Please provide the updated PSUR report.