Taiwan Food and Drug Administration

Assessment Report

Trade Name :伏醯佳注射劑 **1** 公克**/FETROJA for Injection 1g**

Active Ingredient : Cefiderocol Sulfate Tosylate

License Number : N/A

Applicant: 台灣塩野義製藥股份有限公司

Approval Date : N/A

Indication :適用於治療成人病人對 **Fetroja®** 具有感受性之革蘭氏陰性微生物**(susceptible Gram negative microorganisms)**所引起的下列感染：

- 複雜性泌尿道感染**(Complicated Urinary Tract Infections, cUTI)**，包含腎盂腎炎**(Pyelonephritis)**
- 院內感染型肺炎**(Hospital acquired Bacterial Pneumonia, HABP)**和呼吸器相關肺炎**(Ventilator associated Bacterial Pneumonia, VABP)**

FETROJA is indicated in patients 18 years of age or older for the treatment of following infections caused by susceptible Gram-negative microorganisms:

- **Complicated urinary tract infections (cUTIs), including pyelonephritis.**
- **Hospital-acquired bacterial pneumonia (HABP), and ventilator-acquired associated bacterial pneumonia (VABP).**

Background Information

Trade Name	伏醱佳注射劑 1 公克/ FETROJA for Injection 1g
Active Ingredient(s)	Cefiderocol Sulfate Tosylate
Applicant	台灣野義製藥股份有限公司
Dosage Form & Strengths	凍晶注射劑 1g
Indication	適用於治療成人病人對 Fetroja® 具有感受性之革蘭氏陰性微生物 (susceptible negative microorganisms) 所引起的下列感染： • 複雜性泌尿道感染 (Complicated Urinary Tract Infections, cUTI)，包含腎盂腎炎 (Pyelonephritis) • 院內感染型肺炎 (Hospital acquired Bacterial Pneumonia, HABP) 和呼吸器相關肺炎 (Ventilator associated Bacterial Pneumonia, VABP) FETROJA is indicated in patients 18 years of age or older for the treatment of following infections caused by susceptible Gram-negative microorganisms: • Complicated urinary tract infections (cUTIs), including pyelonephritis. • Hospital-acquired bacterial pneumonia (HABP), and ventilator-acquired associated bacterial pneumonia (VABP).
Posology	詳見仿單 / Please refer to the approved package insert
Pharmacological Category **ATC Code**	J01DI04

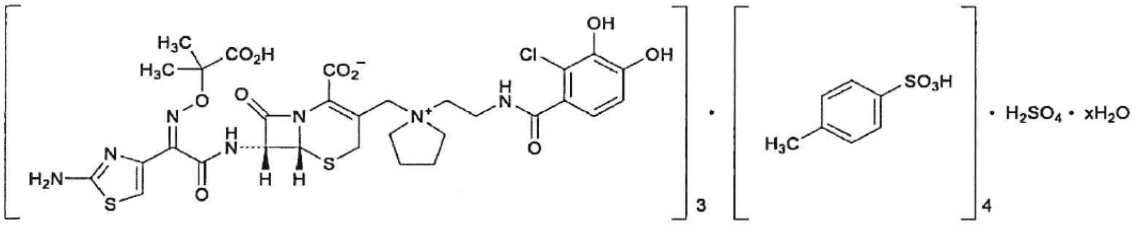
2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug substance

The drug substance, cefiderocol sulfate tosylate, is chemically designated as tris[(6R,7R)-7-[(2Z)-2-(2-amino-1,3-thiazol-4-yl)-2-{[(2-carboxypropan-2-yl)oxy] imino}acetamido]-3-({ 1 -[2-(2-chloro-3,4-dihydroxybenzamido)ethyl]pyrrolidin-1-

ium-1-yl}methyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate]tetrakis (4-methylbenzenesulfonate) monosulfate hydrate and has the following structure:



It is a white to slightly yellow powder. The molecular formula and the molecular weight are $3C_{30}H_{34}ClN_7O_{10}S_2 \bullet 4C_7H_8O_3S \bullet H_2SO_4 \bullet xH_2O$ and 3043.50 Daltons (anhydrous), respectively.

Adequate information of characterization of the drug substance has been provided. The structure of cefiderocol sulfate tosylate is confirmed by ^{1}H-NMR spectroscopy, ^{13}C-NMR spectroscopy, infrared spectroscopy, UV-visible absorption, mass spectrometry and elemental analysis. The specification for the drug substance includes tests for description, identification, assay, sulfuric acid, *p*-toluenesulfonic acid, related substances, residual solvent, residue on ignition, water content, bacterial endotoxins and microbiological examination. Batch analysis data from commercial scale batches of the drug substance are provided and the test results are within the specifications.

2.1.2 Drug product

Cefiderocol Powder for Solution for Infusion, 1 g/vial, is a sterile, white to off-white, lyophilized cake or powder containing 1 g of cefiderocol packaged in a single-use 14 mL clear glass vial. The excipients used in the drug product comply with compendial monographs.

The specification for the drug product includes description, identification, assay, clarity and color of solution, related substances, uniformity of dosage units, visible particulates in injections, particulate matter in injections, bacterial endotoxins, sterility, pH and water content. Batch analysis data from commercial scale batches of the drug product are provided and the test results are within the specifications. Analytical methods are described well and validated.

Stability studies of drug product under long term condition (2-8°C) and accelerated condition (25°C/60% RH) have been carried out. Up to 60 months of long-term and 6 months of accelerated stability data are submitted. Based on available stability data, the shelf life of drug product can be granted for 60 months under the storage condition of 2-8°C.

2.2 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

In vitro and *in vivo* primary pharmacodynamic studies demonstrated that cefiderocol exhibited potent antibacterial activity in a dose-dependent manner. It also improved outcomes in multidrug-resistant infection models. Secondary pharmacodynamic studies demonstrated that cefiderocol had no notable binding effects on a panel of off-targets.

Safety pharmacology studies identified that cefiderocol has no significant effects on respiratory systems. Regarding neurological function, cefiderocol did not affect EEG parameters but increased the convulsions incidence in rats. In terms of the cardiovascular system, cefiderocol prolonged QTc interval and increased blood pressure in monkeys. In general, the safety margins observed in these studies were sufficient compared to the exposures seen with the proposed human doses.

2.2.2 Toxicological Studies

Cefiderocol (IV, QD) was evaluated in GLP-compliant toxicity studies for up to 13 weeks in rats and monkeys. The common findings were chromaturia, abnormal erythrocyte-related parameters, local irritation at the injection site, and the changes in kidney. The NOAELs were 750 mg/kg/day in the 3-month rat study and 100 mg/kg/day in the 13-week monkey study, and the safety margins were sufficient compared to the exposure seen with the proposed human doses. Toxicity findings in rat and monkey pivotal studies partially recovered after the recovery period.

Based on the results of genotoxicity studies, it is unlikely that cefiderocol would cause genotoxicity. Carcinogenicity studies are not warranted according to ICH SI A. Reproductive and developmental toxicology and juvenile animal toxicology were evaluated. In general, cefiderocol had no significant effect on fertility, intrauterine growth, and embryo survival, pre-natal and post-natal development. Of note, cefiderocol appeared transferrable via the placenta but a relatively low amount (<0.5%) was noted in fetuses. In other toxicity studies, cefiderocol is neither phototoxic nor hemolytic. Although weak antigenicity of cefiderocol was noted in guinea pigs, the risks of anaphylaxis or specific antibody production against cefiderocol were considered low when the immune function was not enhanced by Freund's adjuvant.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

In healthy volunteers, the geometric mean cefiderocol C_{max} and AUC was 89.7 mg/L and 386 mg•hr/L, respectively, after a single FETROJA 2-gram dose was infused over 3 hours. Cefiderocol C_{max} and AUC increased proportionally with dose. Based on population PK analysis, the

geometric mean C_{max} and daily AUC estimates after intravenous infusion of 2-g cefiderocol q8h over 3 hours were 101 μg/mL and 1494 μg•hr/mL, respectively. The protein binding ratio at the concentration range from 1 to 1000 μg/mL ranged from 40.8% to 60.4% in human, which was predominantly bound to human serum albumin. The geometric mean volume of distribution during the terminal elimination phase (Vz) (%CV Geometric Mean) was 18.0 L (18.1%). Following a FETROJA 2-gram dose (or renal function equivalent dose) at steady state in patients with pneumonia requiring mechanical ventilation with a 3-hour infusion, the cefiderocol concentrations in epithelial lining fluid ranged from 3.1 to 20.7 mg/L and 7.2 to 15.9 mg/L at the end of infusion and at 2 hours after the end of infusion, respectively.

After single radiolabeled cefiderocol dose of 1 gram (0.5 times the approved recommended dosage) infused over 1 hour, cefiderocol is minimally metabolized (less than 10%) in plasma. Cefiderocol is primarily excreted by the kidneys. After a single radiolabeled cefiderocol 1-gram dose infused over 1 hour, 98.6% of the total radioactivity was excreted in urine (90.6% unchanged) and 2.8% in feces.

2.3.2 Interaction Studies

In in vitro studies, cefiderocol is not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4. Cefiderocol is not an inducer of CYP1A2, CYP2B6, or CYP3A4. In addition, cefiderocol is not an inhibitor of organic anion transporting polypeptide (OATP)1B1, multidrug and toxin extrusion (MATE)1, P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), or bile salt export pump transporters, cefiderocol is not a substrate of organic anion transporter (OAT)1, OAT3, organic cation transporter (OCT)2, MATE1, MATE2-K, P-gp, or BCRP.

In clinical study, no clinically significant differences in the pharmacokinetics of furosemide (OAT1 and OAT3 substrate), metformin (OCT1, OCT2, and MATE2-K substrate), and rosuvastatin (an OATP1B3 substrate) were observed when coadministered with cefiderocol.

2.3.3 Special Populations

According to population PK analysis, no clinically significant differences in the pharmacokinetics of cefiderocol were observed based on age (18 to 93 years of age) and sex. Although body weight remains to be a significant covariate of cefiderocol PK parameters, there is no clinically meaningful effect on cefiderocol PK. Therefore, it's determined that no cefiderocol dose adjustment based on age, sex and body weight are required.

After a single 1-gram dose (0.5 times the approved recommended dosage), cefiderocol AUC fold changes in subjects with renal impairment compared to subjects with CLcr 90 to 119 mL/min are 1.37-fold (1.15, 1.62) in subjects with CLcr 60 to 89 mL/min, 2.35-fold (2.00,

2.77) in subjects with CLcr 30 to 59 mL/min, 3.21-fold (2.64, 3.91) in subjects with CLcr 15 to 29 mL/min and 4.69-fold (3.95, 5.56) in subjects with CLcr < 15 mL/min. Increased cefiderocol clearance has been observed in patients with CLcr 120 mL/min or greater. In addition, a 2-gram dose every 6 hours infused over 3 hours provided cefiderocol exposures comparable to those in patients with CLcr 90 to 119 mL/min. Dosage adjustment is recommended in patients based on renal function. In an in vitro study, effluent flow rate was the major determinant of cefiderocol clearance by CRRT. Variables examined included effluent flow rate, CRRT mode (CVVH or CVVHD), filter type and point of dilution (pre- or post-filter dilution). The effluent flow rate-based dosing recommendations are predicted to provide cefiderocol exposures similar to those achieved with a dose of 2 grams given every 8 hours in patients not receiving CRRT.

The effects of hepatic impairment on the pharmacokinetics of cefiderocol have not been evaluated. Hepatic impairment is not expected to alter the elimination of cefiderocol as hepatic metabolism/excretion represents a minor pathway of elimination for cefiderocol. Dosage adjustments are not necessary in patients with impaired hepatic function.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

The main data package supporting the clinical efficacy of cefiderocol includes Study 1615R2132 [APEKS-NP] and Study 1409R2121 [APEKS-cUTI]. Study 1424R2131 [CREDIBLE-CR] provides descriptive data as the supplemental evidence in the treatment of infections caused by carbapenem resistant Gram-negative pathogens.

Two clinical studies had demonstrated non-inferiority of cefiderocol statistically. Study 1615R2132 [APEKS-NP] in adult subjects with documented nosocomial pneumonia caused by negative bacteria, demonstrated non-inferiority (margin 12.5%) of cefiderocol 2 g IV every 8 hours to meropenem 2 g IV every 8 hours in the all-cause mortality rate at Day 14 (12.4% (18/145) vs. 11.6% (17/146); difference (cefiderocol - meropenem) (95% CI): 0.8 (-6.6, 8.2)).

Study 1409R2121 [APEKS-cUTI] in adult subjects diagnosed with complicated urinary tract infection (cUTI) with or without pyelonephritis or acute uncomplicated pyelonephritis, demonstrated non-inferiority (margin -20% or -15%) of cefiderocol 2 g IV every 8 hours to imipenem/cilastatin 1 g IV every 8 hours in the composite endpoint of microbiological eradication and clinical response at TOC (test of cure) (72.6% (183/252) vs. 54.6% (65/119); difference (cefiderocol - imipenem/cilastatin) (95% CI): 18.58% (8.23, 28.92)).

2.4.2 Safety Results

The overall data supporting the clinical safety includes Study 1409R2121 [APEKS-cUTI], Study 1615R2132 [APEKS-NP]), Studies 1424R2131 [CREDIBLE-CR], and 7 clinical pharmacology studies. The key safety information comes from Study APEKS-cUTI, Study APEKS-NP, and Study CREDIBLE-CR. Among these three studies, a total of 435 subjects received the proposed dose of 2g q8h for 7 to 14 days.

In Study APEKS-cUTI, the safety profile was comparable between cefiderocol (n=300) and imipenem-cilastatin. Severe or serious adverse events were reported infrequently in this study (2% and 4.7% respectively). The most frequently reported individual preferred term for cefiderocol was diarrhea and hypertension (4.3% in each) followed by constipation (3.3%). In Study APEKS-NP, the overall frequency of TEAEs was comparable between cefiderocol (n=148) and meropenem. A total of 87.8% participants in the cefiderocol group reported at least 1 TEAE, 37.8% were severe, and 36.5% reported an SAE. The most frequently reported individual preferred terms for cefiderocol were urinary tract infection (15.5%), followed by hypokalaemia (less frequent than the comparator) and diarrhea (8.8%). TEAEs leading to death were reported in 26.4% (39/148) of participants treated with cefiderocol and 23.3% (35/150) of participants treated with meropenem.

Study CREDIBLE-CR enrolled infected patients with more severe clinical condition. The overall frequency of TEAEs, severe TEAEs and SAEs was similar between cefiderocol (N=101) and best available therapy (BAT). A total of 91.1% participants in the Cefiderocol group reported at least 1 TEAE, 42.6% were severe, and 49.5% reported an SAE. The most frequently reported individual preferred terms for cefiderocol were diarrhea (18.8%), followed by pyrexia, septic shock, and vomiting with all reported in >10% of subjects. There were 43 subjects in the CREDIBLE-CR study died, of which 33.7% (34/101) were treated with cefiderocol and 18.4% (9/49) were treated with BAT. A higher percentage of fatal SAEs was observed in the cefiderocol group than in the BAT group, specifically septic shock (10.9% vs 6.1%) and pneumonia (5.0% vs 0). Concerns for the imbalance of the between groups mortality will be addressed through the package insert.

Increased alanine aminotransferase was only observed among patients administered with cefiderocol in APEKS-cUTI and CREDIBLE-CR, but the absolute frequencies of preferred term were low. In Study APEKS-NP, the frequency of increased alanine aminotransferase was 6.1% in the cefiderocol group and 4.0% in the meropenem group. These were considered as a class effect of cephalosporins and effects on liver enzymes has been listed as an ADR in the proposed package insert. Other known adverse effects of cephalosporins (C. difficile-related diarrhoea, rash/hypersensitivity, seizures/epilepsy, and bone marrow suppression) were reported infrequently.

2.5 Bridging Study Evaluation

Ethnic difference of pharmacokinetic characteristics was evaluated based on the cross-study comparison and population PK analysis. The exposure observed in Japanese population was slightly lower than exposure in non-Japanese population in cross-study comparison. Based on the population PK analysis, the exposure in Asian population was slightly higher than western population. The minor difference in exposure between different ethnic groups was considered not clinically significant considering the inter-individual variability in both cross-study comparison and population PK analysis. , No steep pharmacodynamic (effect-concentration) relationship was found for both efficacy and safety in the range of the recommended dosage and dose regimen. The metabolism enzymes of cefiderocol were not known to show genetic polymorphism and it's not a prodrug.

In summary, the properties of cefiderocol are less likely to be sensitive to ethnic factors according to Appendix D in ICH E5 guideline. Meanwhile, no meaningful ethnic differences between Japanese and non-Japanese population in cross-study comparison and pop-PK analysis. Thus, cefiderocol showed none to minimally ethnically sensitive in PK aspect.

Clinical data of East Asian sub-populations (Taiwan, Japan, and Korea) in three clinical trials (Study 1615R2132 [APEKS-NP], Study 1409R2121 [APEKS-cUTI], and Study 1424R2131 [CREDIBLE-CR]) were used to assess ethnic differences. In addition, analysis of *in vitro* antimicrobial activities of cefiderocol against carbapenem non-susceptible Gram-negative pathogens isolated in Taiwan, Japan, the US, and Europe was provided. East Asian subpopulations consisted of 41 participants who received cefiderocol and 25 participants who received the active comparator. Subgroup analysis of clinical cure rate, microbiological eradication rate, and the safety characteristics in this limited subpopulation (mainly from Study CREDIBLE-CR) showed similar trend to the main population. Overall, the ethnic difference was considered minimal.

2.6 Conclusion

The overall benefit risk balance of Fetroja for Injection 1g (Cefiderocol) is favorable for the treatment of complicated urinary tract infections or hospital acquired bacterial pneumonia/ventilator associated bacterial pneumonia caused by susceptible Gram-negative microorganisms in adult patients. The recommended dosage of FETROJA is intravenous infusion with 2 grams every 8 hours, or adjusted according to the renal function.

3 · Post-Marketing Requirements

Nil