Taiwan Food and Drug Administration

Assessment Report

Trade Name：贊飛得注射劑 2 g/0.5 g
Zavicefta 2 g/0.5 g powder for concentrate for solution for infusion

Active Ingredient：ceftazidime/avibactam

License Number：MOHW-PI 027705

Applicant：輝瑞大藥廠股份有限公司

Approval Date：2019/07/23

Indication：

Zavicefta 適用於治療成人對 Zavicefta 具感受性的革蘭氏陰性微生物(susceptible Gram-negative microorganisms)所引起的下列感染：

- **複雜性腹腔內感染(complicated intra-abdominal infection，cIAI)**
- **複雜性泌尿道感染(complicated urinary tract infection，cUTI)，包括腎盂腎炎(pyelonephritis)**
- **院內感染型肺炎(Hospital-acquired pneumonia，HAP)，包括呼吸器相關肺炎(ventilator associated pneumonia，VAP)**

應考量抗生素的使用準則來合理使用抗生素製劑。

Zavicefta is indicated in adults for the treatment of the following infections caused by designated susceptible Gram-negative microorganisms:

- **Complicated intra-abdominal infection (cIAI)**
- **Complicated urinary tract infection (cUTI), including pyelonephritis**
- **Hospital-acquired pneumonia (HAP), including ventilator associated pneumonia (VAP)**

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

1. **Background Information**

Trade Name	贊飛得注射劑 2 g/0.5 g Zavicefta 2 g/0.5 g powder for concentrate for solution for infusion
Active Ingredient(s)	ceftazidime/avibactam
Applicant	輝瑞大藥廠股份有限公司
Dosage Form & Strengths	Powder for concentrate for solution for infusion (powder for concentrate) 2g/0.5g
Indication	Zavicefta 適用於治療成人對 Zavicefta 具感受性的革蘭氏陰性微生物(susceptible Gram-negative microorganisms)所引起的下列感染： • 複雜性腹腔內感染(complicated intra-abdominal infection，cIAI) • 複雜性泌尿道感染(complicated urinary tract infection，cUTI)，包括腎盂腎炎(pyelonephritis) • 院內感染型肺炎(Hospital-acquired pneumonia，HAP)，包括呼吸器相關肺炎(ventilator associated pneumonia，VAP) 應考量抗生素的使用準則來合理使用抗生素製劑。 Zavicefta is indicated in adults for the treatment of the following infections caused by designated susceptible Gram-negative microorganisms: • Complicated intra-abdominal infection (cIAI) • Complicated urinary tract infection (cUTI), including pyelonephritis • Hospital-acquired pneumonia (HAP), including ventilator associated pneumonia (VAP) Consideration should be given to official guidance on the appropriate use of antibacterial agents.

Posology	See product information
Pharmacological Category **ATC Code**	J01DD52

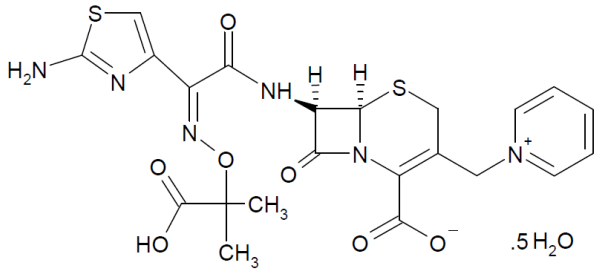
2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug substance

Ceftazidime pentahydrate

The drug substance, ceftazidime pentahydrate, is chemically designated as (Z)-7-[2-(2-amino-1,3-thiazol-4-yl)-2-(1-carboxy-1-methylethyloxyimino)acetylamino]-3-(1-pyridiniumylmethyl)-3-cephem-4-carboxylate pentahydrate and has the following structure:



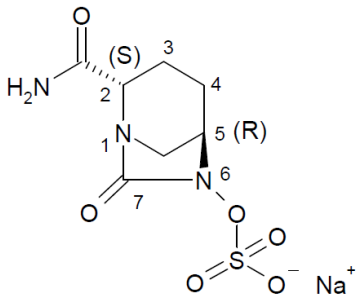
It is a white to almost white crystalline powder. The molecular formula and the molecular weight are $C_{22}H_{22}N_6O_7S_2.5H_2O$ and 636.7, respectively. The structure of drug substance has two chiral centers. Ceftazidime pentahydrate is non-hygroscopic.

The specification for the drug substance includes tests for appearance, identification, residual solvents, water content, colour of solution, clarity of solution, pH of solution, impurities, heavy metals, assay, sterility and bacterial endotoxins.

Batch analysis data on three batches of the drug substance were provided. The results were within the specifications and consistent from batch to batch.

Avibactam sodium

The drug substance, avibactam sodium, is chemically designated as sodium; [(2S,5R)-2-carbamoyl-7-oxo-1,6-diazabicyclo[3.2.1]octan-6-yl] sulfate and has the following structure:



It is a white to pale yellow powder. The molecular formula and the molecular weight are $C_7H_{10}N_3O_6SNa$ and 287.23, respectively. The structure of drug substance has three chiral centers. Avibactam sodium is hygroscopic.

Adequate information of characterization of the drug substance has been provided. The structure of avibactam sodium is confirmed by IR spectrum, nuclear magnetic resonance (NMR) spectroscopy, X-ray crystallography and mass spectrometry (MS). The specification for the drug substance includes tests for appearance, identification, residual solvents, water content, sodium, impurities, enantiomeric impurity, assay, sterility and bacterial endotoxins.

2.1.2 Drug product

Zavicefta powder (Zavicefta powder for concentrate for solution for infusion) is a powder containing 2 g of ceftazidime and 0.5 g of avibactam packaged in a glass vial. All excipients used in the drug product formulation comply with compendial monographs or in-house specification. The established operating parameters and test results are acceptable.

The release specification for the drug product includes appearance, reconstitution time, pH (reconstituted solution), identification, ceftazidime assay, avibactam assay, degradation products, uniformity of dosage units, particulate matter, water content, sterility and bacterial endotoxins. Analytical methods are described well and validated.

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

2.2 Preclinical Pharmacology/Toxicology Evaluation

Since ceftazidime has been a generic drug and had a large amount of human experience, this review focused on the nonclinical efficacy and safety of avibactam and the ceftazidime/avibactam combination.

2.2.1 Pharmacological Studies

Avibactam was developed as a novel non-β-lactam β-lactamase inhibitor, which was with a

spectrum of activity encompassing clinically relevant β-lactamases of Ambler Class A and Class C varieties, including extended spectrum β-lactamases and serine-based Klebsiella pneumoniae carbapenemases. On the other hand, avibactam showed inhibitory effects on some Ambler Class D β-lactamases but not on Ambler Class B metallo-β-lactamases.

The in vitro and in vivo studies showed that avibactam did not significantly affect the antibacterial activity of ceftazidime and restored the activity of ceftazidime against ceftazidime-resistant microorganisms. No significant activity of avibactam on inhibition of examined receptors/enzymes was detected.

Safety pharmacology studies were conducted with avibactam alone. A dose-dependent low incidence of reduced muscle tone and decreased reactivity to touch were noted in rats. Rats treated with high dose of avibactam also exhibited significant changes in gastrointestinal (delay in mean intestinal transit) and renal (increase in sodium excretion) system. However, no safety concerns for vital signs have been noted in clinical studies, and gastrointestinal effects have been reported clinically. No adverse effects on safety endpoints in regard to respiratory or cardiovascular system in rats as well as in vitro hERG assay were noted up to the highest dose examined.

2.2.2 Toxicological Studies

In general toxicity studies, the major toxicological effect of avibactam/ceftazidime combination in the rat 4-week combination study was severe local intolerance, whilst less severe local intolerance was observed in the dog 4-week combination study.

Avibactam had no adverse effects on fertility of rats up to the highest dose examined. In mid and high dose groups, a slight dose-related increase in the percentage of pre-and post-implantation loss relative to controls, resulting in a slightly lower mean litter size, was noted. Avibactam was not teratogenic in rats or rabbits. In a pre- and post-natal development study in rats, a dose-related dilatation of the ureters and the renal pelvis at the mid and high dose groups was noted. No significant changes related to avibactam/ceftazidime combination were noted in the juvenile study in rats at the highest dose examined.

Avibactam was considered non-genotoxic based on the bacterial reverse mutation assay, in vitro unscheduled DNA synthesis assay, in vitro chromosome aberration test, and in vitro and in vivo micronucleus assay. It is acceptable that no additional studies are conducted with ceftazidime or the ceftazidime/avibactam combination for genotoxicity studies. It is also acceptable that no carcinogenicity studies have been conducted due to the short treatment duration in humans. No immunotoxicity, phototoxicity or hemolytic potential was found under the examined condition.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

Zavicefta powder for concentrate for solution for infusion contained two active ingredients, ceftazidime pentahydrate and avibactam sodium (CAZ-AVI). Ceftazidime belongs to third-generation cephalosporin and has already marketed in Taiwan. Avibactam is a novel non-β-lactam inhibitor of serine β-lactamases.

There was no DDI between ceftazidime and avibactam. Pharmacokinetic parameters of ceftazidime and avibactam were similar for single and multiple dose administration of combination and were similar to those determined when ceftazidime or avibactam were administered alone. The ceftazidime and avibactam peak concentration can reach quickly (about 2 hour) after single and multiple 2-hour intravenous infusions of ceftazidime/avibactam administered every 8 hours. The C_{max} and AUC of ceftazidime and avibactam increased in proportion to dose. The human plasma protein bound rate of both ceftazidime and avibactam were low (<10% and 5.7%~8.2%). Ceftazidime is not metabolized. No metabolism of avibactam was observed in human liver preparations (microsomes and hepatocytes). Both ceftazidime and avibactam are excreted mainly by the kidneys.

2.3.2 Interaction Studies

Avibactam is a substrate of OAT1 and OAT3 transporter *in vitro*. One *in vitro* study showed that probenecid (a potent OAT inhibitor) inhibits OAT uptake of avibactam. Because a clinical DDI study between avibactam or ceftazidime/avibactam and probenecid was absent, co-administration of ceftazidime/avibactam with probenecid is not recommended. There was no DDI between ceftazidime/avibactam and metronidazole.

2.3.3 Special Populations

The effect of renal impairment on the PK of avibactam was evaluated. The results showed that the AUC of avibactam increased 2.6-fold, 3.8-fold, 7-fold and 19.5-fold in subjects with mild (CrCl 50 to 79 mL/min), moderate (CrCl 30 to 49 mL/min), severe (CrCl <30 mL/min) renal impairment and subjects with ESRD requiring hemodialysis , compared to subjects with normal renal function. Dosage adjustment of Zavicefta is required in adult patients with moderate or severe renal dysfunction (CrCl $\leqq$ 50 mL/min), please referred to Chinese labeling to see the detailed posology. This adjustment was based on population PK simulation. Besides, avibactam can be removed from plasma by hemodialysis, thus, it is recommended that Zavicefta is administered after hemodialysis in patients with ESRD. The PK of avibactam in patients with hepatic impairment has not been established. Considering the metabolism pathway of both drugs, the effects of hepatic impairment on the PK of ceftazidime

and avibactam were expected to be minor. No dosage adjustment is required in patients with hepatic impairment.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

A total of five pivotal studies (RECLAIM, RECLAIM3, RECAPTURE, REPRISE and REPROVE) were reviewed to evaluate the efficacy of Zavicefta (Ceftazidime-avibactam, also known as CAZ-AVI) for the treatment of adults with complicated intra-abdominal infections (cIAIs), complicated urinary tract infections (cUTIs) [including pyelonephritis], and hospital-acquired pneumonia (HAP) [including ventilator- associated pneumonia (VAP)].

Complicated intra-abdominal infections

As for the indication in adults with cIAIs, two Phase 3, multinational, multicenter, randomized, double-blind comparative studies (RECLAIM and RECLAIM3) were reviewed to determine the efficacy of CAZ-AVI plus metronidazole (MTZ) versus meropenem.

Efficacy results of Study [RECLAIM]

In the mMITT analysis set, the clinical cure rates at test-of-cure (TOC) visit in the CAZ-AVI plus MTZ group and in the meropenem group were 81.6% and 85.1%, respectively (difference -3.5%; 95% CI: -8.64 to 1.58). For the MITT analysis set, the clinical cure rates at TOC were 82.5% and 84.9%, respectively (difference -2.4%; 95% CI: -6.90 to 2.10). In the CE at TOC analysis set, the clinical cure rates at TOC were 91.7% and 92.5%, respectively (difference -0.8%; 95% CI: -4.61 to 2.89).

The non-inferiority of CAZ-AVI compared with meropenem was demonstrated in clinical response at the TOC visit because+ the lower limit of the 95% CI of the treatment difference was greater than the pre-defined non-inferiority margin of -12.5% in the ROW (Rest of World except United States) co-primary analysis sets (MITT and CE) and in the US FDA primary analysis set (mMITT). Furthermore, in the mMITT set the noninferiority was demonstrated using the 10% margin as requested by US FDA.

Efficacy results of Study [RECLAIM3]

For the CE at TOC analysis set, the clinical cure rates at TOC in the CAZ-AVI plus MTZ group and in the meropenem group were 93.8% and 94.0%, respectively (difference -0.2%; 95% CI: -5.53 to 4.97). The non-inferiority was demonstrated because the lower limit of the 95% CI of the treatment difference was greater than the pre-defined non-inferiority margin of -12.5%

Complicated urinary tract infections

As for the indication in adults with cUTI, two studies (RECAPTURE and REPRISE) were reviewed. RECAPTURE was a Phase 3, prospective, randomized, multicenter, double-blind, double-dummy, parallel-group, comparative study to demonstrate the efficacy of CAZ-AVI compared with doripenem in the treatment of hospitalized patients with cUTIs. REPRISE was a Phase 3, randomized, multicenter, open-label study to evaluate CAZ-AVI and best available therapy (BAT) for the treatment of complicated intra-abdominal infection or cUTI due to CAZ-resistant Gram-negative pathogens.

Efficacy results of Study [RECAPTURE]

In the mMITT analysis set, the proportion of patients reporting symptomatic resolution of UTI-specific symptoms (except flank pain) and resolution of or improvement in flank pain at the Day 5 visit in the CAZ-AVI group and in the doripenem group was 70.2% and 66.2%, respectively (difference 4.0%; 95% CI: -2.39 to 10.42). The proportion of patients with microbiological eradication who also reported symptomatic resolution of all UTI-specific symptoms at the TOC visit was 71.2% and 64.5%, respectively (difference 6.7%; 95% CI: 0.30 to 13.12). In terms of the ROW primary objective, the proportion of patients with a favorable per-patient microbiological response at the TOC visit was 77.4% and 71.0%, respectively (difference 6.4%; 95% CI: 0.33 to 12.36). These results provided adequate evidence to support the non-inferiority either using a margin of 12.5% or 10%.

Efficacy results of Study [REPRISE]

The proportion of cUTI patients (the majority [281/302] patients in REPRISE were cUTI patients) with clinical cure at the TOC visit was 91.7% (95% CI: 86.3 to 95.4) in the CAZ-AVI group and 94.2% (95% CI: 89.3 to 97.2) in the BAT group.

Hospital-acquired pneumonia

Study [REPROVE] was a Phase 3, prospective, randomized, multicenter, double-blind, double dummy, parallel-group, comparative study to determine the efficacy of CAZ-AVI versus meropenem in the treatment of adults with HAP, including VAP.

For the cMITT analysis set, the clinical cure rates at TOC were 68.8% in the CAZ-AVI group and 73.0% in the meropenem group (difference -4.2%, 95% CI: -10.76 to 2.46). For the CE analysis set, the clinical cure rates at TOC were 77.4% and 78.1%, respectively (difference -0.7%, 95% CI: -7.86 to 6.39). The non-inferiority was demonstrated in the cMITT and CE analysis sets because the lower limits of the 95% CI of the treatment difference were greater than the pre-defined margin of -12.5%.

Antimicrobial Susceptibility Testing in Taiwan

The sponsor also provided INFORM Global Surveillance of 2017 to demonstrate in vitro

activity of CAZ-AVI against contemporary clinical isolates collected from medical centers in Taiwan. The MIC results showed most G(-) microorganisms related to cUTI or cIAI are susceptible to CAZ-AVI.

2.4.2 Safety Results

The incidence of all AEs, SAE, discontinuation due to AE, and AE leading to death was comparable between treatment groups. The majority of AEs were mild to moderate in intensity and generally comparable across the treatment groups. The most common AEs ≥5% among patients exposed to CAZ-AVI were Coombs direct test positive, nausea, and diarrhea.

The risks related to ZAVICEFTA included hypersensitivity reactions, *C. difficile*-associated diarrhea, use in patients with renal impairment who do not receive the appropriate dose, hemolytic anemia. The proportion of patients exposed to CAZ-AVI with aforementioned risks was consistent with the known experience of ceftazidime. No new safety concerns were identified for CAZ-AVI.

2.5 Bridging Study Evaluation

From PK perspective, a cross-study comparison between Asian and non-Asian PK was made from 3 studies. The exposure ($C_{ss,max}$ and AUC_{ss}) of ceftazidime and avibactam in Japanese and Chinese healthy volunteers was slightly higher than that in the non-Asian healthy volunteers. It may be caused by differences in body weight. Population PK model estimated the exposure of ceftazidime and avibactam in phase 3 patients. The exposure was highest in Japanese group and lowest in the combined Caucasian/Other group, with Japanese having 32% to 35% higher $C_{ss,max}$ and approximately 21% higher $AUC_{ss,0-24}$ compared with Caucasians/Others. Among Asian patients, the predicted exposure was generally highest in Japanese patients and lowest in Chinese and Taiwanese patients (the difference of $C_{ss,max}$ and $AUC_{ss,0-24}$ for ceftazidime were 16~17%, and for avibactam were 9~10%). Overall, the avibactam was not considered ethnic sensitive on the basis of no significant exposure difference of avibactam between Asian and non-Asian, no in vitro metabolism of avibactam thus not dependent on enzymes known to show genetic polymorphism, no significant accumulation of ceftazidime/avibactam following multiple intravenous infusions of ceftazidime/avibactam and low inter-subject variability.

From clinical perspective, the proportion of Asians pooled from the 5 pivotal studies was 25.5%, all from East Asian or Southeast Asian regions. Among the 5 pivotal studies, RECLAIM3 Study enrolled Asians only. Based on the comparison of clinical data between East-Asian and Westerner subgroups, no ethnic difference with clinical impact was found.

In conclusion, there is no important ethnic difference considering factors such as PK/PD,

microbiology, efficacy or safety. Bridging study waive was recommended.

2.6 Conclusion

The benefit risk ratio is considered positive for the intended population.

ZAVICEFTA is approved in adults for the following indications:

-Complicated intra-abdominal infection (cIAI)

-Complicated urinary tract infection (cUTI), including pyelonephritis

-Hospital-acquired pneumonia (HAP), including ventilator associated pneumonia (VAP)

3. Post-Marketing Requirements

Routine pharmacovigilance is required.