Taiwan Food and Drug Administration

Assessment Report

Trade Name：依嘉凍晶乾燥注射劑 50 毫克 /
Xerava powder for injection 50 mg

Active Ingredient：Eravacycline

License Number：MOHW-PW-028576

Applicant：台灣東洋藥品工業股份有限公司

Approval Date：112/09/21

Indication：
適用於治療由以下具感受性之微生物所引起的成人複雜性腹腔內感染(cIAI)：大腸桿菌(*Escherichia coli*)、克雷伯氏肺炎菌(*Klebsiella pneumoniae*)、弗氏檸檬酸桿菌(*Citrobacter freundii*)、陰溝腸桿菌(*Enterobacter cloacae*)、產酸克雷伯氏菌(*Klebsiella oxytoca*)、糞腸球菌(*Enterococcus faecalis*)、屎腸球菌(*Enterococcus faecium*)、金黃色葡萄球菌(*Staphylococcus aureus*)、咽峽炎鏈球菌群(*Streptococcus anginosus group*)、產氣莢膜芽胞梭菌 (*Clostridium perfringens*)、類桿菌屬 (*Bacteroides species*) 和狄氏副類桿菌 (*Parabacteroides distasonis*)。

XERAVA is indicated for the treatment of complicated intra-abdominal infections (cIAI) caused by susceptible microorganisms: *Escherichia coli, Klebsiella pneumoniae, Citrobacter freundii, Enterobacter cloacae, Klebsiella oxytoca, Enterococcus faecalis, Enterococcus faecium, Staphylococcus aureus, Streptococcus anginosus group, Clostridium perfringens, Bacteroides species,* and *Parabacteroides distasonis* in adult patients.

Background Information

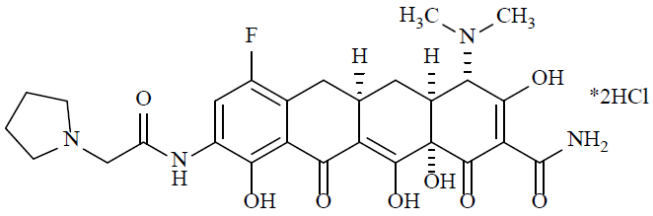
Trade Name	依嘉凍晶乾燥注射劑 50 毫克 / Xerava powder for injection 50 mg
Active Ingredient(s)	Eravacycline
Applicant	台灣東洋藥品工業股份有限公司
Dosage Form & Strengths	凍晶乾燥注射劑 50 mg/vial
Indication	適用於治療由以下具感受性之微生物所引起的成人複雜性腹腔內感染(cIAI)：大腸桿菌(*Escherichia coli*)、克雷伯氏肺炎菌(*Klebsiella pneumoniae*)、弗氏檸檬酸桿菌(*Citrobacter freundii*)、陰溝腸桿菌(*Enterobacter cloacae*)、產酸克雷伯氏菌(*Klebsiella oxytoca*)、糞腸球菌(*Enterococcus faecalis*)、屎腸球菌(*Enterococcus faecium*)、金黃色葡萄球菌(*Staphylococcus aureus*)、咽峽炎鏈球菌群(*Streptococcus anginosus group*)、產氣莢膜芽胞梭菌 (*Clostridium perfringens*)、類桿菌屬(*Bacteroides species*)和狄氏副類桿菌 (*Parabacteroides distasonis*)。 XERAVA is indicated for the treatment of complicated intra-abdominal infections (cIAI) caused by susceptible microorganisms: *Escherichia coli, Klebsiella pneumoniae, Citrobacter freundii, Enterobacter cloacae, Klebsiella oxytoca, Enterococcus faecalis, Enterococcus faecium, Staphylococcus aureus, Streptococcus anginosus group, Clostridium perfringens, Bacteroides species, and Parabacteroides distasonis* in adult patients.
Posology	詳見仿單
Pharmacological Category **ATC Code**	J01AA13

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug Substance

The drug substance, eravacycline dihydrochloride, is chemically designated as [(4*S*,4a*S*,5a*R*,12a*S*)-4-(dimethylamino)-7-fluoro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[2-(pyrrolidin-1-yl)acetamido]-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide] dihydrochloride and has the following structure:



It is a pale yellow to orange solid. The molecular formula and the molecular weight are $C_{27}H_{31}FN_4O_8 \cdot 2HCl$ and 631.48 g/mol, respectively.

Adequate information of characterization of the drug substance has been provided. The molecular structure of eravacycline dihydrochloride has been confirmed by infrared spectrophotometry (IR), nuclear magnetic resonance (NMR), mass spectrometry (MS) and UV spectrophotometry. Stereochemistry is determined by single crystal X-ray diffraction analysis.

Adequate specification has been presented for the drug substance and the test items include appearance, identification, chloride content, polymorph, assay, impurities, residual solvent, moisture content, specific optical rotation, endotoxin, bioburden. 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

The drug product is provided as a lyophilized powder for intravenous use after reconstitution and dilution. The drug product is packaged in a type I glass vial with chlorobutyl rubber stopper and aluminum flip-off seal. Each vial contains 50 mg eravacycline freebase. A 3 mg overfill of eravacycline is applied to allow the withdrawal of 50 mg eravacycline freebase. The lyophilized powder is reconstituted with a volume of 5 mL of sterile water for injections (WFI) to deliver 10 mg/mL solution of eravacycline. For administration, the reconstituted solution is further diluted with 0.9% sodium chloride for injection to a target concentration of 0.3 mg/mL.

The specifications for excipients used in the drug product formulation are adequate.

Adequate specification has been presented for the drug product and the test items include appearance of container, appearance of lyophilizate, appearance of reconstituted solution, visible particles, identification assay, impurities, content uniformity, residual water, pH of reconstituted solution, particulate matter, endotoxins, sterility, and reconstitution time. Analytical methods are described well and validated.

Stability studies of the drug product under long-term conditions (5°C ± 3°C) and accelerated condition (25 ± 2°C/60 ± 5% RH) have been carried out. Up to 36 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 36 months under the storage condition of 2-8°C.

2.2 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

Pharmacodynamic studies support eravacycline use in complex intra-abdominal infections (cIAI), effectively countering a broad range of Gram-negative and positive pathogens, including multidrug-resistant organisms. Eravacycline exhibits high activity against both hospital- and community-acquired methicillin-resistant/susceptible S. aureus strains, vancomycin-resistant/susceptible Enterococcus faecium and Enterococcus faecalis, and penicillin-resistant/susceptible isolates of Streptococcus pneumoniae. Eravacycline showed efficacy in mouse septicemia models, with PD50 values of ≤1 mg/kg daily against S. aureus and Streptococcus pyogenes, including tetracycline-resistant isolates. Eravacycline was also equivalent or more effective than tigecycline in certain mouse models. Eravacycline demonstrated in vitro potency against potential bioweapon pathogens and was effective in respiratory infection models in rabbits and monkeys. An in vitro study did not indicate significant off-target risks.

Safety pharmacology studies showed that eravacycline had no cardiovascular or respiratory effects in dogs after intravenous administration, with a NOEL of 5 mg/kg. A single intravenous dose in rats to examine CNS effects resulted in a NOEL of 4 mg/kg. The NOELs in these in vivo studies represent sufficient eravacycline safety margins. In an in vitro GLP hERG study, the IC50 was not reached even at the highest concentration of 22.2 μM (equivalent to >14.0 μg/mL).

2.2.2 Toxicological Studies

Eravacycline was evaluated in pivotal repeated-dose toxicity studies following i.v. administration up to 40 mg/kg/day in rats and 18 mg/kg/day in cynomolgus monkeys for up to 13 weeks. In the 13-week repeated-dose toxicity studies, the NOAEL was 4 mg/kg/day in monkeys, 16 mg/kg/day in female rats, and 4 mg/kg/day in male rats. Histopathological findings included changes in the gastrointestinal tract (monkey), the bone marrow and

lymphoid tissues (rat and monkey), and the male reproductive system (rat). Most findings in rats were related to histamine intolerance. Eravacycline was not genotoxic in a standard battery of in vitro and in vivo assays. The carcinogenic potential of eravacycline was not evaluated based on the short-term, intermittent use clinically.

Eravacycline did not affect mating or fertility in male rats following intravenous administration at a dose approximating a clinical dose of 0.65 mg/kg/day; however, eravacycline administration at higher doses was associated with adverse reactions on male fertility and spermatogenesis that were at least partially reversible after a 70-day recovery period (1 spermatogenic cycle).

In an embryo-fetal developmental study in rats, rats given 5 mg/kg/day eravacycline exhibited maternal toxicity (reduced body weight and food consumption, and clinical observations). Fetal weight was reduced at 5 and 10 mg/kg/day eravacycline doses, with a delay in skeletal ossification. The NOAEL for maternal and developmental toxicity was 3 mg/kg/day. In a rabbit embryo-fetal study, eravacycline at 4 mg/kg/day led to decreased maternal body weight, food consumption, and abortions. Developmental toxicity included increased post-implantation loss, a dead fetus, reduced fetal weight, and fewer ossified phalanges. The NOAEL for maternal and developmental toxicity was 2 mg/kg/day.

In the pre- and postnatal development study in rats, the NOAEL was 5 mg/kg/day for general toxicity and 10 mg/kg/day for reproductive toxicity. The NOAEL for both toxicity and reproduction in the F1 generation and F2 fetuses was also 10 mg/kg/day. On lactation day 15, eravacycline and its metabolites were measured in milk, with the concentration varying based on the administered dose. Juvenile toxicity studies revealed no new adverse effects compared to adult animals. However, juveniles might be more susceptible to eravacycline-induced toxicity. Immunotoxic effects were observed in various studies with eravacycline. While these effects were reversible in rats, they partially recovered in dogs and monkeys. In an in vivo study in pigmented rats, repeated i.v. administrations of 40 mg/kg/day eravacycline were not phototoxic.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

Maximum plasma concentrations are observed at the end of infusion, and the C_{max} and AUC of eravacycline (TP-434) in healthy adults increased with dose from 1 mg/kg to 3 mg/kg. After multiple dosing, an accumulation of ~45% was seen when eravacycline was administered at 1.0 mg/kg IV as a 60-minute infusion q12h for 10 days. Steady-state is reached by Day 5. The mean V_d at steady-state in healthy subjects following 10 days of 1 mg/kg q12h is ~321 L.

The binding of eravacycline to plasma proteins is low and highly variable with the f_u decreasing from 21% at 0.1 μg/mL to 2.4% at 100 μg/mL in human plasma. Eravacycline was distributed into lung compartments (epithelial lining fluid [ELF] and AM). Unchanged eravacycline is the major drug-related component in human plasma and human urine after a single IV dose. Eravacycline is metabolized primarily by CYP3A4- and FMO-mediated oxidation of the pyrrolidine ring to TP-6208 which is not considered to be pharmacologically active. Renal clearance and biliary and direct intestinal excretion account for approximately 34% and 47% of total body clearance after administration of a single IV dose of 60 mg ^{14}C-eravacycline, respectively. Mean clearance were similar after single or multiple doses, ranging from 11.06 to 15.81 L/h. Mean half-life was estimated to be 18 to 23 h from the population PK model.

Based on the flat exposure-response relationship observed in clinical studies, eravacycline exposure achieved with the recommended dosage regimen appears to be on the plateau of the exposure-response curve.

2.3.2 Interaction Studies

In vitro studies indicated eravacycline is not an inhibitor of CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A4/5. Eravacycline is not an inducer of CYP1A2, 2B6, or 3A4. Eravacycline is not an inhibitor of BCRP, BSEP, OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2, MATE1, or MATE2-K transporters.

Changes in CYP3A4/5 activity have modest effects on the PK of eravacycline. In Study TP-434-016, for subjects who had PK parameters in mono and combination treatment, the ratio of geometric mean (with 90% CI) of eravacycline plus itraconazole over eravacycline alone was 107.88% (97.83%, 118.96%) for C_{max} and 134.28% (124.13%, 145.26%) for $AUC_{0\text{-}t}$. In Study TP-434-020, the ratio of geometric mean (with 90% CI) of eravacycline plus rifampin over eravacycline alone was 106.47% (97.97%, 115.70%) for C_{max} and 67.92% (63.49%, 72.67%) for $AUC_{0\text{-}t}$.

2.3.3 Special Populations

The final population PK model for eravacycline showed that sex or race did not appear to be intrinsic factors which affected exposure. Body weight, age, and hepatic impairment were covariates that influenced clearance and exposure, while the covariates ESRD, cIAI or cUTI did not have a marked effect. In Study TP-434-013, the geometric mean $AUC_{0\text{-}inf}$ for eravacycline was increased by 22.9%, 37.9%, and 110.3% for subjects with mild (Child-Pugh Class A), moderate (Child-Pugh Class B), and severe (Child-Pugh Class C) hepatic impairment versus healthy subjects, respectively. In Study TP-434-014, exposure

parameters are similar in healthy subjects and patients with ESRD, with mean C_{max} increasing 8.8% and $AUC_{0\text{-}inf}$ decreasing 4%, respectively.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

In this submission, the Sponsor provided three phase III studies (TP-434-008, TP-434-025 and TP-434-EM-003) to support the efficacy of eravacycline for the claimed indication. The major design features and results of three studies were summarized as follows:

- ***Study TP-434-008:***

This was a phase III, randomized, double-blind, double-dummy, multicenter study in subjects with complicated intra-abdominal infections (cIAI) requiring surgery or percutaneous drainage to assess the efficacy and safety of eravacycline compared with ertapenem.

The primary efficacy endpoint for the EMA, clinical response at the test-of-cure (TOC) visit, was evaluated in the modified intent-to-treat (MITT) and CE-TOC populations. Clinical response is classified by the investigator as cure, failure or indeterminate. The difference in clinical cure rates between the eravacycline and ertapenem groups in the MITT population at the TOC visit was -1.8% (99% CI: -9.2%, 5.6%). The difference in clinical cure rates between the eravacycline and ertapenem groups in the CE population at the TOC visit population was -1.7% (99% CI: -7.9%, 4.4%). Since the lower limits of the 99% CIs in both the MITT and CE populations exceeded the NI margin of -12.5%, NI of eravacycline to ertapenem was declared.

The primary efficacy endpoint for the US FDA, clinical response at the TOC Visit, was evaluated in the microbiological Intent-to-Treat (micro-ITT) population. The difference in clinical cure rates between the eravacycline and ertapenem groups in this population at the TOC visit was -0.8% (95% CI: -7.1%, 5.5%). The lower limit of the 95% CI was -7.1%, exceeding the established NI margin of -10%. Thus, eravacycline was confirmed to be NI to ertapenem.

- ***Study TP-434-025:***

This was a phase III, randomized, double-blind, double-dummy, multicenter study in hospitalized subjects with cIAIs requiring surgery or percutaneous drainage to assess the efficacy and safety.

The primary efficacy endpoint for the EMA, clinical response at the TOC visit, was evaluated

in the MITT and CE-TOC populations. The difference in clinical cure rates between the eravacycline and meropenem groups in the MITT population at the TOC visit was 0.8% (95% CI: -4.1%, 5.8%). The difference in clinical cure rates between the eravacycline and ertapenem groups in the CE population at the TOC visit population was 0.8% (99% CI: -2.9%, 4.5%). Since the lower limits of the 95% CIs in both the MITT and CE populations exceeded the NI margin of -12.5%, NI of eravacycline to meropenem was declared.

The primary efficacy endpoint for the US FDA, clinical response at the TOC Visit, was evaluated in the microbiological Intent-to-Treat (micro-ITT) population. The difference in clinical cure rates between the eravacycline and ertapenem groups in this population at the TOC visit was -0.5% (95% CI: -6.3%, 5.3%). The lower limit of the 95% CI was -6.3%, exceeding the established NI margin of -12.5%. Thus, eravacycline was confirmed to be NI to meropenem.

- ***Study TP-434-EM-003:***

This is a phase III, prospective, randomized, multi-center, double-blind, double-dummy, parallel-controlled study in China to evaluate the efficacy and safety of eravacycline versus ertapenem in the treatment of cIAI in adults.

The primary efficacy endpoint of this study was the clinical cure rate of subjects at the TOC visit in the MITT population. The difference in the cure rates between the two groups (eravacycline group—ertapenem group) was -12.5%, which is lower than the pre-specified threshold for consistency evaluation of -7.15%.

Based on the prior results of the global trial TP-434-008, the 95% credible interval of the difference in the clinical cure rate at the TOC visit between the eravacycline group and the ertapenem group was from -20.97% to 0.22%. The lower limit of the 95% credible interval is less than the pre-specified non-inferiority margin of -12.5%.

2.4.2 Safety Results

The safety of eravacycline has been evaluated in 20 clinical studies involving 1176 subjects in the all Phase 2/Phase 3 pool. Of subjects in the "cIAI only pool", 576 subjects were treated with eravacycline 1.0 mg/kg q12h, the intended commercial dose. In the all Phase 2/Phase 3 pool, the most commonly reported TEAEs in both the eravacycline and comparator-treated subjects were in the System-Organ-Classes (SOC) of "Gastrointestinal disorders" and included preferred terms (PTs) of nausea, vomiting, and diarrhea. Nausea (11.5% vs 1.9%) is expected adverse effects of the tetracycline class, were typically observed between 2 and 7 days after treatment initiation. Within the SOC of "General disorders and administration site

conditions", more eravacycline -treated subjects than comparator-treated subjects experienced infusion site phlebitis (1.5% vs 0.3%) which were mild or moderate in severity and infrequently led to discontinuation of study drug. Within the SOC of Investigations, lipase increased (1.0%), amylase increased (0.7%), and aPTT prolonged (0.3%) were more frequently captured as treatment emergent adverse events (TEAEs) in eravacycline -treated subjects than in the comparator-treated subjects, although the percentages were low (<1%).

Five (5) eravacycline -treated subjects and 2 comparator-treated subjects satisfied laboratory criteria for potential drug-induced liver injury as defined in Hy's Law. All cases with alternative causes for the abnormalities. The overall incidence of serious TEAEs was similar for eravacycline and comparator in the All Phase 2/Phase 3 Pool. Deaths were reported for 11 (0.9%) subjects who received eravacycline treatment and 7 (0.7%) subjects who received comparator treatment. The only individual TEAE by preferred term with fatal outcome that was reported in more than 1 subject was pulmonary embolism, experienced by 2 subjects in the comparator treatment group. None of the serious AEs or deaths were considered related to eravacycline treatment.

Subgroup analysis on the safety of eravacycline in the all Phase 2/Phase 3 pool did not reveal any significant impact with respect to age, gender, race, ethnicity, BMI, APACHE II score, renal function, or hepatic function. No new safety concerns were observed with eravacycline that would not typically be expected for a tetracycline-class antibiotic. Therefore, the main risks associated with eravacycline are similar to other antibacterial drugs belonging to the tetracycline class. These risks include hypersensitivity reactions, tooth discoloration and enamel hypoplasia, inhibition of bone growth, *C. difficile*-associated diarrhea, adverse reactions specific to tetracyclines, the potential for microbial overgrowth, and the development of drug-resistant bacteria. These characteristics of the safety profile would be included in labeling.

2.5 Bridging Study Evaluation

The PK parameters in China Phase I study (TP-434-EM-002) were compared to US Phase I studies (TP-434-P1-SAD-1 and TP-434-P1-MAD-1). The exposure parameters (C_{max} and AUC) for eravacycline were comparable between Chinese and Caucasian healthy subjects at two different dose groups (0.5 and 1 mg/kg). Steady state was achieved at Day 4 following repeated infusion of 1 mg/kg eravacycline q12h, thus PK data from Chinese subjects received the last dose at Day 6~Day 10 were pooled together. The $C_{max,ss}$ were similar while $AUC_{0\text{-}12hr,ss}$ were 10% lower in Chinese compared to Caucasian. The $t_{1/2}$ was longer in Caucasian (38.7h vs. 29.6h). A new Pop PK model was established to evaluate the ethnic sensitivity. Following 1 mg/kg q12h IV infusion of eravacycline, the systemic exposures (C_{max}, C_{min} and AUC_{tau}) were similar between Chinese and non-Chinese cIAI patients with

differences were <15%. Overall, race is not considered as a sensitive factor on eravacycline PK.

The applicant submitted two identical pivotal studies (TP-434-008 and TP-434-025) and one Chinese study (TP-434-EM-003) to support the clinical efficacy and safety between ethnic groups. Besides, domestic (Taiwanese) *in vitro* MIC profiles was submitted and the observation supported the susceptibility profile of claimed pathogens has similarity in comparison with real-world findings in other countries. Definition of analysis set across all three trials are similar. The demographics and baseline characteristics for the cIAI populations in individual study were basically balanced between eravacycline treatment group and the comparator in all three trials. In TP-434-EM-003 study, by Miettinen-Nurminen method, the difference in the cure rates at the TOC visit between the two groups (eravacycline—ertapenem) was -12.5%, which is lower than the pre-specified threshold for consistency evaluation of -7.15%. When using Bayesian method, analyze China study data with TP-434-008 study results as informative prior, the lower limit of the 95% credible interval of the difference in the cure rates at the TOC visit between the two groups (eravacycline—ertapenem) was -20.97%, which is lower than the pre-specified non-inferiority margin of -12.5%. The difference of clinical cure rates between eravacycline and ertapenem didn't achieve the pre-defined non-inferior margin and the pre-specified threshold for consistency in Trial TP-434-EM-003.

The safety profile of eravacycline has been evaluated in 72 Asian subjects in the trial TP-434-EM-003. The most frequent treatment emergent adverse events (TEAEs, incidence >5%) in the eravacycline group are infusion site pain (8/72, 11.1%), infusion site phlebitis (8/72, 11.1%), abdominal distension (7/72, 9.7%), nausea (7/72, 9.7%), fever (7/72, 9.7%), diarrhea (5/72, 6.9%), increased blood glucose (5/72, 6.9%), increased of amylase (4/72, 5.6%, mild, reversible), increased of lipase (4/72, 5.6%, mild, reversible), pneumonia (4/72, 5.6%), cough (4/72, 5.6%), and anemia (4/72, 5.6%). Abnormal liver function was observed in only one patient treated with eravacycline. There is no potential drug-induced liver injury case observed in this study. Serious AEs in the eravacycline group include acute cholecystitis, cholelithiasis, bile duct stone, acute cholangitis, bowel obstruction, increased WBC, imbalance of electrolytes, and bladder cancer. All were judged as not related to the study intervention. Overall, the ethnic difference was considered minimal.

2.6 Conclusion

Based on the review of data on quality, non-clinical pharmacology/toxicology, pharmacokinetics/pharmacodynamics, safety and efficacy, CDE review team considers by consensus that the benefit-risk balance of Xerava is favorable in the treatment of complicated intra-abdominal infections (cIAI) caused by susceptible microorganisms in adults:

Escherichia coli, *Klebsiella pneumoniae*, *Citrobacter freundii*, *Enterobacter cloacae*, *Klebsiella oxytoca*, *Enterococcus faecalis*, *Enterococcus faecium*, *Staphylococcus aureus*, *Streptococcus anginosus* group, *Clostridium perfringens*, *Bacteroides species*, and *Parabacteroides distasonis*.

3. Post-Marketing Requirements

N/A