Taiwan Food and Drug Administration

Assessment Report

Trade Name：贊必佳凍晶注射劑 4 毫克 / ZEPZELCATM lyophilized powder for solution for infusion 4 mg

Active Ingredient：Lurbinectedin

License Number：MOHW-PI 028485

Applicant：美時化學製藥股份有限公司

Approval Date：2023.05.25

Indication：

適用於使用含鉑化學治療期間或之後病程惡化之轉移性小細胞肺癌（SCLC）成人病人的治療。此適應症係依據腫瘤整體反應率以及反應持續時間加速核准，此適應症仍須執行確認性試驗以證明其臨床效益。

Indicated for the treatment of adult patients with metastatic small cell lung cancer (SCLC) with disease progression on or after platinum-based chemotherapy.
This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

1. Background Information

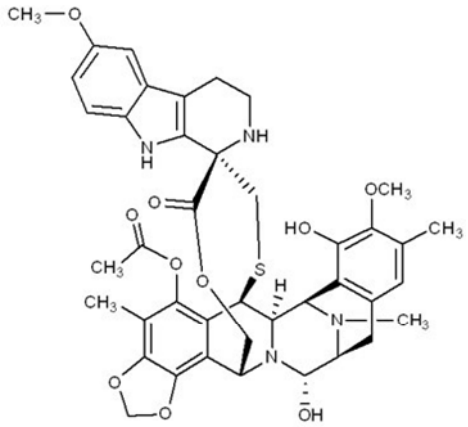
Trade Name	贊必佳凍晶注射劑 4 毫克 / ZEPZELCATM lyophilized powder for solution for infusion 4 mg
Active Ingredient(s)	Lurbinectedin
Applicant	美時化學製藥股份有限公司
Dosage Form & Strengths	凍晶注射劑/ 4 mg
Indication	適用於使用含鉑化學治療期間或之後病程惡化之轉移性小細胞肺癌（SCLC）成人病人的治療。此適應症係依據腫瘤整體反應率以及反應持續時間加速核准，此適應症仍須執行確認性試驗以證明其臨床效益。
Posology	詳見仿單
Pharmacological Category ATC Code	L01XX69

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug Substance

The drug substance, lurbinectedin, is chemically designated as (1'R,6R,6aR,7R,13S,14S,16R)-8,14-dihydroxy-6',9-dimethoxy-4,10,23-trimethyl-19-oxo-2',3',4',6,7,9',12,13,14,16-decahydro-6aH-spiro[7,13-azano-6,16-(epithiopropanooxymethano)[1,3]dioxolo[7,8]isoquinolino[3,2-b][3]benzazocine-20,1'-pyrido[3,4-b]indol]-5-yl acetate and has the following structure:



It is a white to off-white powder. The molecular formula and the molecular weight are $C_{41}H_{44}N_4O_{10}S$ and 784.87 g/mol, respectively.

Adequate information of characterization of the drug substance has been provided. The

molecular structure of lurbinectedin has been confirmed by elemental analysis, NMR, MS, UV, IR and single crystal X-ray diffraction.

The drug substance specification includes tests for appearance, identification, moisture, related substances, residual solvents, assay, residue on ignition and bacterial endotoxins.

2.1.2 Drug Product

The drug product is a sterile lyophilized powder for solution for infusion. The specifications for excipients used in the drug product formulation are adequate.

The drug product specification includes appearance, identity, constituted solution, water determination, uniformity of dosage units, degradation products, assay, sterility and bacterial endotoxins. 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°C / 60% RH) have been carried out.

2.2 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

In vitro pharmacodynamic studies revealed that lurbinectedin was a broad-spectrum anti-cancer reagent with IC_{50} values in the low nanomolar range. *In vivo* studies showed that lurbinectedin exhibited antitumor activities against different experimental models of either subcutaneously or orthotopically xenografted human-derived tumors, including lung, breast, prostate, bladder, kidney, ovary, pancreas cancer and sarcoma. In secondary pharmacological studies, lurbinectedin had no notable off-target effects in a panel of receptors/enzymes/ion-channel/transporters/kinases. Safety pharmacology studies showed that lurbinectedin had no notable effects on neurological function; however, lurbinectedin decreased the tidal volume and induced unclear acute cardiovascular risks at doses that were lower than the clinical dose.

2.2.2 Toxicological Studies

Lurbinectedin (iv infusion over 1 hour) was evaluated in GLP-compliant toxicity studies for up to 24-week duration (Q3W) in rats and monkeys. Toxicity findings of lurbinectedin were the changes in the hematopoietic system and injection site, liver toxicity, gastrointestinal toxicity, reproductive organs toxicity, kidney toxicity, cardiovascular toxicity, and abnormal behavior. The HNSTD was 0.104 mg/kg in monkeys, and the STD_{10} was 0.06/0.03 mg/kg in male and female rats, providing the safety margins of <1 in both gender and species. Toxicity findings in rats and monkeys were partially recovered after a 3-week recovery period. Lurbinectedin was genotoxic and induced embryo-fetal toxicity. The patients should

implement contraception and avoid breastfeeding while receiving lurbinectedin. In accordance with ICH S9 guidance, the absence of FEED, PPND, and carcinogenicity studies is considered acceptable based on the intended clinical use and target patient population. Lurbinectedin was not phototoxic in an in vitro study.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

Lurbinectedin showed both dose proportionality across a dose range of 0.02 to 6.9 mg/m² and time-independency, with geometric mean (CV%) of C_{max} and AUC at 3.2 mg/m² of 107 µg/L (79%) and 551 µg*h/L (94%), respectively. Lurbinectedin plasma accumulation is expected to be negligible when administered every 3 weeks.

In adult cancer patients, the typical volume of distribution at steady state (between subject variability) was estimated to be 504.3 L (39%). The percent of lurbinectedin bound to human plasma proteins was very high (>99%) and independent of drug concentration. Lurbinectedin bound to both human serum albumin and α-1-acid glycoprotein (AAG).

The typical value of lurbinectedin systemic CL was estimated to be 10.6 L/h. The dominant terminal $t_{1/2}$ of lurbinectedin is about 51 h. Following administration of a single-dose of ^{14}C-labeled lurbinectedin to humans, a majority of the radioactivity excreted up to 20 days was recovered in the feces (89% of the dose). Smaller amounts were recovered up to 6 days in the urine (6% of the dose).

2.3.2 Interaction Studies

Experiments performed with human microsomes and selective chemical inhibitors and inhibitory monoclonal antibodies directed against CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4 pointed to CYP3A4 as the main CYP isoform involved in the phase I metabolism of lurbinectedin. The involvement of other CYPs in the microsome-mediated metabolism of lurbinectedin was demonstrated to be negligible.

In vitro studies demonstrated that lurbinectedin is a substrate for P-gp. However, lurbinectedin is administered i.v.; so, a large effect of P-gp inhibitors/inducers on its exposure is not expected. Moreover, lurbinectedin is not a substrate of BCRP and is probably not a substrate of OATP1B1, OATP1B3, OCT1 and MATE1.
Lurbinectedin is an inhibitor of P-gp, OATP1B1, OATP1B3 and OCT1. In addition, lurbinectedin is not an inhibitor of BCRP, BSEP, MATE1, OAT1, OAT 3 and OCT2.

2.3.3 Special Populations

There was no effect of age on the PK of lurbinectedin. No gender differences related to CL

became apparent. No significant correlation between total body weight, ideal body weight, lean body weight, BSA and height, and the PK parameters of lurbinectedin were reported in Study A-001. Thus, no dose adjustment is required by age, gender and body size (BSA).

The impact of renal dysfunction on the exposure of lurbinectedin was evaluated in the final Pop PK analysis. Mild or moderate renal impairment had no effect on total or unbound CL of lurbinectedin as compared to patients with normal renal function. Therefore, no dose adjustment is required in patients with mild or moderate renal impairment. The PK of lurbinectedin has not been evaluated in a sufficient number of patients with severe renal impairment (only one patient) and no patient with end stage renal disease or patients on dialysis have been treated with lurbinectedin.

When total and unbound CL of mild hepatic dysfunction patients was compared with patients with normal hepatic function, no differences were observed. No dose adjustment is required by mild hepatic impairment. The PK of lurbinectedin has not been evaluated in a sufficient number of patients with moderate hepatic impairment and no patient with severe hepatic impairment.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

This NDA submission has been previewed and accepted eligible for the “accelerated approval” designation for the treatment of small cell lung cancer (SCLC).

The efficacy of lurbinectedin is derived from a single arm, multi-cohort, basket trial (B-005) which investigated a cohort of patients with SCLC that had progressed after receiving first-line platinum-containing therapy. An ongoing phase 3 trial (C-003) is not included in this submission.

The SCLC cohort in study B-005 included patients from 26 investigational sites in the USA and Europe (major). Cutoff date for analysis is 15 January 2019. The applicant has claimed that Study B-005 was conducted in accordance with GCP at both Europe and US sites, and according to the US report that both locations have passed the audit.

Eligible adults should have been pathologically confirmed diagnosis of SCLC and treated with only one prior chemotherapy-containing line, have measurable disease, good performance status, and documented progression before study entry. Patients with CNS involvement were excluded. Starting dose was 3.2 mg/m2. If adverse reactions (neutropenia, thrombocytopenia, and hepatotoxicity) occur, sequential dose reductions are permitted, starting at 2.6 mg/m2 and then decreasing to 2.0 mg/m2. The primary efficacy endpoint was

confirmed objective response rate (ORR) per the RECIST v.1.1 according to the IA. The primary evaluation of efficacy is derived on the comparison of ORR for lurbinectedin to a fixed historical control rate of 15% (one-sided test, type I error was 0.025).

A total of 618 cycles were administered to the 105 treated patients. The ORR by IA in All Treated Patients (primary efficacy analysis) was 35.2% (95% CI, 26.2-45.2%). Efficacy in terms of ORR across different subgroups (age group, sex, chemotherapy-free interval category, stage, and prior treatment) were similar. ORR by IRC in all treated patients was 30.5% (95% CI, 21.9-40.2%). Median duration of response was 5.3 (95% CI: 4.1, 6.4) months by IA and 5.1 (95% CI: 4.9, 6.4) months by IRC.

In conclusion, preliminary efficacy results supported the possible benefit with lurbinectedin in SCLC patients treated in the second-line setting.

2.4.2 Safety Results

The overall safety population consisted of 554 patients who received single-agent lurbinectedin at the dose of 3.2 mg/m^2 intravenously once per three weeks, including 335 patients from Study B-005 (all cohorts) and 219 patients with platinum-resistant ovarian cancer from Study C-004. Safety was monitored throughout treatment and up to 30 days after the last dose, until start of a new antitumor therapy or until the date of death, whichever occurred first.

The median duration of exposure was 13.3 weeks (range, 1.1-162.3 weeks) in the overall safety population (n=554). Out of the 554 patients observed, 98.4% (n=545) experienced treatment-emergent adverse events (TEAEs), with 350 patients (63.2%) experienced grade ≥3 events and 140 patients (25.3%) experienced grade ≥4 events. The most common TEAEs (all grades) were fatigue (62.6%), followed by nausea (57.0%) and constipation (32.1%). The most frequent grade ≥3 TEAEs were fatigue (9.7%), followed by febrile neutropenia (6.7%), nausea and vomiting. Treatment-emergent SAEs were reported in 40.4% of the overall safety population and 32.4% of the B-005 SCLC cohort. The most common treatment-emergent SAEs (all grades) were neutropenia, thrombocytopenia, anemia, dyspnea, and respiratory tract infection including pneumonia.

Of all 554 patients, 66.4% experienced an increase in ALT, with 6.9% having a grade ≥3 increase and 0.4% experiencing a grade 4 increase, while AST increase was less frequent. No Hy's Law cases as defined in the FDA's Guidance. Although elevated creatinine and glucose levels were frequently observed in the overall safety population, the percentage of grade 3-4 abnormalities was less than 5%. A total of 6.8% patients experienced CPK increase.

A total of 399 of 554 treated patients (72.0%) died, with most deaths (378, 94.7%) being due to disease progression. Thirty-five deaths occurred within 30 days after the last dose, and eight out of 35 fetal cases were not due to disease progression (sepsis, lung infection, pneumonia, cardiorespiratory arrest, pneumonitis, septic shock, cardiorespiratory arrest). Four deaths were judged treatment-related (sepsis, lung infection, and pneumonia) because of concurrent neutropenia. In the B-005 SCLC subpopulation, 66 patients (62.9%) died and all were due to disease progression.

Consistency was observed between the B-005 SCLC cohort (n=105) and overall safety population with respect to all safety assessment. Myelosuppression, hepatotoxicity, and rhabdomyolysis have been addressed in the "Warnings and Precautions" section of the label with recommendations to manage the probable toxicity.

Overall, the safety profile of lurbinectedin was acceptable on the treatment of a life-threatening disease.

2.5 Bridging Study Evaluation

The sponsor has provided the complete clinical data package (CCDP) of lurbinectedin that includes studies conducted primarily on Caucasian populations, as well as a Phase I study conducted in Japan (A-013) and an ongoing Phase I study in China (Study LY01017/CT-CHN-101).

In a Japanese phase I study (Study A-013, n=13), the escalating doses of lurbinectedin (from 1.5 to 3.5 mg/m^2) without and with G-CSF for primary prophylaxis were explored in Japanese adult patients. According to the PK results after single-dose administration of lurbinectedin (3.2 mg/m^2) between Japanese study (Study A-013) and two USA studies (Study B-005 and Study A-001), there is no significant difference in PK between Asian and non-Asian populations, especially the parameters of CL_t, $t_{1/2}$, V_{ss} and V_z, which may be the most related to race difference in drug metabolism. Based on population PK analysis, Asian patients treated at 3.2 mg/m^2 q3wk had 15% (95% CI: 12-19%) higher lurbinectedin unbound AUC when compared to that of Caucasian patients. This difference on exposure was not significant and mainly due to lower AAG levels detected in Asian population (AAG average levels of 87.4 mg/dL) when compared to the rest of the patients (136.6 mg/dL, $p<0.001$).

Results from limited sample size suggested that lurbinectedin was tolerable and possibly effective in East Asian patients. No significant difference of ethnicity was observed between Asian and non-Asian subjects. Besides, CDE has encouraged the sponsor to provide the preliminary results of Japanese phase II study during the NDA application to further evaluate the uncertainties under limited bridging study information. However, the above Japanese

phase II study was not available during NDA review. Impact of ethnic difference might be low based on limited information. Therefore, the bridging study was conditionally waived and submitting the final report of Study LY01017 was required.

2.6 Conclusion

Under an unmet medical need through limited available therapy in this target population, it suggests a favorable benefit-risk profile. The CDE review team recommended accelerated approval of lurbinectedin for the following indication: for the treatment of adult patients with metastatic small cell lung cancer (SCLC) with disease progression on or after platinum-based chemotherapy.

3. Post-Marketing Requirements

1. Further adequate-designed, well-controlled confirmatory clinical trials are required because the product is approved under accelerated approval. This could be from the Study titled “A Randomized, Multicenter, Open-label, Phase III Study of Lurbinectedin Single-Agent or Lurbinectedin in Combination with Irinotecan versus Investigator’s Choice (Topotecan or Irinotecan) in Relapsed Small Cell Lung Cancer (SCLC) Patients (LAGOON Trial)”.
2. The bridging study was conditionally waived. We remind you of your post-BSE commitments: submit the final report from clinical trials to evaluate the safety, pharmacokinetic profiles and efficacy in East-Asian. This could be from the Study LY01017/CT-CHN-101.