Summary Report of Benefit-Risk Assessment

ZEPZELCA POWDER FOR SOLUTION FOR INFUSION 4MG/VIAL

NEW DRUG APPLICATION

Active Ingredient(s)	Lurbinectedin
Product Registrant	Specialised Therapeutics Asia Pte Ltd
Product Registration Number	SIN16327P
Application Route	Abridged evaluation
Date of Approval	21 September 2021

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A   INTRODUCTION

Lurbinectedin is indicated for the treatment of adult patients with metastatic small cell lung cancer (SCLC) who have progressed after prior platinum-containing therapy.

The active substance, lurbinectedin, is an alkylating agent that inhibits oncogenic transcription by binding covalently to guanine residues in the guanine-cytosine (CG)-rich sequences located around the promoter region of protein-coding genes in the minor groove of DNA, evicting transcription factors and chromatin remodelling complexes.

Zepzelca is available as a powder for solution for infusion containing 4 mg of Lurbinectedin in one vial. Other ingredients in the vial are (S)-lactic acid, Sucrose, Sodium Hydroxide and Water for Injection.

B   ASSESSMENT OF PRODUCT QUALITY

The drug substance, Lurbinectedin, is manufactured at Pharma Mar, S.A., Madrid, Spain. The drug product, Zepzelca Powder for Solution for Infusion 4 mg/vial, is manufactured at GP–Pharm, S.A., Barcelona, Spain and Baxter Oncology GmbH, Halle/Westfalen, Germany.

Drug substance:

Adequate controls have been presented for the starting materials, intermediates and reagents. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance are considered appropriate.

The characterisation of the drug substance and its impurities are in accordance with ICH guidelines. Potential and actual impurities, including potentially genotoxic impurities are adequately controlled.

The drug substance specifications are established in accordance with ICH Q6A and the impurity limits are considered appropriately qualified. The analytical methods used are adequately described and non-compendial methods are appropriately validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing was presented.

The stability data presented for Pharma Mar, S.A., Madrid, Spain were adequate to support the approved storage condition and re-test period. The packaging is type 1 borosilicate vials with screw cap placed inside HDPE bottles. The drug substance is approved for storage at -20°C±5°C with a re-test period of 36 months.

Drug product:

The drug product is a sterile lyophilized powder. The manufacturing process utilises aseptic processing.

All manufacturing sites involved are compliant with Good Manufacturing Practice (GMP). Proper development and validation studies were conducted. It has been demonstrated that the manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications are established in accordance with ICH Q6A and impurity limits are considered adequately qualified. The analytical methods used are adequately described and non-compendial methods were appropriately validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing is presented.

The stability data submitted were adequate to support the approved shelf-life of 48 months when stored between 2-8°C. The reconstituted or diluted drug product can be stored for up to 24 hours with exposure to ambient light or under refrigeration (2° to 8°C). The container closure system is a Type I clear borosilicate glass vial with grey butyl rubber stopper and aluminium flip-off seal.

C   ASSESSMENT OF CLINICAL EFFICACY

The clinical efficacy of Zepzelca for the treatment of adult patients with metastatic SCLC who have progressed after prior platinum-containing therapy was based on one pivotal Phase 2 Study B-005.

Study B-005 was a Phase 2, ongoing, open-label, single-arm, "basket-design" study to determine the efficacy and safety of lurbinectedin in adult patients aged ≥18 years with advanced solid tumours. Patients were administered lurbinectedin 3.2mg/m^2 every 3 weeks (q3wk) until disease progression or unacceptable toxicity. The dosing regimen of 3.2 mg/m^2 q3wk was chosen based on the early phase studies as well as the exposure-safety and exposure-response analyses which determined this dose to achieve an acceptable balance of safety and efficacy. The study included cohorts from 9 different tumour types: SCLC, Head and neck carcinoma, Neuroendocrine tumours (grade 2 and grade 3 according to World Health Organization (WHO) classification), Biliary tract carcinoma, Endometrial carcinoma, BRCA 1/2-associated metastatic breast carcinoma, Carcinoma of unknown primary site, Germ cell tumour, excluding immature teratoma, or teratoma with malignant transformation, and Ewing's family of tumours. As of the data cut-off date (15 January 2019), 105 patients with previously treated SCLC were enrolled in the study which contributed to the data supporting the proposed indication.

The "All Treated Patients" analysis set population (included all patients who received any partial or complete infusion of lurbinectedin) in the SCLC Cohort were of age range 40 to 83 years, with 35.2% who were older than 65 years. Majority were White (75.2%) and female (40.0%) subjects. Overall, 75.2% of patients had a response to prior platinum-based therapy. With respect to chemotherapy-free interval (CTFI), 42.9% of treated patients had resistant disease with CTFI<90 days (20% with CTFI<30 days) and 57.1% had CTFI≥90 days. Most patients (69.5%) had extensive disease (stage IV [T any, N any, M 1a/b], or T3-4 due to multiple lung nodules that are too extensive or have tumour/nodal volume that is too large to be encompassed in a tolerable radiation plan) at diagnosis, of which 84% had resistant disease (CTFI <90 days). Almost all patients (97%) had metastatic disease. The median number of sites involved at baseline was 3 (range, 1-6), with 75.2% of patients having ≥3 disease sites. Lung (n=103; 98.1%), lymph nodes (n=86; 81.9%; mediastinal in 71 patients, 67.6%) and liver (n=43; 41.0%) were the most common disease sites. 34.3% of patients had target lesions with longest diameters summing >100mm. Nine patients (8.6%) had paraneoplastic syndrome. The median time from disease diagnosis to study entry was 8.2 months (range, 2.1-20.0 months). All patients had received previous cancer therapy, of which 93.3% had 1 prior line of chemotherapy-containing regimen.

The primary efficacy endpoint was overall response rate (ORR) according to RECIST v1.1 determined by Investigator Assessment (IA). Key secondary efficacy endpoints included ORR determined by independent review committee (IRC), duration of response by IA (IA-DOR), IRC-DOR, progression-free survival by IA (IA-PFS), IRC-PFS and overall survival (OS). With 100 patients, there was 95% power to test the null hypothesis that 15% or less patients achieved ORR (p ≤ 0.15) versus the alternative hypothesis that 30% or more patients achieved ORR (p ≥ 0.30). If the number of patients who achieved a confirmed response was ≥ 23, this would allow the rejection of the null hypothesis.

The primary efficacy endpoint was met with an ORR by IA of 35.2% (95% CI: 26%, 45%) in the "All Treated Patients" analysis set. Of the 37 patients who responded to treatment, all had a partial response and stable disease (SD) in 35 patients (33.3%), with 10 of them (9.5%) reaching SD≥4 months. ORR by IA was consistent with ORR by IRC (30.5% [95% CI, 21.9-40.2%]) with an agreement of 78.4% between the two assessments patients (Weighted Kappa Coefficient of 0.7349 [p≤0.0001]).

Median DOR by IA in the population of 37 responder patients was 5.3 months (95% CI, 4.1-6.4 months) and was consistent with the DOR assessed by IRC at 5.1 months (95% CI, 4.9-6.4 months) in the 32 responder patients. DOR rate by IA was 69.5%, 43.0% and 11.3%, respectively and by IRC was 82.2%, 34.6% and 5.2% at 4, 6 and 12 months respectively.

Median PFS was 3.5 months (95% CI, 2.6-4.3 months) by IA and 3.5 months (95% CI, 2.6-4.2 months) by IRC. PFS rates at 4 months and 6 months were 46.6% and 32.9%, respectively, by IA and 45.0% and 30.7%, respectively, by IRC. With a median follow-up of 17.1 months and a censoring rate of 37.1%, median OS was 9.3 months (95% CI, 6.3-11.8 months). OS rate at 6 and 12 months was 67.1% and 34.2%, respectively. There was no crossover of therapy allowed, so if patients were to start a new subsequent therapy, they will be considered as have discontinued from the study. This suggested that the OS results reflect the efficacy of lurbinectedin.

Efficacy results in "All Treated Patients" analysis set

	"All Treated Patients" Analysis Set (N=105) 15 Jan 2019	
	IA	IRC
Complete response (CR), n (%)	**0 (0.0%)**	**0 (0.0%)**
Partial response (PR), n (%)	**37 (35.2%)**	**32 (30.5%)**
Stable disease (SD), n (%)	35 (33.3%)	33 (31.4%)
Progressive disease, n (%)	28 (26.7%)	33 (31.4%)
Not evaluable, n (%)	5 (4.8%)	7 (6.7%)
Overall response rate (ORR)ᵃ, n (%)	**37 (35.2%)**	**32 (30.5%)**
95% CI	26%, 45%	22%, 40%
Duration of response (months), median	5.3	5.1
≥ 6 months	43%	35%
≥12 months	11%	5%
PFS, median (months)	3.5	3.5
95% CI	2.6, 4.3	2.6, 4.2
PFS at 4 months, %	47%	45%
PFS at 6 months, %	33%	31%
Duration of OS, median (months)	9.3	
95% CI	6.3, 11.8	
Alive at 12 months, %	34%	

95% CI	23%, 45%

Subgroup analyses in terms of CTFI (< 90 days and ≥ 90 days) were observed to be better for the sensitive patients (CTFI ≥ 90 days) as compared to the resistant patients (CTFI < 90 days). Patients with sensitive disease, defined as a chemotherapy free interval (CTFI) of ≥ 90 days, had an IA-ORR of 45% (95% CI 32, 58) while patients with resistant disease, defined as a CTFI of < 90 days, had an IA-ORR of 22% (95% CI 11, 37). IRC-ORRs in patients with sensitive and resistant disease were 43.3% (95% CI 31, 57) and 13.3% (95% CI 11, 37), respectively. The median DOR was 6.2 months in patients with sensitive disease whereas it was 4.7 months in those with resistant disease.

Efficacy results (IA and IRC) according to CTFI subgroup (<90 days and ≥90days)

	IA		IRC	
	CTFI < 90 days (n=45)	CTFI ≥ 90 days (n=60)	CTFI < 90 days (n=45)	CTFI ≥ 90 days (n=60)
Objective response Responders, n ORR, % (95% CI)	10 22.2 (11, 37)	27 45.0 (32, 58)	6 13.3 (5, 27)	26 43.3 (31, 57)
Best overall response CR, n (%) PR, n (%) SD, n (%) PD, n (%) Missing/NE, n (%)	0 (0.0) 10 (22.2) 13 (28.9) 18 (40.0) 4 (8.9)	0 (0.0) 27 (45.0) 22 (36.7) 10 (16.7) 1 (1.7)	0 (0.0) 6 (13.3) 15 (33.3) 19 (42.2) 5 (11.1)	0 (0.0) 26 (43.3) 18 (30.0) 14 (23.3) 2 (3.3)
Duration of Response Patients with event, n (%) Median, months (95% CI)	9 (90.0) 4.7 (3, 7)	20 (74.1) 6.2 (4, 7)	5 (83.3) 4.8 (2, 5)	17 (65.4) 5.3 (5, 7)
Progression-free Survival Patients with event, n (%) Median, months (95% CI)	41 (91.1) 26 (1, 4)	49 (81.7) 4.6 (3, 7)	37 (82.2) 1.4 (1, 4)	44 (73.3) 4.3 (3, 6)
	CTFI < 90 days (n=45)		CTFI ≥ 90 days (n=60)	
Overall Survival Patients with event, n (%) Median, months (95% CI)	37 (82.2) 5.0 (4, 6)		29 (48.3) 11.9 (10, 16)	

Overall, Study B-005 provided evidence of treatment benefit in terms of a clinically meaningful investigator-assessed ORR (IA-ORR) of 35% (95% CI 26.2, 45.2). Despite the limitations of being a single-arm Phase 2 study, the results observed in heavily pre-treated metastatic SCLC patients who had progressed after platinum-based chemotherapy was considered promising when compared against the current standard of care, topotecan, where ORR ranged between 7.6% to 24.3%. The observed benefits were also supported by reasonable median IA-DOR of 5.3 months, median PFS of 3.5 months and median OS of 9.3 months. Consistent results were observed with the IRC assessments. While the results were observed to be numerically better in those subjects with sensitive disease compared to those with resistant disease, the results in the latter were considered clinically meaningful given the lack of approved regimens for this patient population.

The current available evidence from Study B-005 would be supplemented by results from the on-going Phase 3 confirmatory active-comparator study with lurbinectedin as monotherapy at a dose of 3.2mg/m^2 in the same patient population, when the data becomes available.

D ASSESSMENT OF CLINICAL SAFETY

The clinical safety of lurbinectedin was based primarily on safety data derived from Study B-005 and the Phase 3 ALTANTIS study, comprised a total of 697 patients who received at least one dose of study treatment. ATLANTIS study was a Phase 3, ongoing, randomised, controlled, superiority study to determine the efficacy and safety of lurbinectedin and doxorubicin followed by lurbinectedin alone (if applicable) versus best investigator's choice of therapy (topotecan or cyclophosphamide/doxorubicin/vincristine (CAV)) in adult patients (≥18 years of age) with SCLC after disease progression following one prior platinum-containing regimen. This study assessed a combination regimen with a different dosing regimen for lurbinectedin and hence, was not considered relevant for supporting the indication sought, but the safety results were presented for characterisation of the safety profile of lurbinectedin. In Study B-005, the median duration of exposure to lurbinectedin was 14.3 weeks. In the ATLANTIS study, the median duration of exposure was longer in the lurbinectedin arm (18.1 weeks) compared to topotecan (16.9 weeks) and CAV (14.3 weeks).

The most common adverse events (AEs) considered to be related to lurbinectedin in the B-005 SCLC population were fatigue (77.1%), nausea (37.1%), decreased appetite (33.3%), constipation (31.4%), dyspnoea (30.5%), vomiting (21.9%) and diarrhoea (20.0%). Similar common AEs were reported in both lurbinectedin/doxorubicin arm and control arm in the ATLANTIS study. Grade ≥ 3 and ≥ 4 AEs were observed in 59.0% and 23.8% of patients, respectively, in Study B-005. The control arm in the ATLANTIS study reported higher incidences of Grade ≥ 3 and ≥ 4 AEs, at 86.5% and 60.2%, respectively.

The incidence of AEs leading to discontinuation was low with the study treatment in Study B-005 (1.9%). In the ATLANTIS study, the incidences were reported to be higher in the control arm (21.5%) compared to the lurbinectedin/doxorubicin arm (12.9%).

Treatment-emergent serious adverse events (SAEs) were observed in 34.3% of patients in Study B-005, with the most common treatment-emergent SAEs being neutropenia (5.7%), febrile neutropenia (4.8%), pneumonia (4.8), anaemia (3.8%), thrombocytopenia (3.8%). In the ATLANTIS study, 30.8% of patients in the control arm and 13.9% of patients in the lurbinectedin/doxorubicin arm reported treatment-emergent SAEs, with the most common being neutropenia (1.3%), febrile neutropenia (4.0%), thrombocytopenia (3.0%) and anaemia (2.3%). Incidences of these treatment-emergent SAEs were lower than the control arm.

The AEs of special interest reported with lurbinectedin are shown below:

| | Study B-005 | ATLANTIS study | |
	Lurbinectedin (n=105)	Experimental arm (n=302)	Control arm (n=288)
Haematological abnormalities (%)			
Anaemia	95.2	94.7	96.5
Lymphopenia	85.7	68.2	88.2
Leukopenia	79.0	83.8	88.9
Neutropenia	71.4	57.9	83.3
Thrombocytopenia	43.8	63.9	80.9
Biochemical abnormalities (%)			
ALT increase	71.8	38.1	36.6
AST increase	44.8	31.6	26.5
Total bilirubin increase	9.7	8.0	11.8
Peripheral neuropathy (%)	11.4	1.7	3.1
Musculoskeletal and connective tissue disorders (%)			

| Arthralgia | 6.7 | 1.3 | 0.7 |
| Myalgia | 1.9 | 1.3 | 1.0 |

Overall, the adverse events profile of lurbinectedin was considered acceptable in adult patients with SCLC who progressed upon a platinum-containing first-line regimen, given the life-threatening nature of metastatic SCLC. The adverse event profile has been presented adequately in the package insert.

E   ASSESSMENT OF BENEFIT-RISK PROFILE

Small cell lung cancer is a serious and life-threatening condition that represents 10-15% of all lung cancers. The disease nature tends to be aggressive and is associated with high relapse rates and poor prognosis. After progression on first-line chemotherapies, comprising a platinum compound and etoposide, and/or immunotherapies, treatment options are limited with topotecan as the only currently approved second-line standard of care for the sensitive disease (progressed after 60 days). No treatments are approved currently for the resistant disease, and lurbinectedin could potentially offer a treatment option.

While Study B-005 was a single arm, non-comparative early phase study, the study presented reasonable evidence supporting the use of lurbinectedin monotherapy in SCLC patients who failed a prior line of platinum-containing chemotherapy with a clinically meaningful ORR (35%) and DOR (5.3 months). The ORR in the sensitive population (45.0%) compared favourably with the current standard of care, topotecan (ORR ranging between 7.6% to 24.3%; median DOR of 3.3 months). There is no approved regimen for resistant disease and the observed ORR of 22% with lurbinectedin in this population was considered clinically meaningful. It was also considered that the disease condition is characterised by short survival and low response to subsequent therapies. In order to confirm the efficacy observed in Study B-005, it is required that confirmatory evidence from a planned Phase 3 study investigating monotherapy lurbinectedin at a dose of 3.2 mg/m^2 against either investigator's choice of therapy (topotecan or irinotecan) or the combination use of lurbinectedin and irinotecan in second-line SCLC patients to be submitted as part of the registration condition.

The most notable safety concerns with lurbinectedin were myelosuppression, hepatotoxicity, musculoskeletal pain and peripheral neuropathy, the relevant warnings and precautions, as well as recommendations for dose adjustments have been adequately described in the package insert. The safety profile of lurbinectedin was considered acceptable relative to the benefits.

Based on the preliminary evidence of clinically relevant efficacy in second-line SCLC and the acceptable safety profile, the benefit-risk profile of lurbinectedin in the treatment of patients with SCLC who progressed upon a platinum-containing first-line regimen was considered favourable in the setting of a high unmet medical need.

F   CONCLUSION

Based on the review of quality, safety and efficacy data, the benefits of Zepzelca outweighed the risks for the treatment of adult patients with metastatic small cell lung cancer (SCLC) who have progressed after prior platinum-containing therapy, and approval of the product registration was granted on 21 Sep 2021.

APPROVED PACKAGE INSERT AT REGISTRATION

ZEPZELCA™ (LURBINECTEDIN)
POWDER FOR SOLUTION FOR INFUSION

1 NAME OF THE MEDICINE

ZEPZELCA 4 mg powder for solution for infusion.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

4 mg of lurbinectedin as lyophilised powder in a single-dose vial for reconstitution.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

ZEPZELCA is indicated for the treatment of adult patients with metastatic small cell lung cancer (SCLC) who have progressed after prior platinum-containing therapy.

This indication is approved under provisional approval based on overall response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials [*see 5.1 Clinical Trials*].

4.2 DOSE AND METHOD OF ADMINISTRATION

Recommended Dose and Schedule

The recommended dose is 3.2 mg/m^2 by intravenous infusion over 60 minutes repeated every 21 days until disease progression or unacceptable toxicity.

Dose Modifications for Adverse Reactions

Do not administer ZEPZELCA until neutrophils recover to greater than or equal to 1.5×10^9/L, platelet counts greater than or equal to 100×10^9/L and haemoglobin levels recover to greater than or equal to 5.6 mmol/L (with transfusion if necessary).

Reduce the dose of ZEPZELCA if any of the following adverse reactions occurs: ≥Grade 3 (severe) non haematological toxicity, Grade 4 thrombocytopenia (Platelet count less than 25×10^9/L), Grade 3 thrombocytopenia (Platelet count less than 50×10^9/L) with bleeding that requires transfusion, Grade 4 neutropenia (Neutrophil count less than 0.5×10^9/L), any grade neutropenia (Neutrophil count < lower limit of normal [LLN]) that is associated with infection/sepsis, or any adverse reaction that requires frequent or prolonged (>2 weeks) dose delays.

Patients who experience an adverse reaction must recover before being retreated.

Patients with isolated Grade 4 neutropenia (Neutrophil count less than 0.5×10^9/L) may receive secondary G-CSF prophylaxis rather than undergo lurbinectedin dose reduction.

The recommended dose modifications for adverse reactions are listed in Table 1.

Table 1:   ZEPZELCA Dose Reduction Schedule

Dose	1st Dose Reduction	2nd Dose Reduction	3rd Dose Reduction
3.2 mg/m^2	2.6 mg/m^2	2.0 mg/m^2	Stop

Premedication

Pre-infusion Medication:

Administer the following pre-infusion medications for antiemetic prophylaxis:

- Corticosteroids (intravenous dexamethasone 8 mg or equivalent)

- Serotonin antagonists (intravenous ondansetron 8 mg or equivalent)

Post-infusion Medication:

Administer post-infusion medication for extended antiemetic treatment for 2 days after the infusion if needed:

- Corticosteroids (oral dexamethasone 4 mg or equivalent)

- Serotonin antagonists (oral ondansetron 8 mg or equivalent) or

- Metoclopramide (intravenous or oral 10 mg or equivalent every 8 hours)

Preparation and Administration

The ZEPZELCA vial is for single-use only.

Prepare the solution for infusion using aseptic technique as follows:

- Inject 8 mL of Sterile Water for Injection USP into the vial. Shake the vial until complete dissolution. The reconstituted solution is a clear, colourless or slightly yellowish solution, essentially free of visible particles.

- Visually inspect the solution for particulate matter and discoloration. Dilute the reconstituted solution with 0.9% Sodium Chloride Injection USP or 5% Dextrose Injection USP.

- Calculate the required volume of reconstituted solution as follows:

$$\text{Volume (mL)} = \frac{\text{Body Surface Area (m}^2\text{) x Individual Dose (mg/m}^2\text{)}}{0.5 \text{ mg/mL}}$$

- For administration through a central venous line, withdraw the appropriate amount of reconstituted solution from the vial and add to an infusion container containing at least 100 mL of diluent (0.9% Sodium Chloride Injection USP or 5% Dextrose Injection USP).

- For administration through a peripheral venous line, withdraw the appropriate amount of reconstituted solution from the vial and add to an infusion container containing at least 250 mL of diluent (0.9% Sodium Chloride Injection USP or 5% Dextrose Injection USP).

- If not used immediately after reconstitution or dilution, the solution can be stored prior to administration for up to 24 hours following reconstitution, including infusion time, at either room temperature/ light or under refrigerated (2° to 8° C) conditions.

Dose Modification for Renal Impairment

- Avoid administration of ZEPZELCA to patients with calculated creatinine clearance less than 30 mL/min.

Dose Modification for Hepatic Impairment

- Do not administer ZEPZELCA to patients with AST or ALT greater than 3 x upper limit of normal (ULN) and/or total bilirubin greater than 1.5 x ULN.

4.3   CONTRAINDICATIONS

ZEPZELCA is contraindicated in patients with history of significant drug allergy to the active substance or any of the excipients.

4.4   SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Bone Marrow Suppression

Bone marrow suppression (primarily neutropenia) is the dose-limiting toxicity of ZEPZELCA.

Monitor blood counts including neutrophil count and platelet count prior to each administration. Dose modifications may be required [*see 4.2 Dose and Method of Administration*].

Neutropenia

Neutropenia is not cumulative over time. In a clinical study in patients with SCLC, 71% of patients experienced neutropenia (all grades, i.e. absolute neutrophil count less than LLN), 46% experienced Grade 3/4 neutropenia, and 5% experienced febrile neutropenia.

From pooled data of 554 patients receiving ZEPZELCA, which included patients with SCLC and other solid tumours, Grade 3/4 neutropenia (less than 1 x 10^9/L) occurred in 41% of patients, with a median onset at Day 15 and a duration of 7 days. Therapy-related febrile neutropenia/neutropenic sepsis occurred in 7% of patients.

In case of neutrophil counts of less than 0.5 x 10^9/L or any value less than LLN that is associated with infection/sepsis, the use of G-CSF is recommended.

Thrombocytopenia

In a SCLC cohort, 44% of patients experienced thrombocytopenia (all grades) and 7% experienced Grade 3/4 thrombocytopenia. Platelet transfusions were given to 3% of patients.

From pooled data of 554 patients receiving ZEPZELCA, Grade 3/4 thrombocytopenia (less than 50 x 10^9/L) occurred in 10% of patients, with a median onset at Day 10 and a median duration of 7 days.

Administer ZEPZELCA only to patients with adequate bone marrow reserves, including baseline neutrophil count of at least 1.5 x 10^9/L and platelet count of at least 100 x 10^9/L.

In case of Grade 4 thrombocytopenia (less than 25 x 10^9/L) or Grade 3 thrombocytopenia (less than 50 x 10^9/L) with bleeding, platelet transfusion is recommended.

Infection in the Absence of Neutropenia

In the small cell lung population receiving ZEPZELCA, thirty-five patients (37/105: 35.2%) had infection events without concomitant neutropenia. The most common of these events were lower respiratory tract infections (17.1%). These infection events generally occurred 14 days (range, 1-29 days) after drug administration and lasted a median of 13.5 days (range, 2-59 days). The majority of the cases (46/54: 85.2%) were resolved, and there were no fatal outcomes associated with the infection. Dose delay was the most common action taken (3/54: 5.6% of events).

Among the 554 patients treated with ZEPZELCA, 130 patients (23.5%) had 192 infections (all grades) without concomitant neutropenia. These infections generally occurred 14 days (range, 1-35 days) after administration and lasted a median of 8 days (range, 1-85 days). The majority of the cases (165/192: 85.9%) were resolved. Fatal outcome was reported in three patients (0.5%). Dose delay was the most common action taken (20/192: 10.4%), and treatment discontinuation was required in two patients (2/554: 0.4%).

Hepatotoxicity

In a SCLC cohort of 105 patients, ALT increase was reported in 72% of patients (4% ≥Grade 3), while AST increase was reported in 45% of patients (2% ≥Grade 3).

Among the 554 patients treated with ZEPZELCA at the recommended dose and schedule, there were 6.0%/2.7% of patients who had Grade 3 elevations of ALT/AST and 0.4%/0.5% of patients who had Grade 4 elevations of ALT/AST. There were no patients who met Hy's law criteria.

No dose adjustment is recommended for patients with mild hepatic impairment (total bilirubin ≤ULN and AST >ULN, or total bilirubin 1.0-1.5×ULN and any AST).

ZEPZELCA has not been studied in patients with moderate or severe hepatic impairment. Patients with AST >3×ULN and/or bilirubin >1.5×ULN were not allowed to participate in clinical trials of ZEPZELCA.

Monitor liver tests, including ALT, AST, and bilirubin.

Dose modifications may be required [*see 4.2 Dose and Method of Administration*].

Renal Impairment

No dose adjustment is recommended in patients with mild (CL_{CR} 60-89 mL/min) or moderate (CL_{CR} of 30-59 mL/min) renal impairment.

Lurbinectedin has not been evaluated in a sufficient number of patients with severe renal impairment (CL_{CR} <30 mL/min) or end-stage renal disease to estimate the risk.

Embryo-Fetal Toxicity

ZEPZELCA can cause fetal harm when administered to a pregnant woman.

Studies in pregnant rats administered a single dose of 0.6 mg/m^2 ZEPZELCA (approximately equivalent to 20% of the estimated human dose of 3.2 mg/m^2) during the period of organogenesis demonstrated 100% embryo-fetal lethality as well as maternal toxicity evidenced by clinical signs, decreases in body weight/body weight gain, and decreased food consumption. Advise pregnant women of the potential risk to the fetus. Advise female patients of reproductive potential to use effective contraception during treatment with ZEPZELCA and for 6 months after the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with ZEPZELCA and for 4 months after the last dose [*see 4.6 Fertility, Pregnancy and Lactation - Use in Pregnancy*].

Use in the elderly

Of the 554 patients that received ZEPZELCA at the recommended dose, 30.5% were aged 65 to 75 years and 6.9% were aged 75 years and older. Overall, no difference in efficacy or safety was observed between these patients and younger adult patients.

Paediatric use

The safety and effectiveness of ZEPZELCA in paediatric patients have not been established.

Effects on laboratory tests

Refer to section 4.8 Adverse Effects (Undesirable Effects) for laboratory abnormalities.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Effect of CYP3A Inhibitors on Lurbinectedin

In a Phase 1 study with lurbinectedin, patients who received aprepitant, a weak-moderate CYP3A4 inhibitor used as an antiemetic, showed a 33% reduction of lurbinectedin plasma clearance when compared with patients who did not receive it.

In a population PK model of lurbinectedin developed with data from 755 patients, co-administration of CYP3A4 inhibitors was found in 7% of patients and resulted in a moderate (40%) decrease in plasma clearance of lurbinectedin.

Population PKPD models of the time course of absolute neutrophil count and platelets indicated that the concomitant use of CYP3A4 inhibitors produced an absolute 11% and a 6.2% increase of Grade 3/4 neutropenia and thrombocytopenia, respectively.

Effect of CYP3A Inducers on Lurbinectedin

In a population PK model of lurbinectedin developed with data from 755 patients, co-administration of CYP3A4 inducers was found in 98% of patients, thus precluding a comparison in lurbinectedin pharmacokinetics.

Effect of Lurbinectedin on CYP Enzymes

In vitro, lurbinectedin has limited inhibition or induction potential of major CYP enzymes (CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4).

Dose Modification for Coadministration with Strong or Moderate CYP3A Inhibitors
Avoid coadministration of strong or moderate CYP3A inhibitors with ZEPZELCA. If coadministration with moderate CYP3A inhibitors cannot be avoided, consider dose reduction of ZEPZELCA, if clinically indicated *[see 4.2 Dose and Method of Administration]* and monitor neutrophils and platelet counts closely.

Dose Modification for Coadministration with Strong or Moderate CYP3A Inducers

Avoid coadministration of strong or moderate CYP3A inducers with ZEPZELCA. Consider alternative agents with less CYP3A induction.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Pregnancy Testing

Due to potential risks to the fetus *[see 4.6 Fertility, Pregnancy and Lactation - Use in Pregnancy]*, verify the pregnancy status of females of reproductive potential prior to initiating ZEPZELCA.

Contraception

Females

Advise female patients of reproductive potential to use effective contraception during and for 6 months after the use of ZEPZELCA.

Males

Advise males with a female sexual partner of reproductive potential to use effective contraception during and for 4 months after the use of ZEPZELCA.

Use in pregnancy – Pregnancy Category X

There are no available data to inform a risk with the use of ZEPZELCA during human pregnancy. Animal studies in pregnant rats during the period of organogenesis demonstrated embryo-fetal

lethality and maternal toxicity. Based on its mechanism of action [*see 5.1 Pharmacodynamic Properties - Clinical Trials*] lurbinectedin can cause fetal harm when administered during pregnancy.

Advise pregnant woman and females of reproductive potential of the potential risk to a fetus. The background risk of major birth defects and miscarriage for the indicated population are unknown. If this drug is used during pregnancy, or if a patient becomes pregnant while receiving ZEPZELCA, the patient should be apprised of the potential risk to the fetus [*see 4.4 Special Warnings and Precautions for Use*].

Use in lactation.

There are no data on the presence of lurbinectedin in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions from ZEPZELCA in breastfed children, advise a nursing woman to discontinue nursing during treatment with ZEPZELCA and for 2 weeks after the final dose.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The following safety profile of ZEPZELCA is based on adverse events and reactions reported in clinical trials.

Table 2: Adverse Events regardless of the relationship, by worst grade by Patient, with a cut off at 5% comparing the frequency of AEs of the Basket trial SCLC cohort (n: 105 patients) versus Basket trial all cohorts + Corail trial (n: 554 patients); (very common and common)

Preferred Term	Basket trial SCLC Cohort (N = 105)		Basket trial All cohorts + Corail trial (N = 554)	
	G>=1	G>=3	G>=1	G>=3
	n (%)	n (%)	n (%)	n (%)
Neutropenia	31 (29.5)	25 (23.8)	162 (29.2)	121 (21.8)
Anaemia	13 (12.4)	9 (8.6)	119 (21.5)	94 (17.0)
Febrile neutropenia	5 (4.8)	5 (4.8)	37 (6.7)	37 (6.7)
Thrombocytopenia	6 (5.7)	4 (3.8)	36 (6.5)	27 (4.9)
Nausea	39 (37.1)	0	316 (57.0)	24 (4.3)
Constipation	33 (31.4)	0	178 (32.1)	4 (0.7)
Vomiting	23 (21.9)	0	168 (30.3)	24 (4.3)
Diarrhoea	21 (20.0)	4 (3.8)	105 (19.0)	10 (1.8)
Abdominal pain	8 (7.6)	1 (1.0)	104 (18.8)	18 (3.2)
Abdominal pain upper	3 (2.9)	0	40 (7.2)	1 (0.2)
Ascites	1 (1.0)	0	30 (5.4)	15 (2.7)

Preferred Term	Basket trial SCLC Cohort (N = 105)		Basket trial All cohorts + Corail trial (N = 554)	
	G>=1	G>=3	G>=1	G>=3
	n (%)	n (%)	n (%)	n (%)
Dysphagia	6 (5.7)	1 (1.0)	9 (1.6)	2 (0.4)
Fatigue	81 (77.1)	13 (12.4)	350 (63.2)	56 (10.1)
Pyrexia	14 (13.3)	0	74 (13.4)	1 (0.2)
Oedema peripheral	4 (3.8)	0	52 (9.4)	1 (0.2)
Mucosal inflammation	4 (3.8)	0	31 (5.6)	2 (0.4)
Chest pain	11 (10.5)	0	23 (4.2)	0
Upper respiratory tract infection	8 (7.6)	4 (3.8)	15 (2.7)	5 (0.9)
Pneumonia	8 (7.6)	5 (4.8)	14 (2.5)	8 (1.4)
Respiratory tract infection	6 (5.7)	0	10 (1.8)	1 (0.2)
Neutrophil count decreased	4 (3.8)	3 (2.9)	29 (5.2)	23 (4.2)
Weight decreased	8 (7.6)	1 (1.0)	29 (5.2)	3 (0.5)
Decreased appetite	35 (33.3)	1 (1.0)	138 (24.9)	7 (1.3)
Hypoalbuminaemia	6 (5.7)	1 (1.0)	21 (3.8)	4 (0.7)
Back pain	17 (16.2)	3 (2.9)	54 (9.7)	9 (1.6)
Arthralgia	7 (6.7)	0	35 (6.3)	0
Musculoskeletal pain	9 (8.6)	1 (1.0)	27 (4.9)	2 (0.4)
Pain in extremity	7 (6.7)	0	25 (4.5)	2 (0.4)
Headache	10 (9.5)	1 (1.0)	50 (9.0)	1 (0.2)
Dysgeusia	6 (5.7)	0	21 (3.8)	0
Insomnia	5 (4.8)	0	48 (8.7)	0
Dyspnoea	32 (30.5)	6 (5.7)	87 (15.7)	14 (2.5)
Cough	19 (18.1)	0	57 (10.3)	1 (0.2)
Dysphonia	6 (5.7)	0	11 (2.0)	0

Adverse reactions are listed by System Organ Class and frequency. The frequencies are classified as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100) and rare (≥ 1/10,000 to < 1/1000).

Table 3. Related Adverse Reactions with a cut off at 5% by System Organ Classes (SOC)

System Organ Class	Adverse Reactions*
Blood and lymphatic system disorders	Neutropenia, Anaemia, Thrombocytopenia, Febrile neutropenia
Gastrointestinal disorders	Nausea, Vomiting, Constipation, Diarrhoea, Abdominal pain
General disorders and administration site conditions	Fatigue, Mucosal inflammation
Investigations	Neutrophil count decreased
Metabolism and nutrition disorders	Decreased appetite

* Includes ADRs of SCLC cohort and Basket + Corail

The following clinically significant adverse reactions are described in detail in other sections of the prescribing information:
• Bone Marrow Suppression *[see Special Warnings and Precautions (4.4)]*
• Infection in the Absence of Neutropenia *[see Special Warnings and Precautions (4.4)]*
• Hepatotoxicity *[see Special Warnings and Precautions (4.4)]*
• Embryo-Fetal Toxicity *[see Special Warnings and Precautions (4.4)]*

Clinical trials

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described below reflect exposure to ZEPZELCA in 554 patients treated with single agent. The safety of ZEPZELCA was evaluated in one open-label trial in selected solid tumours and one randomised trial in platinum-resistant ovarian cancer (CORAIL). All patients received ZEPZELCA at the recommended dosing regimen of 3.2 mg/m^2 every 21 days. Those patients include 105 with SCLC, 230 patients with various cancers (endometrial carcinoma [n=73], neuroendocrine tumours [n=32], Ewing's family of tumours [n=28], germ cell tumours [n=23], BRCA 1/2-associated metastatic breast carcinoma [n=21], biliary tract carcinoma [n=19], carcinoma of unknown primary site [n=19], and head and neck carcinoma [n=15]) and 219 ovarian cancer.

For the 554 patients treated with single agent ZEPZELCA, the median duration of treatment was 13.3 weeks (range: 1.1-162.3) with a median cumulative dose of 12.6 mg/m^2 (range: 3.1-167.1).

Table 4 and Table 5 present selected haematological and non-haematological adverse reactions, respectively, observed in the SCLC cohort from the Basket trial and from the combined experience of 554 patients of the Basket and CORAIL trials.

Among the subset of patients with SCLC, the most common (≥20%) haematological adverse events (all grades regardless of relationship) were anaemia (95%), lymphopenia (86%), leukopenia (79.0%), neutropenia (71%), and thrombocytopenia (44%). Grade 3/4 haematological adverse events occurring in ≥5% of patients were neutropenia (46%), lymphopenia (44%), leukopenia (29%), anaemia (10%), thrombocytopenia (7%), and febrile neutropenia (5%) [*see 4.4 Special Warnings and Precautions for Use*].

Among the subset of patients with SCLC, the most common (≥20%) non-haematological adverse reactions (all grades) were fatigue (59%); nausea (32%); decreased appetite (21%); abnormal liver function tests including increased ALT (72%), AST (45%), and alkaline phosphatase (33%); and abnormal kidney function tests including increased creatinine (83%). Most episodes of creatinine increase during treatment were non-clinically significant, and the observed high rate of abnormalities is mainly due to the definition of grade 1 or 2 creatinine increase in NCI-CTCAE v.4, in which normal creatinine values are considered grade 1 or 2. Grade 3/4 non-haematological adverse reactions were uncommon; the most frequent (occurring in ≥5% of patients) events were fatigue (8%) and ALT increased (4%).

Dose reductions due to an adverse reaction occurred in 27% of patients with SCLC who received ≥ 2 cycles of ZEPZELCA.

Adverse reactions requiring dose reduction in >2% of patients with SCLC who received ZEPZELCA included neutropenia, febrile neutropenia, thrombocytopenia, pneumonia, and fatigue.

Treatment delays due to an adverse event occurred in 23% of patients with SCLC who received ≥ 2 cycles of ZEPZELCA. The most common adverse events leading to treatment delays included neutropenia, thrombocytopenia, anaemia, hypoalbuminaemia.

Treatment discontinuation due to treatment related adverse event occurred in 1.9% of patients with SCLC who received ZEPZELCA.

Table 4: Grade 3/4 Haematological Abnormalities Experienced by ≥10% of Patients

Haematological Abnormalities (Gr 3/4)	% Incidence	
	SCLC (n=105)	All Patients (n=554)
Neutropenia*		
$<1 \times 10^9$/L (Gr 3/4)	46%	41%
$<0.5 \times 10^9$/L (Gr 4)	25%	22%
Febrile neutropenia/Neutropenic sepsis	5%	7%
Leukopenia*		
$<2 \times 10^9$/L (Gr 3/4)	29%	30%
$<1 \times 10^9$/L (Gr 4)	10%	11%
Lymphopenia*		
$<0.5 \times 10^9$/L (Gr 3/4)	44%	34%
Thrombocytopenia*		
$<50 \times 10^9$/L (Gr 3/4)	7%	10%
Anaemia*		
<5 mmol/L (Gr 3/4) or transfusion indicated	10%	17%

*regardless of relationship

Table 5: Non-haematological Adverse Reactions Experienced by ≥10% of Patients, Including 105 Patients with Small Cell Lung Cancer

Non-Haematological Adverse Reactions	% Incidence			
	All Grades		Grade 3/4	
	SCLC (n=105)	All Patients (n=554)	SCLC (n=105)	All Patients (n=554)
Gastrointestinal disorders				
Constipation	10%	17%	0%	<1%
Diarrhea	13%	13%	1%	1%
Nausea	32%	51%	0%	3%
Vomiting	18%	25%	0%	3%
General disorders and administrative site conditions				
Fatigue	59%	53%	8%	7%

Non-Haematological Adverse Reactions	% Incidence			
	All Grades		Grade 3/4	
Investigations (laboratory abnormalities regardless of relationship)				
AP increased*	33%	46%	3%	5%
ALT increased*	72%	66%	4%	6%
AST increased*	45%	53%	2%	3%
Bilirubin increased*	10%	12%	0%	2%
Creatinine increased*	83%	84%	0%	2%
Metabolism and nutrition disorders				
Decreased appetite	21%	17%	0%	0%

Abbreviations: ALT=alanine aminotransferase; AP=alkaline phosphatase; AST=aspartate aminotransferase
*Biochemical abnormalities (regardless of relationship)

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. "Healthcare professionals are encouraged to report any suspected adverse reactions at https://www.hsa.gov.sg/adverse-events and drugsafety-STA@stbiopharma.com.

Overdose

If an overdose is suspected, monitor the patient closely for myelosuppression and hepatic enzymes and institute supportive-care measures as appropriate.

Haemodialysis is not expected to enhance the elimination of ZEPZELCA because lurbinectedin is highly bound to plasma proteins (99%), and renal excretion is negligible.

There is no known antidote for overdosage with ZEPZELCA.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Lurbinectedin (ZEPZELCA) inhibits the oncogenic transcription process through (i) its binding to CG-rich sequences of DNA, mainly located around promoters of protein-coding genes; (ii) the eviction of oncogenic transcription factors from their binding sites; and (iii) the stalling of elongating RNA polymerase II on those gene promoters and its specific degradation by the ubiquitin/proteasome machinery with all these processes leading to subsequent cellular apoptosis.

Cardiac Electrophysiology

The potential for QTc prolongation with lurbinectedin was evaluated in 39 patients with advanced cancer. No large effect (>20 ms) on the QTc interval was detected with lurbinectedin dosed at 3.2 mg/m² every 3 weeks.

Clinical Trials

In an open-label, multicentre, single-arm study (phase II Basket trial that included 9 different indications), 105 SCLC patients were treated with 3.2 mg/m² ZEPZELCA, administered as a 60-minute IV infusion repeated every 21 days. Of the 105 treated patients, 60% were male, 75.2% were white, 92.4% had ECOG PS 0 or 1, and the median age was 60 years (range, 40-83 years; 35.2% were

≥ 65 years old). Two of the 105 treated patients (1.9%) had previously undergone surgery (curative resection in one patient). Prior radiotherapy had been administered to 75 patients (71.4%). The patients had received a median of one prior line of chemotherapy for advanced disease (range, 1-2 lines).

Treatment continued until disease progression, unacceptable toxicity, treatment delay >3 weeks from the treatment due date (except in case of clear clinical benefit, upon Sponsors' approval), requirement of >2 dose reductions, intercurrent illness of sufficient magnitude to preclude safe continuation of the study, a major protocol deviation that may affect the risk/benefit ratio for the participating patient, Investigator's decision, non-compliance with study requirements, or patient's refusal.

The primary efficacy outcome measure was overall response rate (ORR), as assessed by an Independent Review Committee based on RECIST v1.1. An additional efficacy outcome measure was response duration. Efficacy results are shown in Table 6.

Table 6   Efficacy of ZEPZELCA in Small Cell Lung Cancer Patients (primary outcomes)

Parameter	Assessment by	Overall (n=105)	Resistant Disease (CTFI<90 days) (n=45)	Sensitive Disease (CTFI≥90 days) (n=60)
Overall response rate (CR+PR)* (95% CI)	Investigator	35.2% (26.2 - 45.2)	22.2% (11.2 - 37.1)	45.0% (32.1 - 58.4)
	IRC	30.5% (21.9 - 40.2)	13.3% (5.1 - 26.8)	43.3% (30.6 - 56.8)
Duration of response, median, months (95% CI)	Investigator	5.3 months (4.1 - 6.4)	4.7 months (2.6 - 5.6)	6.2 months (3.5 - 7.3)
	IRC	5.1 months (4.9 - 6.4)	4.8 months (2.4 - 5.3)	5.3 months (4.9 - 7.0)

CI: confidence interval, CR: complete response, PR: partial response, SD: stable disease, IRC: Independent Review Committee, CTFI: chemotherapy free interval * All responses were PR, no complete responses were recorded.

Median overall survival in the whole population is 9.3 months (CI: 6.3-11.8), with 5.0 months (CI: 4.1-6.3) in the platinum-resistant population and 11.9 months (CI: 9.7-16.2) in the platinum-sensitive population.

Figure 1   Kaplain-Meier plot of duration of response by Investigator assessment according to CTFI (<90 days and ≥90 days).
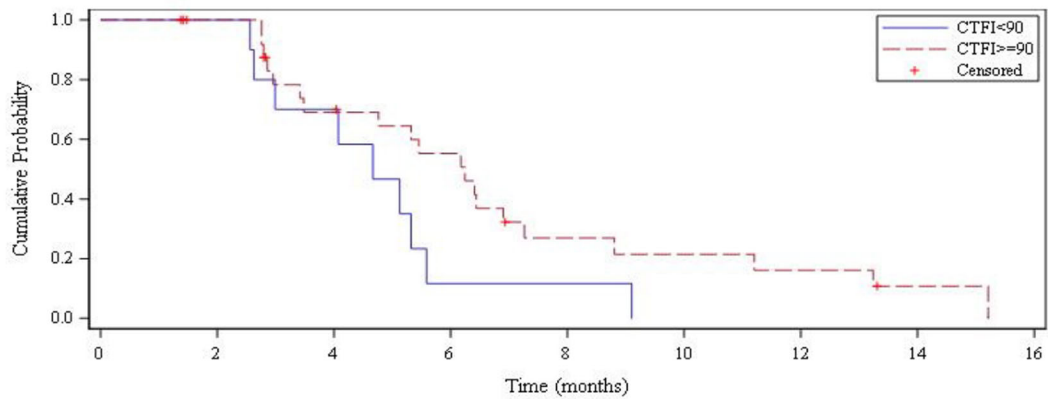
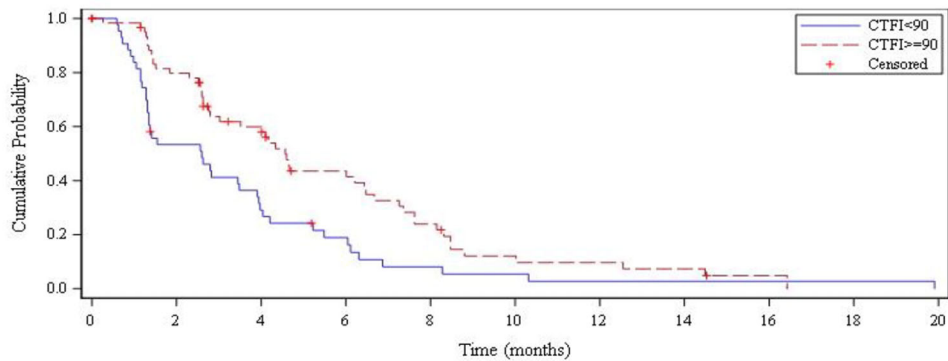The secondary outcome measures included progression free survival (PFS) and overall survival (OS), the results of which are shown in Table 7.

**Table 7   Investigator Assessed Efficacy of ZEPZELCA in Small Cell Lung Cancer Patients (secondary outcomes)**

	N	PFS months median (95% CI)	PFS at 6 months % (95% CI)	OS months median (95% CI)	OS at 12 months % (95% CI)
All	105	3.5 (2.6-4.3)	32.9 (23.3-42.5)	9.3 (6.3-11.8)	34.2 (23.2-45.1)
Resistant CTFI <90d	45	2.6 (1.3-3.9)	18.8 (6.8-30.9)	5.0 (4.1-6.3)	15.9 (3.6-28.2)
Sensitive CTFI ≥90d	60	4.6 (2.8-6.5)	43.5 (30.1-56.9)	11.9 (9.7-16.2)	48.3 (32.5-64.1)

Figure 2. **Kaplan-Meier plot of progression free survival by Investigator assessment according to CTFI (<90 days and ≥90 days).**

Figure 3. **Kaplan-Meier plot of overall survival according to CTFI (<90 days and ≥90 days).**
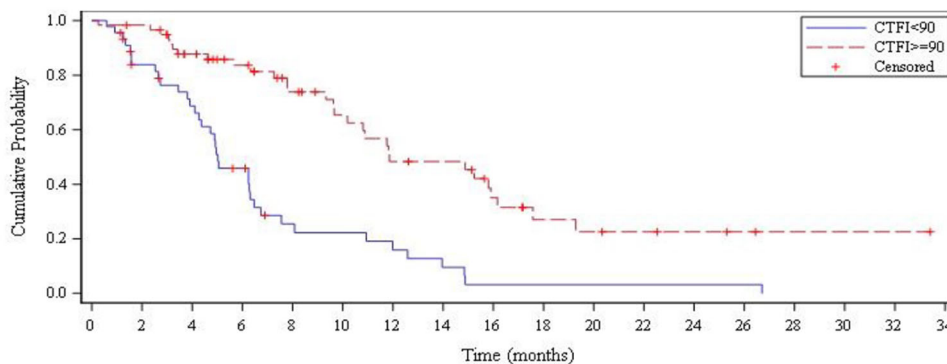
5.2 PHARMACOKINETIC PROPERTIES

After a 3.2 mg/m^2 lurbinectedin dose administered as a 1-hour IV infusion, geometric means of total plasma C_{max} and $AUC_∞$, were 107 µg/L and 551 µg*h/L, respectively. No accumulation of lurbinectedin in plasma is observed upon repeated administrations every 3 weeks.

Distribution

Typical volume of distribution of lurbinectedin at steady state is 504 L. Binding to plasma proteins is approximately 99%, to both albumin and α-1-acid glycoprotein.

Metabolism

In vitro studies with human liver microsomes and supersomes indicate that CYP3A4 is the only CYP enzyme responsible for the hepatic metabolism of lurbinectedin.

Excretion

The terminal half-life of lurbinectedin is 51 hours. Total plasma clearance of lurbinectedin is 11 L/h.

The major route of lurbinectedin-related radioactivity excretion was via faeces (89% of dose). The most abundant metabolite found in faeces accounted for 1% of the dose and only traces of unchanged lurbinectedin were detected in faeces (<0.2% of dose). Excretion in urine was the minor route (6% of dose), mainly as unchanged compound (1% of dose) and one metabolite (up to 1% of dose).

Pharmacokinetics in Specific Populations

Population pharmacokinetics analyses showed that weight (range: 39-154 kg), age (range: 18-85 years), and sex do not have a clinically meaningful influence on the systemic exposure of lurbinectedin.

Hepatic impairment

Based on population pharmacokinetic analysis, no apparent pharmacokinetic difference was observed in 125 patients with mild hepatic impairment (total bilirubin ≤ULN and AST >ULN, or total bilirubin between 1.0-1.5×ULN and any AST) who received ZEPZELCA 3.2 mg/m² every 3 weeks as compared to 625 patients with normal hepatic function.

The pharmacokinetic characteristics of lurbinectedin in patients with moderate to severe hepatic impairment (total bilirubin >1.5×ULN) are unknown.

Renal impairment

Based on population pharmacokinetic analyses, no apparent pharmacokinetic difference was observed in 165 patients with mild renal impairment (CL_{CR} of 60-89 mL/min], 73 patients with moderate renal impairment (CL_{CR} of 30-59 mL/min), and one patient with severe renal impairment (CL_{CR} of 26 mL/min) who received ZEPZELCA 3.2 mg/m² every 3 weeks as compared to 166 patients with normal renal function. The pharmacokinetic characteristics of lurbinectedin in patients with CL_{CR} <30 mL/min or patients on dialysis are unknown.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Lurbinectedin is known to be genotoxic to mammalian cells. Lurbinectedin was not mutagenic *in vitro* in a bacterial reverse mutation (Ames) assay.

Carcinogenicity

Carcinogenicity testing of lurbinectedin has not been performed.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

(S)-lactic acid

Sucrose

Sodium Hydroxide

Water for Injection

6.2 INCOMPATIBILITIES

ZEPZELCA must not be mixed or diluted with other medicinal products except those mentioned in Section 4.2.

6.3   SHELF LIFE

Unopened vials

48 months.

After reconstitution

Chemical and physical stability has been demonstrated for 24 hours up to 25°C with exposure to ambient light or under refrigeration (2° to 8°C).

From a microbiological point of view, the reconstituted drug product is also stable for up to 24 hours when stored in the vial at either room temperature with exposure to ambient light or under refrigeration 2° to 8°C).

The reconstituted solution should be diluted and used immediately. If not diluted and used immediately, in-use storage times and conditions prior to use of the reconstituted product are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless reconstitution has taken place in controlled and validated aseptic conditions.

After dilution

Chemical and physical stability has been demonstrated for 24 hours up to 25°C with exposure to ambient light or under refrigeration (2° to 8°C).

The expiry date can be found on the packaging.

6.4   SPECIAL PRECAUTIONS FOR STORAGE

Store unopened vial in refrigerator at 2° to 8°C.

6.5   NATURE AND CONTENTS OF CONTAINER

ZEPZELCA (lurbinectedin) powder for solution for infusion is supplied as a sterile, preservative-free, white to off white lyophilised powder in a 30 mL clear glass vial. Each carton contains one single-dose vial.

6.6   SPECIAL PRECAUTIONS FOR DISPOSAL

ZEPZELCA is a cytotoxic drug. Follow applicable special handling and disposal procedures.

Any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7   PHYSICOCHEMICAL PROPERTIES

ZEPZELCA is a synthetic molecule, which binds to the minor groove of DNA and is a selective inhibitor of oncogenic transcription. The chemical name of ZEPZELCA (lurbinectedin) is (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.

Molecular formula: $C_{41}H_{44}N_4O_{10}S$.

Molecular weight: 784.87 g/mol.

Chemical structure:
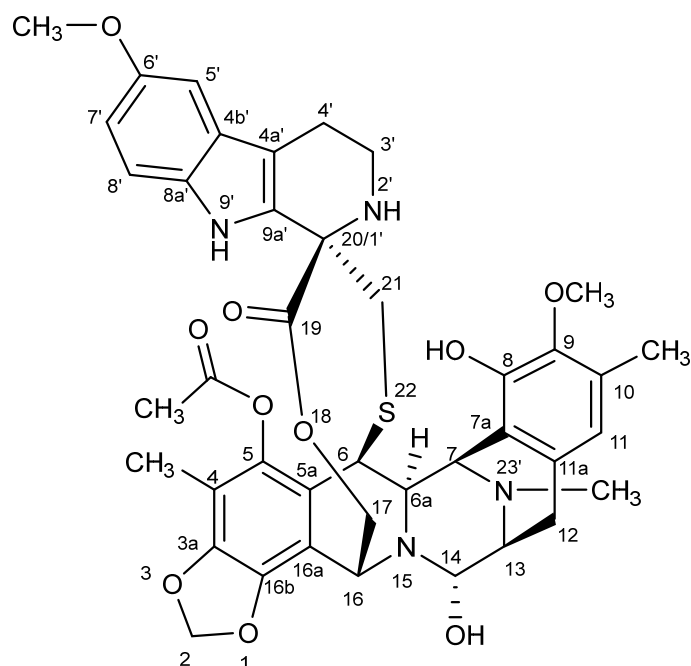
CAS number

497871-47-3

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8 DATE OF FIRST APPROVAL

To be inserted upon approval.

9 DATE OF REVISION

N/A

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information