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

ZEPZELCA must be administered under the supervision of a physician experienced in the use of chemotherapy. Its use should be confined to qualified oncologists or other health professionals specialised in the administration of cytotoxic agents.

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.

Only administer ZEPZELCA to patients with an absolute neutrophil count above 1.5 x 10^9/L, and a platelet count above 100 x 10^9/L.

Dose modifications for adverse reactions

The recommended dose reduction levels for adverse reactions are listed in Table 1. Dosage modifications for ZEPZELCA for adverse reactions are presented in Table 2. Permanently discontinue ZEPZELCA in patients who are unable to tolerate 2.0 mg/m^2 or require a dose delay greater than two weeks.

Table 1: ZEPZELCA dose reduction schedule

Dose level	Dose amount
Initial dose	3.2 mg/m^2
On 1st dose reduction	2.6 mg/m^2
On 2nd dose reduction	2.0 mg/m^2

Discontinue ZEPZELCA if patients are unable to tolerate 2.0 mg/m^2 every 21 days.

Table 2: Dosage modifications for ZEPZELCA for adverse reactions

Adverse reaction	Severity*	Dosage modification
Neutropenia [see *4.4 Special warnings and precautions for use*]	Grade 4** or Any grade febrile neutropenia	• Withhold ZEPZELCA until Grade ≤ 1 • Resume ZEPZELCA at a reduced dose
Thrombocytopenia [see *4.4 Special warnings and precautions for use*]	Grade 3 with bleeding or Grade 4	• Withhold ZEPZELCA until platelet ≥ 100 x 10^9/L • Resume ZEPZELCA at a reduced dose
Hepatotoxicity [see *4.4 Special warnings and precautions for use*]	Grade 2	• Withhold ZEPZELCA until Grade ≤ 1 • Resume ZEPZELCA at a reduced dose
	Grade ≥ 3	• Withhold ZEPZELCA until Grade ≤ 1 • Resume ZEPZELCA at a reduced dose or permanently discontinue
Rhabdomyolysis [see *4.4 Special warnings and precautions for use*]	Grade 2	• Withhold ZEPZELCA until Grade ≤ 1 • Resume ZEPZELCA at same dose
	Grade ≥ 3	• Permanently discontinue ZEPZELCA.
Other Adverse Reactions [*see Post-marketing (4.8)*]	Grade 2	• Withhold ZEPZELCA until Grade ≤ 1 • Resume ZEPZELCA at same dose
	Grade ≥ 3	• Withhold ZEPZELCA until Grade ≤ 1 • Resume ZEPZELCA at a reduced dose or permanently discontinue

* National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0.
** Patients with isolated Grade 4 neutropenia (neutrophil count less than 0.5 x 10^9/L) may receive G-CSF prophylaxis rather than undergo lurbinectedin dose reduction.

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

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:

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

- 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.

Administration

- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If particulate matter is observed, do not administer.
- ZEPZELCA can be administered with or without an in-line filter. If infusion lines containing in-line filters are utilized for administration of ZEPZELCA, Polyethersulfone (PES) in-line filters with pore sizes of 0.22 micron are recommended.
    - Do not use in-line nylon membrane filters when the reconstituted ZEPZELCA solution is diluted using 0.9% Sodium Chloride Injection, USP. Adsorption of ZEPZELCA to the Nylon membrane filters has been observed when 0.9% Sodium Chloride Injection, USP is used as the diluent.

- Compatibility with other intravenous administration materials and the diluted ZEPZELCA solution has been demonstrated in the following materials:
    - Polyolefin containers (polyethylene, polypropylene and mixtures).
    - Polyvinyl Chloride (PVC) (non-DEHP-containing), polyurethane and polyolefin infusion sets (polyethylene, polypropylene and polybutadiene).

    - Implantable venous access systems with titanium and plastic resin ports and with polyurethane or silicone intravenous catheters.
- Do not co-administer ZEPZELCA and other intravenous drugs concurrently within the same intravenous line.

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.

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*].

Extravasation Resulting in Tissue Necrosis
Extravasation of ZEPZELCA resulting in skin and soft tissue injury, including necrosis requiring debridement, can occur. Consider use of a central venous catheter to reduce the risk of extravasation, particularly in patients with limited venous access. Monitor patients for signs and symptoms of extravasation during the ZEPZELCA infusion. If extravasation occurs, immediately discontinue the infusion, remove the infusion catheter, and monitor for signs and symptoms of tissue necrosis. The time to onset of necrosis after extravasation may vary.
Administer supportive care and consult with an appropriate medical specialist as needed for signs and symptoms of extravasation. Administer subsequent infusions at a site that was not affected by extravasation.

Rhabdomyolysis
Rhabdomyolysis has been reported in patients treated with ZEPZELCA. Monitor creatine phosphokinase (CPK) prior to initiating ZEPZELCA and periodically during treatment as clinically indicated. Withhold or reduce the dose based on severity *[see Dosage and Administration (4.2)]*.

If rhabdomyolysis occurs, supportive measures such as parenteral hydration, urine alkalinization and dialysis should be promptly established, as indicated. Caution should be taken if medicinal products with known association with rhabdomyolysis (e.g. statins), are administered concomitantly with lurbinectedin, since the risk of rhabdomyolysis may be increased.

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 3: 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)

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 (%)
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)
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)

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 (%)
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 4. 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)]*
• Hepatotoxicity *[see Special Warnings and Precautions (4.4)]*
• **Extravasation Resulting in Tissue Necrosis** *[see Special Warnings and Precautions (4.4)]*
• **Rhabdomyolysis** *[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 5 and Table 6 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 5: 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 x 10^9/L (Gr 3/4)	46%	41%
<0.5 x 10^9/L (Gr 4)	25%	22%
Febrile neutropenia/Neutropenic sepsis	5%	7%
Leukopenia*		
<2 x 10^9/L (Gr 3/4)	29%	30%
<1 x 10^9/L (Gr 4)	10%	11%
Lymphopenia*		
<0.5 x 10^9/L (Gr 3/4)	44%	34%
Thrombocytopenia*		
<50 x 10^9/L (Gr 3/4)	7%	10%
Anaemia*		
<5 mmol/L (Gr 3/4) or transfusion indicated	10%	17%

*regardless of relationship

Table 6: 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%

Non-Haematological Adverse Reactions	% Incidence			
	All Grades		Grade 3/4	
General disorders and administrative site conditions				
Fatigue	59%	53%	8%	7%
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)

Postmarketing Experience

The following adverse reactions have been identified during post-approval use of ZEPZELCA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

General disorders and administration site conditions: Extravasation (including tissue necrosis requiring debridement).

Musculoskeletal and Connective Tissue Disorders: Rhabdomyolysis.

Metabolism and nutrition disorders: Tumor lysis syndrome.

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/m^2 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 7.

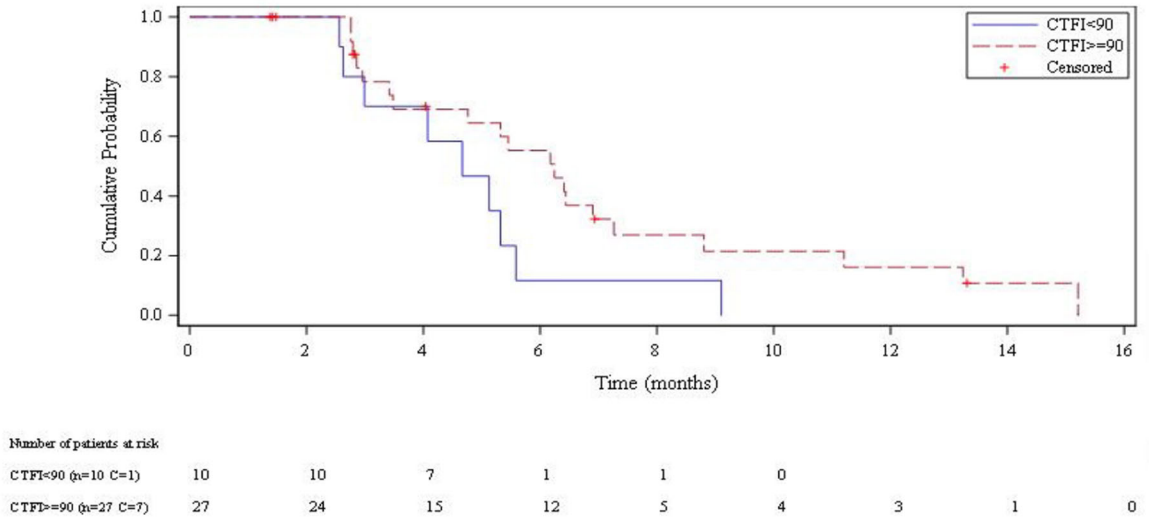
Table 7 Efficacy of ZEPZELCA in Small Cell Lung Cancer Patients (primary outcomes)

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 8.

Table 8 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).

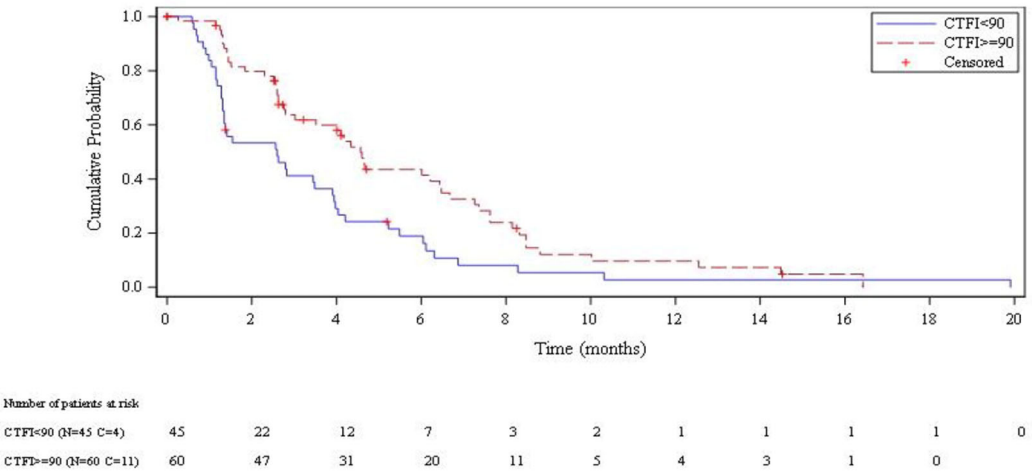
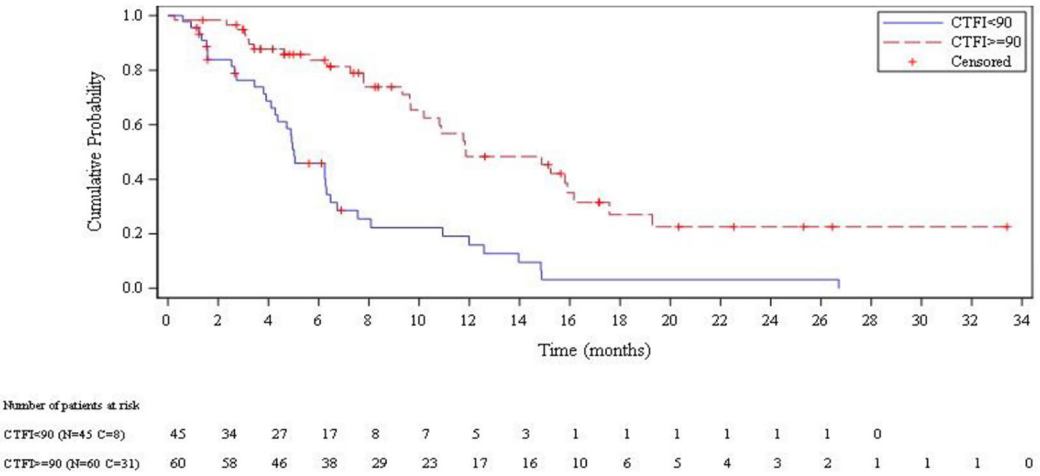


Figure 3. Kaplan-Meier plot of overall survival according to CTFI (<90 days and ≥90 days).



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.

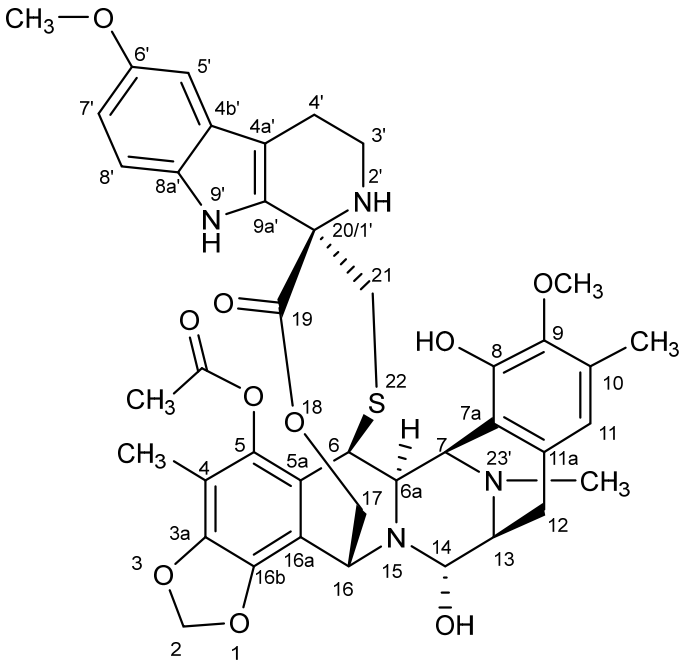
6.7 PHYSICOCHEMICAL PROPERTIES

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

21 September 2021

9 DATE OF REVISION

15 NOVEMBER 2022

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.2	Dose Modifications for Adverse Reactions and Administration Instructions
4.4	SPECIAL WARNINGS AND PRECAUTIONS FOR USE
4.8	ADVERSE EFFECTS (UNDESIRABLE EFFECTS)