FULL PRESCRIBING INFORMATION

1. NAME OF THE MEDICINAL PRODUCT

Zepzelca

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 vial contains 4 mg of Lurbinectedin (lyophilized powder)

For the full list of excipients, see section 16.1.

3. PHARMACEUTICAL FORM

Lyophilized Powder for solution for infusion.

A sterile, preservative-free, white to off-white lyophilized powder in a single-dose vial for reconstitution prior to intravenous infusion.

4. THERAPEUTIC INDICATIONS

ZEPZELCA is indicated for the treatment of adult patients with metastatic small cell lung cancer (SCLC) with disease progression on or after platinum-based chemotherapy.

5. DOSAGE AND ADMINISTRATION

5.1 Recommended Dosage

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

Initiate treatment with ZEPZELCA only if absolute neutrophil count (ANC) is at least 1,500 cells/mm^3 and platelet count is at least 100,000/mm^3.

5.2 Dosage Modifications for Adverse Reactions

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

Table 1: Dose Reduction for ZEPZELCA for Adverse Reactions

Dose Reduction	Total Dose
First	2.6 mg/m^2 every 21 days
Second	2 mg/m^2 every 21 days

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

Dosage modifications for ZEPZELCA for adverse reactions are presented in Table 2.

Table 2: Dosage Modifications for ZEPZELCA for Adverse Reactions

Adverse Reaction	Severity[a]	Dosage Modification
Neutropenia[b] *[see Warnings and Precautions (7.1)]*	Grade 4 or Any grade febrile neutropenia	• Withhold ZEPZELCA until Grade ≤ 1 • Resume ZEPZELCA at a reduced dose
Thrombocytopenia *[see Warnings and Precautions (7.1)]*	Grade 3 with bleeding or Grade 4	• Withhold ZEPZELCA until platelet ≥ 100,000/mm^3 • Resume ZEPZELCA at reduced dose
Hepatotoxicity *[see Warnings and Precautions (7.2)]*	Grade 2	• Withhold ZEPZELCA until Grade ≤ 1 • Resume ZEPZELCA at same dose
	Grade ≥ 3	• Withhold ZEPZELCA until Grade ≤ 1 • Resume ZEPZELCA at reduced dose or permanently discontinue
Rhabdomyolysis *[see Warnings and Precautions (7.4)]*	Grade 2	• Withhold ZEPZELCA until Grade ≤ 1 • Resume ZEPZELCA at same dose
	Grade ≥ 3	• Permanently discontinue ZEPZELCA.
Other Adverse Reactions *[see Postmarketing (8.2)]*	Grade 2	• Withhold ZEPZELCA until Grade ≤ 1 • Resume ZEPZELCA at same dose

	Grade ≥ 3	• Withhold ZEPZELCA until Grade ≤ 1 • Resume ZEPZELCA at reduced dose or permanently discontinue

[a] National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0.
[b] Patients with isolated Grade 4 neutropenia (neutrophil count less than 500 cells/mm^3) may receive G-CSF prophylaxis rather than undergo lurbinectedin dose reduction.

5.3 Premedication

Consider administering the following pre-infusion medications for antiemetic prophylaxis *[see Adverse Reactions (8.1)]:*

- Corticosteroids (dexamethasone 8 mg intravenously or equivalent)
- Serotonin antagonists (ondansetron 8 mg intravenously or equivalent)

5.4 Preparation, Administration and Storage

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

Preparation

- Inject 8 mL of Sterile Water for Injection USP into the vial, yielding a solution containing 0.5 mg/mL lurbinectedin. Shake the vial until complete dissolution.
- Visually inspect the solution for particulate matter and discoloration. The reconstituted solution is a clear, colorless or slightly yellowish solution, essentially free of visible particles.
- 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).

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.

Storage of Infusion Solution

- If not used immediately after reconstitution or dilution, the ZEPZELCA solution can be stored prior to administration for up to 24 hours following reconstitution, including infusion time, at either room temperature/ ambient light or under refrigeration at 2ºC-8ºC (36ºF-46ºF) conditions.

6. CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients listed in section 16.1.

7. WARNINGS AND PRECAUTIONS

7.1 Myelosuppression

ZEPZELCA can cause myelosuppression.

In clinical studies of 554 patients with advanced solid tumors receiving ZEPZELCA *[see Adverse Reactions (8.1)]*, Grade 3 or 4 neutropenia occurred in 41% of patients, with a median time to onset of 15 days and a median duration of 7 days. Febrile neutropenia occurred in 7% of patients. Sepsis occurred in 2% of patients and was fatal in 1% (all cases occurred in patients with solid tumors other than SCLC). Grade 3 or 4 thrombocytopenia occurred in 10%, with a median time to onset of 10 days and a median duration of 7 days. Grade 3 or 4 anemia occurred in 17% of patients.

Administer ZEPZELCA only to patients with baseline neutrophil count of at least 1,500 cells/mm^3 and platelet count of at least 100,000/mm^3. Monitor blood counts including neutrophil count and platelet count prior to each administration. For neutrophil count less than 500 cells/mm^3 or any value less than lower limit of normal, the use of G-CSF is recommended. Withhold, reduce the dose, or permanently discontinue ZEPZELCA based on severity *[see Dosage and Administration (5.2)]*.

7.2 Hepatotoxicity

ZEPZELCA can cause hepatotoxicity.

In clinical studies of 554 patients with advanced solid tumors receiving ZEPZELCA *[see Adverse Reactions (8.1)]*, Grade 3 elevations of ALT and AST were observed in 6% and 3% of patients, respectively, and Grade 4 elevations of ALT and AST were observed in 0.4% and 0.5% of patients, respectively. The median time to onset of Grade ≥3 elevation in transaminases was 8 days (range: 3 to 49), with a median duration of 7 days.

Monitor liver function tests prior to initiating ZEPZELCA and periodically during treatment as clinically indicated. Withhold, reduce the dose, or permanently discontinue ZEPZELCA based on severity *[see Dosage and Administration (5.2)]*.

7.3 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.

7.4 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 (5.2)]*.

7.5 Embryo-Fetal Toxicity

Based on animal data and its mechanism of action ZEPZELCA can cause fetal harm when administered to a pregnant woman. Intravenous administration of a single dose of lurbinectedin (approximately 0.2 times the 3.2 mg/m^2 clinical dose) to pregnant animals during the period of organogenesis caused 100% embryolethality in rats. Advise pregnant women of the potential risk to a fetus. Advise female patients of reproductive potential to use effective contraception during treatment with ZEPZELCA and for 6 months after the final dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with ZEPZELCA and for 4 months after the final dose *[see Use in Specific Populations (10.1, 10.3)]*.

8. ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Myelosuppression
  Advise patients to immediately contact their healthcare provider for fever, other signs of infection, unusual bruising, bleeding, tiredness or pallor
  [see Warnings and Precautions (7.1)]
- Hepatotoxicity
  Advise patients to contact their healthcare provider immediately for signs and symptoms suggestive of hepatotoxicity [see Warnings and Precautions (7.2)]
- Extravasation Resulting in Tissue Necrosis
  Advise patients to contact their healthcare provider immediately for signs and symptoms of extravasation. The time to onset of necrosis after extravasation may vary
  [see Warnings and Precautions (7.3)]
- Rhabdomyolysis
  Advise patients to contact their healthcare provider immediately for signs and symptoms of rhabdomyolysis [see Warnings and Precautions (7.4)]

8.1 Clinical Trials Experience

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 pooled safety population described in the WARNINGS AND PRECAUTIONS reflects exposure to ZEPZELCA as a single agent at a dose of 3.2 mg/m^2 intravenously every 21 days in 554 patients with advanced solid tumors. Among 554 patients who received ZEPZELCA, including 105 patients with small cell lung cancer (SCLC) in PM1183-B-005-14 (Study B-005), 24% were exposed for 6 months or longer and 5% were exposed for greater than one year.

Small Cell Lung Cancer (SCLC)

The safety of ZEPZELCA was evaluated in a cohort of 105 patients with previously treated SCLC in Study B-005 *[see Clinical Studies (14)]*. Patients received ZEPZELCA 3.2 mg/m^2 intravenously every 21 days. All patients in this study received a pre-specified anti-emetic regimen consisting of a corticosteroid and serotonin antagonist. Patients could receive G-CSF for secondary prophylaxis (i.e., after patients had an initial decrease in WBC), but not primary prophylaxis. Among patients who received ZEPZELCA, 29% were exposed for 6 months or longer and 6% were exposed for greater than one year.

Serious adverse reactions occurred in 34% of patients who received ZEPZELCA. Serious adverse reactions in ≥ 3% of patients included pneumonia, febrile neutropenia, neutropenia, respiratory tract infection, anemia, dyspnea, and thrombocytopenia.

Permanent discontinuation due to an adverse reaction occurred in two patients (1.9%) who received ZEPZELCA. Adverse reactions resulting in permanent discontinuation in ≥ 1% of patients who received ZEPZELCA, which included peripheral neuropathy and myelosuppression.

Dosage interruptions due to an adverse reaction occurred in 30.5% of patients who received ZEPZELCA. Adverse reactions requiring dosage interruption in ≥ 3% of patients who received ZEPZELCA included neutropenia, and hypoalbuminemia.

Dose reductions due to an adverse reaction occurred in 25% of patients who received ZEPZELCA. Adverse reactions requiring dosage reductions in ≥ 3% of patients who received ZEPZELCA included neutropenia, febrile neutropenia and fatigue.

The most common adverse reactions, including laboratory abnormalities, (≥ 20%) were leukopenia, lymphopenia, fatigue, anemia, neutropenia, increased creatinine, increased alanine aminotransferase, increased glucose, thrombocytopenia, nausea, decreased appetite, musculoskeletal pain, decreased albumin, constipation, dyspnea, decreased sodium, increased aspartate aminotransferase, vomiting, cough, decreased magnesium and diarrhea.

Table 3 summarizes the adverse reactions in the SCLC cohort of Study B-005.

Table 3: Adverse Reactions (≥ 10%) in Patients with SCLC Who Received ZEPZELCA in Study B-005

Adverse Reaction	ZEPZELCA (n=105)	
	All Grades[a,b] (%)	Grades 3-4 (%)
General disorders		
Fatigue	77	12
Pyrexia	13	0
Chest pain	10	0
Gastrointestinal disorders		
Nausea	37	0
Constipation	31	0
Vomiting	22	0
Diarrhea	20	4
Abdominal pain[c]	11	1
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain[d]	33	4
Metabolism and nutrition disorders		
Decreased appetite	33	1
Respiratory, thoracic and mediastinal disorders		
Dyspnea	31	6
Cough[e]	20	0
Infections and infestations		
Respiratory tract infection[f]	18	5
Pneumonia[g]	10	7
Nervous system disorders		

Peripheral neuropathy[h]	11	1
Headache	10	1

[a] Graded per NCI CTCAE 4.0.
[b] No grade 5 adverse reactions were reported.
[c] Includes abdominal pain, abdominal pain upper and abdominal discomfort.
[d] Includes musculoskeletal pain, back pain, arthralgia, pain in extremity, musculoskeletal chest pain, neck pain, bone pain and myalgia.
[e] Includes cough and productive cough.
[f] Includes upper respiratory tract infection, viral upper respiratory tract infection, respiratory tract infection and bronchitis.
[g] Includes pneumonia and lung infection.
[h] Includes neuropathy peripheral, neuralgia, paresthesia, peripheral sensory neuropathy, hypoesthesia, and hyperesthesia.

Clinically relevant adverse reactions in < 10% of patients who received ZEPZELCA include dysgeusia, febrile neutropenia and pneumonitis.

Table 4 summarizes the laboratory abnormalities in Study B-005.

Table 4: Select Laboratory Abnormalities (≥ 20%) Worsening from Baseline in Patients with SCLC Who Received ZEPZELCA in Study B-005

	ZEPZELCA[a] (n=105)	
Laboratory Abnormality	**All Grades[b] (%)**	**Grades 3-4 (%)**
Hematology		
Decreased leukocytes	79	29
Decreased lymphocytes	79	43
Decreased hemoglobin	74	10
Decreased neutrophils	71	46
Decreased platelets	37	7
Chemistry		
Increased creatinine	69	0
Increased alanine aminotransferase	66	4
Increased glucose	52	5
Decreased albumin	32	1
Decreased sodium	31	7
Increased aspartate aminotransferase	26	2
Decreased magnesium	22	0

[a] The denominator used to calculate the rate varied from 95 to 105 based on the number of patients with a baseline value and at least one post-treatment value.
[b] Graded per NCI CTCAE 4.0.

8.2 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 of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il

9 DRUG INTERACTIONS

9.1 Effect of Other Drugs on ZEPZELCA

Strong and Moderate CYP3A Inhibitors

Coadministration of ZEPZELCA with a strong or a moderate CYP3A inhibitor increases lurbinectedin systemic exposure *[see Clinical Pharmacology (12.3)]* which may increase the incidence and severity of adverse reactions to ZEPZELCA.

Avoid grapefruit and seville oranges during ZEPZELCA treatment, as these contain strong or moderate inhibitors of CYP3A.

Strong CYP3A Inhibitors
Avoid coadministration of ZEPZELCA with strong CYP3A inhibitors.

Moderate CYP3A Inhibitors
Avoid coadministration of ZEPZELCA with moderate CYP3A inhibitors. If coadministration cannot be avoided, consider dose reduction of ZEPZELCA, if clinically indicated *[see Dosage and Administration (5.2)]*.

Strong CYP3A Inducers

Avoid coadministration of ZEPZELCA with strong CYP3A inducers. Coadministration of ZEPZELCA with a strong CYP3A inducer may decrease lurbinectedin systemic exposure, which may decrease the efficacy of ZEPZELCA*[see Clinical Pharmacology (12.3)]*.

10 USE IN SPECIFIC POPULATIONS

10.1 Pregnancy

Risk Summary

Based on animal data and its mechanism of action *[see Clinical Pharmacology (12.1)]*, ZEPZELCA can cause fetal harm when administered to a pregnant woman. There are no available data to inform the risk of ZEPZELCA use in pregnant women. Intravenous administration of a single lurbinectedin dose (approximately 0.2 times the 3.2 mg/m^2 clinical dose) to pregnant rats during the period of organogenesis caused embryolethality *(see Data)*.

Advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Animal Data

In a reproductive toxicity study, administration of a single lurbinectedin dose of 0.6 mg/m^2 (approximately 0.2 times of the human dose of 3.2 mg/m^2) to pregnant rats on Gestation Day 10 resulted in 100% post-implantation loss.

10.2 Lactation

Risk Summary

There are no data on the presence of lurbinectedin in human milk or its effects on the breastfed child or on milk production. Because of the potential for serious adverse reactions from ZEPZELCA in breastfed children, advise women not to breastfeed during treatment with ZEPZELCA and for 2 weeks after the final dose.

10.3 Females and Males of Reproductive Potential

ZEPZELCA can cause embryolethality at doses lower than the human dose of 3.2 mg/m^2 *[see Use in Specific Populations (10.1)]*.

Pregnancy Testing

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 treatment with ZEPZELCA and for 6 months after the final dose.

Males

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

10.4 Pediatric Use

The safety and effectiveness of ZEPZELCA in pediatric patients under the age of 18 years have not been established.

10.5 Geriatric Use

Of the 105 patients with SCLC administered ZEPZELCA in clinical studies, 37 (35%) patients were 65 years of age and older, while 9 (9%) patients were 75 years of age and older. No overall difference in effectiveness was observed between patients aged 65 and older and younger patients.

There was a higher incidence of serious adverse reactions in patients ≥ 65 years of age than in patients < 65 years of age (49% vs. 26%, respectively). The serious adverse reactions most frequently reported in patients ≥ 65 years of age were related to myelosuppression and consisted of febrile neutropenia (11%), neutropenia (11%), thrombocytopenia (8%), and anemia (8%) *[see Adverse Reactions (8.1)]*.

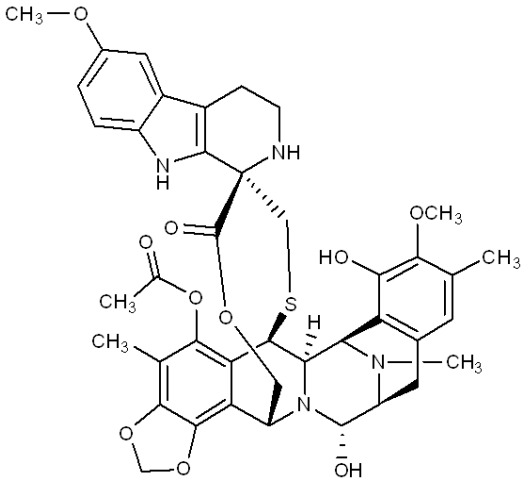
10.6 Hepatic Impairment

The effect of moderate or severe hepatic impairment (total bilirubin > 1.5 × ULN and any AST) on the pharmacokinetics of lurbinectedin has not been studied. No dose adjustment of ZEPZELCA 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) *[see Clinical Pharmacology (12.3)]*.

11 DESCRIPTION

ZEPZELCA is an alkylating drug. 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.

The molecular formula is $C_{41}H_{44}N_4O_{10}S$. The molecular weight is 784.87g/mol, and the chemical structure is:



ZEPZELCA for injection 4 mg is supplied as a lyophilized powder in a single-dose vial for reconstitution for intravenous use. The ZEPZELCA lyophilized formulation is comprised of 4 mg lurbinectedin, sucrose (800 mg), lactic acid (22.1 mg), and sodium hydroxide (5.1 mg). Before use, the lyophilizate is reconstituted by addition of 8 mL Sterile Water for Injection USP, yielding a solution containing 0.5 mg/mL lurbinectedin (the calculated concentration is 0.47 mg/mL based on the final volume of 8.5 mL).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Lurbinectedin is an alkylating drug that binds guanine residues in the minor groove of DNA, forming adducts and resulting in a bending of the DNA helix towards the major groove. Adduct formation triggers a cascade of events that can affect the subsequent activity of DNA binding proteins, including some transcription factors, and DNA repair pathways, resulting in perturbation of the cell cycle and eventual cell death.

Lurbinectedin inhibited human monocyte activity in vitro and reduced macrophage infiltration in implanted tumors in mice.

12.2 Pharmacodynamics

Lurbinectedin exposure-response relationships and the pharmacodynamic time-course for efficacy have not been fully characterized.

Increased incidence of Grade 4 neutropenia and Grade ≥ 3 thrombocytopenia were observed with increased lurbinectedin exposure.

Cardiac Electrophysiology

No large mean increase in QTc (i.e. > 20 ms) was detected following treatment with ZEPZELCA at the recommended dose of 3.2 mg/m^2.

12.3 Pharmacokinetics

Following the approved recommended dosage, geometric means (%CV) of plasma C_{max} and $AUC_{0\text{-}inf}$, were 107 µg/L (79%) and 551 µg•h/L (94%), respectively. No accumulation of lurbinectedin in plasma is observed upon repeated administrations every 3 weeks.

Distribution

The volume of distribution of lurbinectedin at steady state is 504 L (39%). Plasma protein binding is approximately 99%, to both albumin and α-1-acid glycoprotein.

Elimination

The terminal half-life of lurbinectedin is 51 hours. Total plasma clearance of lurbinectedin is 11 L/h (50%).

Metabolism

Lurbinectedin is metabolized by CYP3A4, in vitro.

Excretion

After a single dose of radiolabeled lurbinectedin administration, 89% of the radioactivity was recovered in feces (< 0.2% unchanged) and 6% in urine (1% unchanged).

Specific Populations

No clinically significant differences in the pharmacokinetics of lurbinectedin were identified based on age (18-85 years), sex, body weight (39-154 kg), mild to moderate renal impairment (CLcr 30 to 89 mL/min) or mild hepatic impairment (total bilirubin ≤ ULN and AST > ULN, or total bilirubin between 1.0 – 1.5 × ULN and any AST). The effects of severe renal impairment (CLcr < 30 mL/min) and moderate or severe hepatic impairment (total bilirubin > 1.5 × ULN and any AST) on the pharmacokinetics of lurbinectedin have not been studied.

Drug Interactions Studies

Clinical Studies

Effects of CYP3A Inhibitors on Lurbinectedin: Coadministration of itraconazole (a strong CYP3A inhibitor) increased systemic exposure (AUC) of total lurbinectedin by 2.7-fold and unbound lurbinectedin by 2.4-fold.

Effects of CYP3A Inducers on Lurbinectedin: Coadministration of bosentan (a moderate CYP3A inducer) decreased systemic exposure (AUC) of total lurbinectedin by 20% and unbound lurbinectedin by 19%. These changes are not considered clinically relevant.

In vitro Studies

Cytochrome P450 (CYP) Enzymes: Lurbinectedin is not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4. Lurbinectedin is not an inducer of CYP1A2 or CYP3A4.

Transporter Systems: Lurbinectedin is a substrate of MDR1, but is not a substrate of OATB1P1, OATP1B3, OCT1, or MATE1. Lurbinectedin inhibits MDR1, OATP1B1, OATP1B3, and OCT1 but not BCRP, BSEP, MATE1, OAT1, OAT3, or OCT2.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity testing of lurbinectedin has not been performed. Lurbinectedin is genotoxic to mammalian cells in the presence and absence of metabolic activation. Lurbinectedin was not mutagenic in vitro in a bacterial reverse mutation (Ames) assay.

Fertility studies with lurbinectedin were not performed. There were no findings in reproductive organs in general toxicology studies in rats, dogs, or monkeys; however, the highest doses and exposures in these studies were all at levels lower than those at the human dose of 3.2 mg/m^2.

14 CLINICAL STUDIES

PM1183-B-005-14 (Study B-005; NCT02454972) is a multicenter, open-label, multi-cohort trial evaluating ZEPZELCA as a single agent in patients with advanced or metastatic solid tumors. A cohort of patients with small cell lung cancer (SCLC) with disease progression on or after platinum-based chemotherapy received ZEPZELCA 3.2 mg/m^2 by intravenous infusion every 21 days (one cycle). Patients received a median of 4 cycles of ZEPZELCA (range 1 to 24 cycles). The trial excluded patients with central nervous system (CNS) involvement, grade ≥3 dyspnea, daily intermittent oxygen requirement, hepatitis or cirrhosis, and immunocompromised patients. Tumor assessments were conducted every 6 weeks for the first 18 weeks and every 9 weeks thereafter. The major efficacy outcome measure was confirmed investigator-assessed overall response rate (ORR). Additional efficacy outcome measures included duration of response (DoR), and an Independent Review Committee (IRC) assessed ORR using Response Evaluation Criteria in Solid Tumors (RECIST v1.1).

A total of 105 patients with SCLC who progressed on or after platinum-based chemotherapy were enrolled. The median age was 60 years (range: 40 to 83) with 65% of patients < 65 years and 35% of patients ≥ 65 years, and 60% were male. The majority (75%) of the patients were White, 1% were Asian, 1% were Black and 23% were not reported. Baseline ECOG performance status was 0 or 1 in 92% of patients, and 92% were former/current smokers. All patients received at least one line of platinum-based chemotherapy (range 1-2 lines), and prior radiotherapy had been administered to 71% of patients. Eight patients (8%) had prior immunotherapy in addition to platinum-based chemotherapy. Sixty patients (57%) had platinum-sensitive SCLC, defined as recurrence or progression ≥ 90 days after the last dose of platinum-containing therapy (chemotherapy free interval [CTFI] ≥ 90 days). The remaining 45 patients had platinum-resistant SCLC, defined as recurrence or progression < 90 days after the last dose of platinum-containing therapy (CTFI < 90 days).

Table 5 summarizes investigator-assessed and independent review committee assessed key efficacy measures in all patients and in platinum-resistant and platinum-sensitive subgroups.

Table 5: Efficacy Results in SCLC Cohort of Study B-005

Investigator Assessed Response[a]	**ZEPZELCA All Patients (n=105)**	**ZEPZELCA CTFI <90 days (n=45)**	**ZEPZELCA CTFI ≥90 days (n=60)**
Overall Response Rate (95% CI)	35% (26%, 45%)	22% (11%, 37%)	45% (32%, 58%)
Complete response	0%	0%	0%
Partial response	35%	22%	45%
Duration of Response			
Median in months (95% CI)	5.3 (4.1, 6.4)	4.7 (2.6, 5.6)	6.2 (3.5, 7.3)
% with ≥6 months[b]	35%	10%	44%
Independent Review Committee Assessed Response[a]	**All Patients (n=105)**	**CTFI <90 days (n=45)**	**CTFI ≥90 days (n=60)**
Overall Response Rate (95% CI)	30% (22%, 40%)	13% (5%, 27%)	43% (31%, 57%)
Complete response	0%	0%	0%
Partial response	30%	13%	43%
Duration of Response			
Median in months (95% CI)	5.1 (4.9, 6.4)	4.8 (2.4, 5.3)	5.3 (4.9, 7.0)
% with ≥6 months[b]	25%	0%	31%

CI: confidence interval, CTFI: chemotherapy free interval.
[a] Confirmed overall response rate.
[b] Based on observed duration of response.

15 STORAGE AND HANDLING

Storage and Handling

Store refrigerated at 2° to 8°C.

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

Storage and Stability after reconstitution

Drug product reconstituted to lurbinectedin 0.5 mg/mL with 8 mL of WFI is stable for up to 24 hours when stored in the vials at either room temperature with exposure to ambient light or under refrigeration (2- 8 ºC).

Storage and Stability after dilution

In-use stability of the diluted drug product solution in either 0.9 % Sodium Chloride injection USP (NSS) or 5 % Dextrose Injection USP (D5W) for intravenous infusion has been

demonstrated for up to 24 hours at either room temperature with ambient light exposure or under refrigerated (2- 8 ºC) conditions.

If not used immediately after reconstitution and dilution, the reconstituted and diluted drug product solution can be stored prior to administration for up to 24 hours, including the infusion time, at either room temperature with ambient light exposure or under refrigerated (5 ºC ± 3 ºC) conditions.

16. PHARMACEUTICAL PARTICULARS

16.1 List of excipients

Sucrose, Lactic acid, Sodium hydroxide

16.2 Shelf life

The expiry date of the product is indicated on the packaging materials.

17. MANUFACTURER

Pharma Mar, S.A
Avenida de los Reyes 1, Pol., Ind. La Mina, Colmenar Viejo 28770, Madrid, Spain

18. MARKETING AUTHORISATION HOLDER

Megapharm Ltd,
HATIDHAR ST. 15, RA'ANANA, ISRAEL

19. MARKETING AUTHORISATION NUMBER(S)

171-62-36588-99

21. Revised in November 2024