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Date: 1 June 2023
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Zepzelca

International non-proprietary name: lurbinectedin

Pharmaceutical form: lyophilisate for concentrate for solution for infusion

Dosage strength(s): 4 mg

Route(s) of administration: intravenous use

Marketing authorisation holder: PharmaMar AG

Marketing authorisation no.: 67729

Decision and decision date: temporary authorisation in accordance with Art. 9a TPA approved on 7 March 2023

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

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1 Terms, Definitions, Abbreviations

1L	First-line
2L	Second-line
ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CNS	Central nervous system
cORR	Confirmed overall response rate
CPP	Critical Process Parameters
CQA	Critical Quality Attributes
CTFI	Chemotherapy-free interval
CYP	Cytochrome P450
DDI	Drug-drug interaction
DNA	Deoxyribonucleic acid
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group (Performance Status)
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
G-CSF	Granulocyte colony-stimulating factor
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
IRC	Independent review committee
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
mOS	Median overall survival
MRHD	Maximum recommended human dose
MTD	Maximum tolerated dose
N/A	Not applicable
NCCN	National Comprehensive Cancer Network
NO(A)EL	No observed (adverse) effect level
ORR	Objective response rate
OS	Overall survival
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PFS	Progression-free survival
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics

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PopPK	Population pharmacokinetics
PS	Performance status
PSP	Pediatric study plan (US FDA)
QTPP	Quality Target Product Profile
RECIST	Response Evaluation Criteria in Solid Tumors
RMP	Risk management plan
SAE	Serious adverse event
SCLC	Small cell lung cancer
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)
TRAE	Treatment-related adverse events
ULN	Upper limit of normal
WFI	Water for injection

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2 Background Information on the Procedure

2.1 Applicant's Request(s)

New active substance status
The applicant requested new active substance status for lurbinectedin in the above-mentioned medicinal product.

Orphan drug status
The applicant requested orphan drug status in accordance with Article 4 a^{decies} no. 2 of the TPA. Orphan drug status was granted on 20 November 2019.

Temporary authorisation for human medicinal products
The applicant requested a temporary authorisation in accordance with Article 9a TPA.

2.2 Indication and dosage

2.2.1 Requested indication

Zeplzelca is indicated for the treatment of patients with metastatic small cell lung cancer (SCLC) with disease progression on or after platinum-containing therapy and with no central nervous system (CNS) metastases.

2.2.2 Approved indication

Zepzelca is indicated for the treatment of adult patients with metastatic small cell lung cancer (SCLC) who have progressed after platinum-containing therapy with a subsequent chemotherapy-free interval (CTFI) ≥30 days and with no central nervous system (CNS) metastases.

2.2.3 Requested dosage

Summary of the requested standard dosage:
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.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	20 June 2022
Formal control completed	6 July 2022
List of Questions (LoQ)	7 September 2022
Response to LoQ	28 November 2022
Preliminary decision	17 January 2023
Response to preliminary decision	15 February 2023
Final decision	7 March 2023
Decision	approval (temporary authorisation in accordance with Art. 9a TPA)

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3 Medical context

The World Health Organization (WHO) estimates that lung cancer is the cause of 1.59 million deaths globally per year, with 71% of them caused by smoking. Tobacco smoking remains the main cause of lung cancer. Both smoking prevention and smoking cessation can lead to a reduction in a large proportion of lung cancers[1]. Small cell lung cancer (histological type of lung cancer) is an aggressive neuroendocrine carcinoma defined by rapid tumour growth, high metastases rates and dismal clinical outcomes[2]. Although small cell lung cancer (SCLC) is initially highly sensitive to chemotherapy and ionising radiation, the vast majority of patients will experience a recurrence, and the average survival time is only about 10 months[3]. Despite a high medical need due to poor survival prognosis, advancements in the field of SCLC therapy are very limited.

International guidelines currently recommend platinum-based chemotherapy with or without immune checkpoint inhibitor for fit patients with extensive stage small cell lung cancer as the first-line treatment for extensive disease[1, 3]. In the second-line setting, the only authorised treatment option in Switzerland at the time of the assessment was a topoisomerase inhibitor.

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 tumours in mice.

[1] B.W. Loo, W. Akerley, M. Bassetti et al. NCCN Guidelines Small Cell Lung Cancer, Version 2.2020, 10 December 2019
[2] Basumallik N, Agarwal M. Small Cell Lung Cancer. [Updated 2022 Jul 12]. StatPearls, January 2023
[3] M Wolf et. al, Onkopedia Leitlinien, Lungenkarzinom, kleinzellig (SCLC), January 2023

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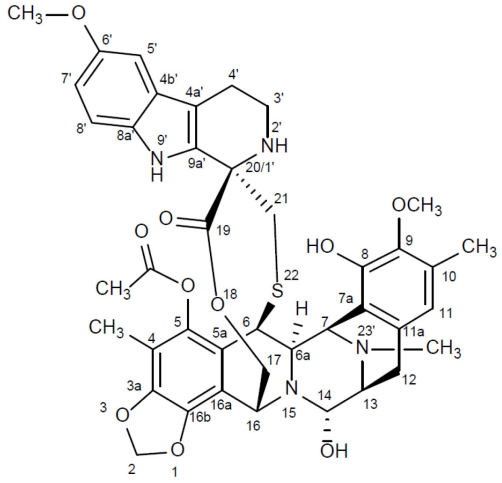
4 Quality aspects

4.1 Drug substance

INN:	Lurbinectedin
Chemical name:	(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 mass:	784.87 g/mol
Molecular structure:	



Physico-chemical properties: Lurbinectedin is a white to off-white powder. Lurbinectedin has a total of seven stereogenic centres, and is presented as the only stereoisomer of well-defined structure. Lurbinectedin is insoluble or practically insoluble in water but solubility increases at acidic pH. Lurbinectedin is hygroscopic and sensitive to heat.

Synthesis: The drug substance is manufactured by multiple step chemical synthesis.

Specification: The drug substance specification includes relevant tests for proper quality control, encompassing tests relating to identification, assay, impurities and bacterial endotoxins.

Stability: Appropriate stability data have been presented and justify the established re-test period.

4.2 Drug product

Description and composition: Lurbinectedin 4 mg for injection is presented as a sterile, preservative-free, white to off-white, lyophilised powder in a 30-mL, single-dose, type I clear-glass vial.
Before use, the powder is reconstituted with 8 mL of water for injection (WFI) to give a solution containing lurbinectedin 0.5 mg/mL.
The reconstituted solution is then further diluted in either sodium chloride 9 mg/mL (0.9%) solution for infusion or glucose 50 mg/mL (5%) solution for infusion.
The composition of the drug product is adequately described, qualitatively and quantitatively.

Pharmaceutical development: Suitable pharmaceutical development data have been provided for the finished product composition and manufacturing process, including establishment of the Quality Target Product Profile (QTPP), the Critical Quality Attributes (CQA) and the Critical Process Parameters (CPP).

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Manufacture: The manufacturing process is described narratively and in sufficient detail, taking into account pharmaceutical development data. Batch manufacturing formulas and in-process controls are included. Adequate validation data pertaining to the commercial manufacturing process are available.

Specification: The drug product specification covers relevant physicochemical characteristics and also includes identification, assay, purity, sterility and bacterial endotoxin tests. They allow for proper control of the finished drug product. The control methods are validated according to international guidelines. Batch data show consistent quality of the drug product.

Container-closure system: The drug product is packaged in clear-glass vials made from borosilicate glass. The closure is composed of a coated grey butyl rubber stopper and an aluminium flip-off seal.

Stability: Appropriate stability data have been generated in the packaging material intended for commercial use and following the relevant international guidelines. The data show good stability of the finished product and allow for a distinct assignment of the shelf life.

4.3 Quality conclusions

Satisfactory and consistent quality of the drug substance and drug product has been demonstrated.

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5 Nonclinical aspects

Regarding the marketing authorisation application for Zepzelca (lurbinectedin), the Nonclinical Assessment Division conducted an abridged evaluation, which was based on the published US FDA assessment report (Multi-Discipline Review).
Overall, the submitted nonclinical documentation is considered appropriate to support the approval of Zepzelca in the proposed indication. The pharmaco-toxicological profile has been sufficiently characterised. There are no safety margins, which can be accepted considering the proposed indication.
All nonclinical data that are relevant for safety are adequately mentioned in the information for healthcare professionals.

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6 Clinical and clinical pharmacology aspects

6.1 Clinical pharmacology

The evaluation of the clinical pharmacology data in this application has been carried out in reliance on previous regulatory decisions by the FDA. The available assessment reports and corresponding product information from the FDA were used as a basis for the clinical pharmacology evaluation. For further details concerning clinical pharmacology, refer to the information for healthcare professionals.

6.2 Dose finding and dose recommendation

During early Phase 1 clinical trials, the applicant evaluated different dose intervals and regimens of lurbinectedin. Based on the early pharmacokinetic and clinical data the applicant selected lurbinectedin 3.2 mg/m^2 every 3 weeks as the recommended Phase 2 dose.

6.3 Efficacy

The pivotal efficacy data presented for the lurbinectedin application for temporary authorisation are from the SCLC cohort with patients who were previously treated with platinum-based chemotherapy of the Phase 2, single-arm basket Study PM1183-B-005-14. The applicant presented the results of the final analysis (data cut-off from November 2020).

Participants were required to meet the following study entry criteria: age ≥18 years, Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0-2, received at least one previous line of chemotherapy, no study disease involvement in the central nervous system (CNS), measurable disease as well as adequate bone marrow, liver and kidney function. Patients with previous chemoimmunotherapy were permitted to enter the study. The study also permitted inclusion of patients with refractory disease, i.e. chemotherapy-free interval (CTFI) <30 days. The exclusion of patients with CNS involvement was considered of particular relevance since 40% of SCLC patients develop symptomatic CNS metastases during their disease course and patients who develop such metastases are known to have poor outcomes[4].

In Study PM1183-B-005-14, patients were treated with lurbinectedin 3.2 mg/m^2 administered intravenously every three weeks. Study treatment was administered until disease progression, unacceptable toxicity, more than two dose reductions, or treatment delay longer than 3 weeks. Disease was radiologically assessed prior to study entry, then every two cycles until cycle 6, and thereafter every three cycles. Patients were followed up until death.

The primary endpoint of the study was objective response rate (ORR) in treated patients as assessed by the investigator, which was defined as a percentage of patients with confirmed complete or partial response according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 in all treated patients. Other relevant endpoints were progression-free survival (PFS), duration of response (DOR), and overall survival (OS). ORR, DOR, and PFS were additionally assessed by the independent review committee (IRC).

Overall, 110 participants were enrolled in the SCLC cohort of the study, of whom 105 received study treatment. Three patients were not treated due to rapid disease progression, one patient was not treated due to increased AST ≥3xULN (upper limit of normal) and one patient was not able to take part in required visits.

[4] Bunn PA, Nugent JL, Matthews MJ. Central nervous system metastases in small-cell bronchogenic carcinoma. Semin Oncol 1978; 5: 314-22.

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According to the data cut-off from November 2020, all patients have discontinued treatment, 91% due to progressive disease, 4% due to investigator decision, 2% due to treatment emergent adverse event, 2% due to death related to disease and 2% due to patient refusal.

Patients in the Study PM1183-B-005-14 SCLC cohort were mostly male (60%) and “white” (75%). Regarding ECOG Performance Status (PS), 36% of all patients had an ECOG PS score of 0, 56% had an ECOG PS of 1 and 8% had an ECOG PS of 2. The median age of the overall study population was 60 years. Ninety-two percent had a history of smoking. Seventy percent had extended disease at diagnosis and one patient had a non-metastatic study disease at baseline. Seventy five percent of patients had three or more disease sites. Lung, lymph nodes and liver were the most common disease sites.

In metastatic SCLC patients without CNS metastases who have progressed after platinum-containing therapy with a subsequent CTFI ≥30 days, the ORR by IRC assessment was 33.7% (November 2020 data cut-off); median PFS by IRC assessment and median OS were 3.7 months and 10.2 months, respectively.

6.4 Safety

Safety results from the Study PM1183-B-005-14 SCLC cohort:
The median duration of treatment was 14 weeks and the median number of cycles received was four. Ninety percent of treated patients received more than one study treatment cycle.

Summary of adverse events: 98% of participants experienced a treatment-emergent adverse event (TEAE) of any grade, 60% had a grade ≥3 TEAE, 34% had serious adverse events (SAE), 2% had TEAE leading to death, and 5% had a TEAE leading to treatment discontinuation.

The most frequent TEAEs of any grade were fatigue, nausea, decreased appetite, constipation, dyspnoea, vomiting, diarrhoea, cough, back pain and pyrexia.

The most frequent grade ≥3 TEAEs were fatigue, dyspnoea, febrile neutropenia, pneumonia, diarrhoea and upper respiratory tract infection.

The most frequent SAEs of any grade were febrile neutropenia, neutropenia, pneumonia, anaemia, thrombocytopenia, general physical health deterioration and dyspnoea.

Safety results from the Study PM1183-B-004-14
Additional safety results from the Phase 3 Study PM1183-B-004-14 in platinum-resistant ovarian cancer patients were provided with direct comparison of lurbinectedin with topotecan. Comparing the safety results of the lurbinectedin treatment arm to topotecan of Study PM1183-C-004-14, haematological abnormalities were numerically less frequent in the lurbinectedin arm compared to topotecan (in particular the grade ≥3 events). Treatment modifications (such as dose delays and treatment dose reduction) were less frequent in the lurbinectedin-treated patients compared to topotecan. Notably, lurbinectedin-treated patients required fewer supportive measures compared to topotecan-treated patients, such as reduced use of granulocyte colony-stimulating factor (G-CSF), platelet transfusion, red blood cell concentrate transfusion and erythropoetin use.

6.5 Final clinical and clinical pharmacology benefit risk assessment

Small cell lung carcinoma (SCLC) is a histological subtype of lung cancer that is defined by poor survival prognosis. Although most patients with metastatic disease initially respond to platinum-based therapy, the vast majority of patients will relapse and/or progress after the initial treatment. There has been a lack of advancements in the second-line setting for decades. Monotherapy with topoisomerase inhibitor is associated with a high frequency of haematological toxicities. There is an

unmet medical need for a therapy option with a more favourable safety profile that improves the survival outcomes of these patients.

The pivotal data to support the requested indication are based on 105 patients from the SCLC cohort of the Phase 2 single-arm Study PM1183-B-005-14. This study included SCLC patients after platinum-based chemotherapy, but excluded patients with central nervous system (CNS) metastases. The exclusion of patients with CNS involvement is considered to be relevant because it is a common metastatic site for SCLC and is associated with exceptionally poor prognosis.

The final analysis demonstrated an independent review committee confirmed overall response rate of 33.7% and median overall survival of 10.2 months in the patient population relevant to the authorised indication. These results are considered to be clinically meaningful in the context of the published data for the current standard of care[5]. However, the major limitation of the pivotal study results presented is the lack of a randomised control arm.

In order to provide confirmatory evidence to support the conversion from a temporary authorisation to a regular authorisation, the applicant commits to provide results from a Phase 3 Study PM1183-C-008-21, which directly compares lurbinectedin monotherapy or lurbinectedin combined with irinotecan versus either topotecan or irinotecan in post-platinum SCLC patients with CTFI ≥30 days.

Regarding safety, the most frequent treatment emergent adverse events in the Study PM1183-B-005-14 SCLC cohort were fatigue, nausea, dyspnoea, constipation and decreased appetite. The most common grade ≥3 haematological toxicities were neutropenia, lymphopenia, leukopenia, anaemia and thrombocytopenia. The reported adverse drug reactions for lurbinectedin are consistent with other alkylating agents. Phase 3 Study PM1183-C-004-14 of platinum-resistant ovarian cancer patients, in which lurbinectedin was directly compared with topotecan, provided additional supportive evidence. In this study haematological adverse events were numerically less frequent and less severe in patients treated with lurbinectedin compared with topotecan. Grade ≥3 haematological toxicities, in particular neutropenia and febrile neutropenia, were less frequent in patients treated with lurbinectedin compared with topotecan. Patients in the lurbinectedin arm also required less supportive measures compared with topotecan-treated patients.

In conclusion, the efficacy results for lurbinectedin are considered clinically meaningful in the context of published data for the current standard of care, especially considering the poor survival outcomes and the lack of therapeutic advancements for decades in the requested second-line SCLC indication[5]. Safety analyses of platinum-resistant ovarian cancer patients demonstrate a more favourable toxicity profile for lurbinectedin compared with topotecan. The main weakness of the submitted dossier is the lack of direct comparison of lurbinectedin 3.2 mg/m^2 every 3 weeks compared to topotecan in SCLC patients. Study PM1183-C-008-21 (LAGOON) will be required as confirmatory evidence for the conversion of a temporary to a regular marketing authorisation for the requested indication.

[5] Von Pawel J et al. Randomized phase III trial of amrubicin versus topotecan as second-line treatment for patients with small-cell lung cancer. J Clin Oncol. 2014 Dec 10;32(35):4012-9.

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7 Risk management plan summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

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8 Appendix

Approved Information for healthcare professionals

Please be aware that the following version of the information for healthcare professionals for Zepzelca was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the information for healthcare professionals approved in one of the official Swiss languages.

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▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the “Undesirable effects” section for advice on the reporting of adverse reactions.
ZEPZELCA is temporally authorised - see “Properties/Effects” section

ZEPZELCA

Composition

Active substances

Lurbinectedin

Excipients

Sucrose, lactic acid and sodium hydroxide, equivalent to 2.9 mg sodium.

Pharmaceutical form and active substance quantity per unit

Powder for concentrate for solution for infusion (IV)
ZEPZELCA is supplied as a lyophilised powder in a single-dose 30 mL glass vial for reconstitution. The ZEPZELCA lyophilised formulation is comprised of 4 mg lurbinectedin. Before use, the lyophilisate is reconstituted by addition of 8 mL water for injections, yielding a solution containing 0.5 mg/mL lurbinectedin.

Indications/Uses

ZEPZELCA is indicated for the treatment of adult patients with metastatic small cell lung cancer (SCLC) who have progressed after platinum-containing therapy with a subsequent chemotherapy-free interval (CTFI) ≥30 days and with no central nervous system (CNS) metastases.

Dosage/Administration

For intravenous (IV) infusion use only.
Zepzelca therapy should be initiated and supervised by a health professional experienced in oncology.
For instructions on reconstitution and dilution of the medicinal product before administration, see “Instructions for handling”.

General target population

The recommended dose is 3.2 mg/m^2 by intravenous infusion over 1 hour repeated every 21 days until disease progression or unacceptable toxicity.
Patients must meet the following criteria before starting their treatment or re-treatment with Zepzelca:

Treatment criteria - prior to administration of the first course

a) Haemoglobin ≥9.0 g/dL, prior packed red blood cell (PRBC) transfusions are allowed if clinically indicated; absolute neutrophil count (ANC) ≥1.5 x 10^9/L; and platelet count ≥ 100 x 10^9/L.
b) Alanine aminotransferase (ALT), and aspartate aminotransferase (AST) ≤3.0 x upper limit of normal (ULN).
c) Total bilirubin ≤ 1.5 x ULN, or direct bilirubin ≤ULN (when total bilirubin >1.5 x ULN).
d) Albumin ≥3 g/dL.
e) Calculated creatinine clearance (CrCl) ≥30 mL/min (using Cockcroft and Gault's formula).

Re-Treatment criteria:

a) Haemoglobin ≥8.0 g/dL, prior red blood cell (RBC) transfusions are allowed if clinically indicated (to start treatment)
b) Absolute neutrophil count (ANC) ≥1.5 x 10^9/L
c) Platelet count ≥100 x 10^9/L.
d) Alanine aminotransferase (ALT), and aspartate aminotransferase (AST) ≤3.0 x upper limit of normal (ULN).
e) Total bilirubin ≤1.5 x ULN, or direct bilirubin ≤ULN (when total bilirubin >1.5 x ULN).
f) Albumin ≥3 g/dL.
g) Calculated creatinine clearance (CrCl) ≥30 mL/min (using Cockcroft and Gault's formula).

Treatment continuation and treatment delays

Further treatment cycles (i.e., Cycle 2 or subsequent) will be administered every 21 days if the patient fulfils all the treatment and re-treatment criteria listed above.

If a patient does not meet the requirements for re-treatment on Day 1 of any cycle after Cycle 1, treatment will be withhold until appropriate recovery, for a maximum of 21 days after the treatment due date. If there is no recovery after a 21-day delay, treatment must be stopped.

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:

If needed, post-medication can include:

Administration of extended antiemetic treatment for 2 days after the infusion of any of the following:

- Corticosteroids (oral dexamethasone 4 mg or equivalent)
- Serotonin antagonists (oral ondansetron 8 mg or equivalent)
- Metoclopramide (intravenous or oral 10 mg or equivalent every 8 hours)

Dose adjustment following undesirable effects/interactions

Dosage Modifications for Adverse Reactions

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

Table 1: Dose Reduction for ZEPZELCA for Adverse Reactions

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	Termination of therapy

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

Table 2. Dosage Modifications Criteria for ZEPZELCA for Adverse Reactions

Adverse Reaction	Severity[a]	Dosage Modification
Neutropenia[b] *[see Warnings and Precautions]*	Grade 4 Neutropenia or any grade of febrile Neutropenia	• Withhold ZEPZELCA until Grade ≤1 AND • Resume ZEPZELCA at a reduced dose
Thrombocytopenia *[see Warnings and Precautions]*	Grade 3 with bleeding or Grade 4	• Withhold ZEPZELCA until platelet count ≥100,000/mm^3 AND • Resume ZEPZELCA at reduced dose
Hepatotoxicity *[see Warnings and Precautions]*	Grade 2	• Withhold ZEPZELCA until Grade ≤ 1 AND • Resume ZEPZELCA at same dose
	Grade ≥ 3	• Withhold ZEPZELCA until Grade ≤ 1 AND • Resume ZEPZELCA at reduced dose
Rhabdomyolysis *[see Warnings and Precautions]*	Grade 2	• Withhold ZEPZELCA until Grade ≤ 1 AND • Resume ZEPZELCA at same dose
	Grade ≥3	• Permanently discontinue ZEPZELCA

Adverse Reaction	Severity[a]	Dosage Modification
Non haematological toxicity	Grade 2	• Withhold ZEPZELCA until Grade ≤ 1 AND • Resume ZEPZELCA at same dose
	Grade ≥ 3	• Withhold ZEPZELCA until Grade ≤ 1 AND • Resume ZEPZELCA at reduced dose
Neutropenia associated with infection/sepsis	Any grade	• Reduce the dose of ZEPZELCA
Any adverse reaction that requires frequent or prolonged (>2 weeks) dose delays	-	• Reduce the dose of ZEPZELCA or discontinuation

[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.

Once the dose is reduced dose re-escalation is not allowed.

Special dosage instructions

Paediatric population

The safety and efficacy of lurbinectedin in paediatric patients have not yet been established. Therefore, this medicinal product must not be used in children and adolescents.

Renal impairment

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

Lurbinectedin has not been evaluated in a sufficient number of patients with severe renal impairment (CrCl <30 mL/min) or end-stage renal disease to estimate the risk. However, it should only be used with caution and careful monitoring.

Do not administer ZEPZELCA to patients with calculated creatinine clearance less than 30 mL/min.

Hepatic impairment

No dose adjustment is required for patients with mild hepatic impairment (total bilirubin ≤ULN and AST >ULN, or total bilirubin 1.0−1.5×ULN and any AST). Lurbinectedin has not been studied in patients with moderate or severe hepatic impairment (total bilirubin >1.5×ULN and any AST).

Do not administer Zepzelca to patients with AST or ALT greater than 3×ULN and/or bilirubin greater than 1.5×ULN.

Contraindications

- Moderate or severe hepatic impairment
- ZEPZELCA use is contraindicated in patients with hypersensitivity to the active substance(s) or to any of the excipients listed in section “Composition”
- Pregnancy

Warnings and precautions

Bone Marrow Suppression

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

Monitor whole blood counts including differential blood cells and platelet count at baseline and prior to each cycle of ZEPZELCA. Dose modifications may be required.

ZEPZELCA should not be administered to patients with baseline neutrophil counts of less than 1.5 x 10^9/L and platelet counts of less than 100 x 10^9/L.

Neutropenia

In a clinical study in patients with SCLC, 71% of patients experienced neutropenia (47% experienced Grade 3/4 neutropenia, and 5% experienced febrile neutropenia).

From pooled data of 554 patients receiving ZEPZELCA, as a single agent every 21 days, which included patients with SCLC and other solid tumours, Grade 3/4 neutropenia (fewer than 1000 cells/mm^3) occurred in 41% of patients, with median onset at Day 15 and a duration of 7 days. Febrile neutropenia/neutropenic sepsis occurred in 6% of patients.

In case of febrile neutropenia or neutropenia with serious infection complication the use of granulocyte colony-stimulating factors (G-CSF) 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%/3% 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. No patients met the criteria of high risk of fatal drug-induced liver injury, consisting of ALT/AST elevation of >3× the upper limit of normal (ULN) and total

bilirubin (TBL) elevation of >2× ULN in absence of initial findings of cholestasis (i.e., absence of elevation of alkaline phosphatase [ALP] to >2× ULN) or other reasons explaining the combination of increased ALT and TBL.

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 function test, including ALT, AST, and bilirubin.
Dose modifications may be required.

Extravasation Resulting in Tissue Necrosis

Extravasation of ZEPZELCA resulting in skin and soft tissue injury, including necrosis requiring debridement, may occur. Consider the 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 management of 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/Administration].

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

Sodium content

Zepzelca contains less than 1 mmol sodium (23 mg) per vial, so it is essentially ‘sodium-free’.

Interactions

Strong or Moderate CYP3A Inhibitors

In a Phase 1 study with lurbinectedin, patients who received aprepitant, a weak-moderate CYP3A inhibitor used as an antiemetic, showed a 33% reduction of lurbinectedin plasma clearance compared with patients who did not receive aprepitant.

In the updated population pharmacokinetic (PK) model of lurbinectedin with data from 1174 patients, co-administration of CYP3A inhibitors was found in 29% of patients and resulted in a moderate decrease in plasma clearance of lurbinectedin of 15% and 33% for moderate and strong inhibitors, respectively.

Therefore, avoid co-administration of moderate CYP3A inhibitors (i.e., aprepitant, ciprofloxacin, erythromycin, cyclosporine, fluconazole, grapefruit juice, diltiazem, verapamil) with ZEPZELCA. If coadministration with moderate CYP3A inhibitors cannot be avoided, neutrophils and platelet counts should be carefully monitored.

In patients receiving ZEPZELCA in combination with strong CYP3A4 inhibitor (i.e. ketoconazole, itraconazole, posaconazole, voriconazole, clarithromycin, lopinavir, ritonavir, atazanavir) the recommended dose is 1.2 mg/m^2 body surface area administered as a 1-hour intravenous infusion every 21 days. In a drug-drug interaction study (n=8) with itraconazole, a strong CYP3A4 inhibitor, systemic exposure of total lurbinectedin was increased by approximately 2.7-fold ($AUC_{0-\infty}$) and total plasma clearance was reduced by 63%, when lurbinectedin was given concomitantly with itraconazole (total daily dose of 200 mg, for 12 days, 4 days before and up to 8 days after the lurbinectedin administration).

Strong or Moderate CYP3A Inducers

Co-administration of strong CYP3A4 inducers is expected to reduce the systemic exposure of lurbinectedin, thus reducing its antitumor activity. Therefore, avoid co-administration of strong CYP3A inducers (i.e., carbamazepine, phenobarbital, phenytoin, rifampicin, rifabutin, rifapentine, St. John's Wort [Hypericum perforatum]) with ZEPZELCA. Consider alternative agents with less CYP3A induction.

In a drug-drug interaction study (n=8) with bosentan, a moderate CYP3A4 inducer, systemic exposure of total lurbinectedin was decreased by approximately 20% ($AUC_{0-\infty}$) and total plasma clearance was increased by 25%, when lurbinectedin was given concomitantly with bosentan (125 mg twice daily for 5 days). Therefore, the magnitude of these changes precludes a clinically relevant effect of co-administration of moderate CYP3A4 inducers (i.e., bosentan, cenobamate, dabrafenib, efavirenz, etravirine, lorlatinib, phenobarbital, primidone, sotorasib) on lurbinectedin exposure and no dose adjustment was required.

Effect of Zepzelca on CYP enzymes

In vitro, lurbinectedin has a limited inhibition or induction potential on major CYP enzymes (CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4). Therefore, the potential of Zepzelca to affect CYP3A4 substrates is limited.

Pregnancy, lactation

Contraception

Review the pregnancy status in women of childbearing potential before starting treatment with ZEPZELCA.

Women of childbearing potential should be instructed to use effective contraception during treatment with ZEPZELCA and for 7 months afterwards. Male patients with female partners of childbearing potential should be instructed to use effective contraception during treatment with ZEPZELCA and for 4 months afterwards. Women of childbearing potential must be educated about the potential risk to the foetus.

Pregnancy

There is no experience to date in the use of ZEPZELCA in pregnant women. Animal experiments on pregnant rats during organogenesis have shown embryofoetal lethality and maternal toxicity (see “Preclinical data”). The administration of lurbinectedin during pregnancy may harm the foetus due to the mode of action of the medicinal product. ZEPZELCA must not be used during pregnancy (see “Contraindications”).

Lactation

There is no experience in the transfer of lurbinectedin into human milk, on the effects on the breastfed child or the effect on milk production. Due to the potential of serious adverse effects of ZEPZELCA on the breastfed child, breastfeeding should be interrupted during treatment with ZEPZELCA and for at least 4 weeks after the last dose.

Fertility

There are no data on the effect of lurbinectedin on human fertility. No fertility studies were conducted in animal species but there were effects on male reproductive organs in the general toxicity studies (see “Preclinical data”).

Effects on ability to drive and use machines

No studies on the effects of the ability to drive and to use machines have been performed. However, some events of fatigue, headache, dizziness, vomiting, nausea and muscle spasms have been reported in patients receiving lurbinectedin. Patients who experience such events during therapy should not drive or operate machinery.

Undesirable effects

Unless otherwise specified, the following safety profile of lurbinectedin is based on the evaluation of patients treated in clinical studies.

Summary of the safety profile

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 phase 2 trial in selected solid tumours [Basket (n=335)] and one randomised phase 3 trial in platinum-resistant ovarian cancer [CORAIL (n=219)]. 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 3 and Table 4 present selected adverse reactions and laboratory abnormalities, respectively, observed in the SCLC cohort from the Basket trial and from the combined experience of 554 patients of the Basket and CORAIL trials.

In the cohort of patients with SCLC, the most common (≥20%) haematological adverse events (all grades regardless of relationship) were anaemia (94%), lymphopenia (86%), leukopenia (79%), neutropenia (71%), and thrombocytopenia (44%). Grade 3/4 haematological adverse events occurring in ≥5% of patients were neutropenia (47%), lymphopenia (44%), leukopenia (29%), anaemia (10%), thrombocytopenia (7%), and febrile neutropenia (5%) (see Warnings and Precautions).

In the cohort of patients with SCLC, the most common (≥20%) non-haematological adverse reactions (all grades) were fatigue (59%); nausea (33%); decreased appetite (22%); abnormal liver function tests including increased ALT (72%), AST (45%), and alkaline phosphatase (33%); and abnormal kidney function tests including increased creatinine (83%) according to increase from baseline value and 25% according to upper normal limit. The majority of grade 3/4 non-haematological adverse reactions were uncommon; the most frequent (occurring in ≥5% of patients) events was fatigue (8%).

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

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

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

Tabulated summary of Adverse drug reactions and Laboratory Abnormalities from clinical trials

Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

Table 3: Adverse Reactions Experienced by ≥1% of Patients

	Percentage and Frequency category	
		All patients (n=554)
Infections and infestations		
Pneumonia[a]		Common
Blood and lymphatic system disorders		
Febrile neutropenia/Neutropenic sepsis Leukopeniak Anaemiak Thrombocytopeniak Neutropeniak Lymphopeniak		Common Very Common (29.6) Very Common (17.3) Common Very Common (40.6) Very Common (33.6)
Metabolism and nutrition disorders		
Decreased appetite		Very common (24.9)
Dehydration		Common
Psychiatric disorders		
Insomnia		Common
Nervous system disorders		
Neuropathy peripheral[b]		Common
Headache		Common
Dysgeusia		Common
Dizziness		Common
Vascular disorders		
Hypotension		Uncommon
Phlebitis		Uncommon
Respiratory, thoracic and mediastinal disorders		
Dyspnoea		Common
Epistaxis		Common
Gastrointestinal disorders		
Nausea		Very common (57.0)
Vomiting		Very common (30.3)
Constipation		Very common (32.1)
Diarrhoea		Very common (19.0)
Abdominal pain[c]		Common
Stomatitis[d]		Common
Dyspepsia		Common
Gastroesophageal reflux disease		Common
Dry mouth		Uncommon
Hepatobiliary disorders		
Blood bilirubin increased[k]		Common
Alanine aminotransferase (ALT) increased[k]		Common
Aspartate aminotransferase (AST) increased[k]		Common
Alkaline phosphatase (AP) increased[k]		Common

	Percentage and Frequency category	
		All patients (n=554)
Skin and subcutaneous tissue disorders		
Rash[e]		Common
Alopecia		Common
Dry skin		Common
Pruritus[f]		Common
Skin hyperpigmentation		Uncommon
Renal and urinary disorders		
Blood creatinine increased[k]		Common
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain[g]		Common
Arthralgia		Common
Muscle spasms		Uncommon
Muscular weakness		Uncommon
General disorders and administration site conditions		
Fatigue[h]		Very common (63.2)
Mucosal inflammation		Common
Pyrexia		Common
Oedema[i]		Common
Malaise		Common
Injection site reaction[j]		Common
Investigations		
Weight decreased		Common
Weight increased		Uncommon

Notes:
[a] Merged: lung infection, atypical pneumonia and *Pneumocystis jirovecii* pneumonia
[b] Merged: paraesthesia, peripheral sensory neuropathy, hypoesthesia, dysesthesia, hyperesthesia, peripheral motor neuropathy and polyneuropathy
[c] Merged: abdominal pain upper, abdominal discomfort, abdominal pain lower, gastrointestinal pain and epigastric discomfort
[d] Merged: glossitis, mouth ulceration, aphthous ulcer and gingivitis
[e] Merged: rash maculo-papular, urticaria, rash erythematous, rash popular and erythema
[f] Merged: pruritus generalised
[g] Merged: back pain, pain in extremity, myalgia, musculoskeletal chest pain and neck pain
[h] Merged: asthenia
i Merged oedema and enema peripheral
[j] Merged: catheter site pain, catheter site inflammation, catheter site related reaction, device related infection, catheter site infection, infusion related reaction, infusion site phlebitis, injection site erythema and injection site rash
[k] Laboratory data grade ≥3 regardless of the relationship

One fatal case of pneumonitis was reported in a patient from the Basket study.

Table 4: Laboratory Abnormalities Experienced by ≥10% of Patients Regardless of relationship

	Percentage and Frequency category	
		All Patients **(n=554)**
Blood and lymphatic system disorders Haematological abnormalities (Grade 3/4)		
Neutropenia *		
<1,000 cells/mm^3 (Grade 3/4)		40.6
<500 cells/mm^3 (Grade 4)		22.0

Lymphopenia		
<500 cells/mm^3 (Grade 3/4)		33.6
Leukopenia		
<2000 cells/mm^3 (Grade 3/4)		29.6
<1000 cells/mm^3 (Grade 4)		11.0
Anaemia		
<8 g/dL (Grade 3/4) or transfusion indicated		17.3
Thrombocytopenia		
<50,000/mm^3 (Grade 3/4)		9.7
Hepatobiliary disorders (Grade 3/4)		
ALT increased		6.4
AST increased		3.3
AP increased		4.5
Bilirubin increased		2.4

* See description of selected adverse drug reactions (ADRs) in section Warning and Precautions
** NCI- CTCAE v 4.0 / NCI- CTCAE v 3.0

Listing of Adverse Drug Reactions from post-marketing spontaneous reports

Cases of extravasation have been uncommonly reported with post-marketing use of ZEPZELCA. Tissue necrosis requiring debridement was reported in few cases.

Rare cases of rhabdomyolysis have been reported with post-marketing use of ZEPZELCA.

Description of selected Adverse Drug Reactions

Bone marrow suppression and hepatotoxicity (see “Warnings and Precautions”).

Other special populations

Elderly population (age ≥65 years)

Based on the pivotal Basket study, overall, grade ≥3 adverse effects occurred during treatment with lurbinectedin with a frequency >5% were the following: fatigue (18.9%), febrile neutropenia (10.8%); sepsis (10.8%); hyponatremia (8.1%), peripheral neuropathy (5.4%); dyspnoea (8.1%); hyperglycaemia (5.4%); pneumonia (5.4%). Serious adverse events grade ≥3, occurring with a frequency >5% were the following: febrile neutropenia (10.8%); sepsis (10.8%); hyponatremia (5.4%); neuropathy peripheral (5.4%) and pneumonia (5.4%).

Treatment-emergent grade ≥3 laboratory abnormalities occurring with a frequency >5% included: neutropenia (59.5%), lymphopenia (54.1%), leukopenia (37.8%), anaemia (13.5%) and thrombocytopenia (10.8%).

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 largely bound to plasma proteins (99%), and renal excretion is negligible.

There is no known antidote for overdosage with ZEPZELCA.

Properties/Effects

ATC code L01XX69 - Other antineoplastics agents.

Mechanism of action

Lurbinectedin (ZEPZELCA) is an alkylating agent that binds to guanine residues in the DNA minor groove. Adduct development causes the DNA helix to bend towards the major groove and can inhibit the binding/activity of transcription factors.

This process interrupts the cell cycle and leads to cell apoptosis. Lurbinectedin inhibited the macrophage infiltration in human tumours implanted in mice.

Pharmacodynamics

Cardiac Electrophysiology

The potential for QTc prolongation with lurbinectedin was evaluated in 39 patients with advanced cancer. Large effects (>10 ms) on the QTc interval were not detected with lurbinectedin dosed at 3.2 mg/m² every 21 days.

Clinical efficacy

In a phase 2 open-label, multi-centre, single-arm study, 105 SCLC-patients with no CNS involvement 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% were white, 92% had ECOG PS 0 or 1, and the median age was 60 years (range, 40-83 years; 35% were ≥65 years old). Two of the 105 treated patients (2%) had previously undergone surgery (curative resection in one patient). Prior radiotherapy had been administered to 76 patients (72%). The patients had received a median of one prior line of chemotherapy for advanced disease.

Treatment continued until disease progression, unacceptable toxicity, treatment delay >21 days 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 endpoint was overall response rate (ORR) assessed by Investigator based on RECIST v1.1 and verified by an Independent Review Committee. An additional efficacy endpoint was response duration. Efficacy results are shown in Table 5.

Table 5- Efficacy of ZEPZELCA according to Investigator Assessment (IA) and Independent Review Committee (IRC) in Small Cell Lung Cancer Patients

Parameter	**Overall (n=83)**
Overall response rate (CR+PR) (95% CI) (IA)	**41.0 (30.3-52.3)**
Overall response rate (CR+PR) (95% CI) (IRC)	**33.7 (23.7-44.9)**
Duration of response, median, months (95% CI) (IA)	**5.3 (3.5-5.9)**
Duration of response, median, months (95% CI) (IRC)	**5.1 (4.8-5.9)**
Disease control rate, % (95% CI) (n=83) (IA)	**69.9 (58.8-79.5)**
Disease control rate, % (95% CI) (n=83) (IRC)	**67.5 (56.3-77.4)**
Median PFS, (months) (95% CI) (n=83) (IA)	**4.0 (2.6-4.7)**
PFS at 6 months, % (95% CI) (IA)	36.7 (26.0-47.2)
Median PFS (months) (95% CI) (n=83) (IRC)	**3.7 (2.6-4.6)**
PFS at 6 months, % (95% CI) (IRC)	32.8 (22.2-43.5)
Median OS, (months) (95% CI) (n=83)	**10.2 (7.6-12.0)**
OS at 12 months, % (95% CI)	39.4 (28.6-50.1)

CI: confidence interval, CR: complete response, PR: partial response, IA: Investigator Assessment, IRC: Independent Review Committee, CTFI: chemotherapy free interval, n.r.: not reached, OS: overall survival, PFS: progression-free survival

Temporary authorisation

The medicinal product ZEPZELCA has been granted temporary authorisation as the clinical data was incomplete at the time the authorisation application was assessed (Art. 9a TPA). The temporary authorisation is contingent on the timely fulfilment of conditions. After they have been met, the temporary authorisation can be transformed into an ordinary authorisation.

Pharmacokinetics

Lurbinectedin pharmacokinetics is linear at the dose range of 0.02−6.9 mg/m^2. 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 21 days.

Absorption

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 main CYP enzyme responsible for the hepatic metabolism of lurbinectedin.

Elimination

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

Excretion

The major route of radiolabelled lurbinectedin 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).

Kinetics in specific patient 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 obvious 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 21 days 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 obvious pharmacokinetic difference was observed in 165 patients with mild renal impairment [creatinine clearance (CrCl) of 60−89 mL/min], 73 patients with moderate renal impairment (CrCl of 30-59 mL/min) who received ZEPZELCA 3.2 mg/m² every 21 days as compared to 166 patients with normal renal function.

The pharmacokinetic characteristics of lurbinectedin in patients with CrCl <30 mL/min or patients on dialysis are unknown.

Preclinical data

Repeated dose toxicity

The main target organs for toxicity in the preclinical species (rat, dog and monkey) were the haematopoietic system, gastrointestinal tract and liver. Other findings concerned the kidneys, heart (myocardial degeneration), injection sites and male reproductive organs (*see reproductive toxicity*). The findings were observed at doses below the clinical dosage.

Genotoxicity

Lurbinectedin is genotoxic in mammalian cells.

Carcinogenicity

Long-term carcinogenicity studies have not been conducted.

Reproductive toxicity

No fertility studies have been conducted with Lurbinectedin. In the general toxicity studies, testicular atrophy and hypospermia were observed in rats and dogs at doses below the recommended clinical dose.

In studies on pregnant rats that received ZEPZELCA as a single dose of 0.6 mg/m^2 (corresponds to about 20% of the estimated dose of 3.2 mg/m^2 in humans) during organogenesis, 100% embryo-foetal lethality and clinical signs of maternal toxicity were observed, as well as decreases in body weight/body weight gain, and decreased food consumption.

Other information

Incompatibilities

Since no compatibility studies have been carried out, the medicinal product must not be mixed with other medicinal products.
The medicinal product may only be mixed with the diluents listed under “Instructions for use”.

Zepzelca diluted solution is compatible with:

- Polyolefin containers (polyethylene, polypropylene, and mixtures).
- PVC infusion sets (without DEHP), polyurethane and polyolefin infusion sets (polyethylene, polypropylene, and polybutadiene).
- Polyethersulphone in-line filters with pore sizes of 0.22 micron.
- Implantable venous access systems with titanium and plastic resin ports and with polyurethane or silicone intravenous catheters.

Infusion lines containing nylon membrane filters should not be used when the reconstituted ZEPZELCA solution is diluted with sodium chloride 9 mg/mL (9%) solution for infusion

Shelf life

Do not use this medicine after the expiry date (“EXP”) stated on the container.

Shelf life after opening

The reconstituted and diluted infusion solution is not preserved. Chemical and physical in-use stability has been demonstrated for 24 hours after reconstitution and dilution (including duration of infusion) at room temperature (15−25°C) or in the refrigerator (2-8°C). For microbiological reasons, the ready-to-use product should be used immediately after reconstitution and dilution, unless reconstitution and dilution have been carried out in controlled and validated aseptic conditions and the solution has not been stored at 2−8°C for longer than 24 hours. If this is not possible, use-by periods and storage conditions are the responsibility of the user. Any remaining amount should be discarded.

Special precautions for storage

Store in a refrigerator (2−8°C).
Store in the original packaging.
Keep out of the reach of children.

Instructions for handling

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

Prepare the solution for infusion using aseptic technique as follows:

- Inject 8 mL of water for Injections into the vial, yielding a solution containing 0.5 mg/mL lurbinectedin. 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 sodium chloride 9 mg/mL (0.9%) solution for infusion or glucose 50 mg/mL (5%) solution for infusion.

- 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 sodium chloride 9 mg/mL (0.9%) solution for infusion or glucose 50 mg/mL (5%) solution for infusion.
- 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 sodium chloride 9 mg/mL (0.9%) solution for infusion or glucose 50 mg/mL (5%) solution for infusion.

Authorisation number

67729 (Swissmedic)

Packs

ZEPZELCA 1 x 4 mg vial (A).

Marketing authorisation holder

PharmaMar AG
c/o OBC Suisse AG
Aeschengraben 29
4051 Basel

Manufacturer

Manufactured by
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