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Swiss Public Assessment Report
Extension of therapeutic indication

Zepzelca

International non-proprietary name:	lurbinectedin
Pharmaceutical form:	powder 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:	extension of therapeutic indication approved on 20.11.2025

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
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CTX	Chemotherapy
CYP	Cytochrome P450
DCO	Data cut-off
DDI	Drug-drug interaction
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
ERA	Environmental risk assessment
ES-SCLC	Extensive-stage small cell lung cancer
FDA	Food and Drug Administration (USA)
HR	Hazard ratio
HRQoL	Health-related quality of life
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
IRF	Independent review facility
ITT	Intention-to-treat
LS-SCLC	Limited stage small cell lung cancer
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
NCCN	National Comprehensive Cancer Network
ORR	Objective response rate
OS	Overall survival
PD	Pharmacodynamics
PFS	Progression-free survival
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PS	Performance status
QLQ-C30	Quality of Life Questionnaire Core 30
RMP	Risk management plan
RT	Radiotherapy
SAE	Serious adverse event
SCLC	Small cell lung cancer
SOC	System organ class
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)

2 Background information on the procedure

2.1 Applicant's request(s) and information regarding procedure

Extension(s) of the therapeutic indication(s)
The applicant requested the addition of a new therapeutic indication or modification of an approved one in accordance with Article 23 TPO.

Orphan drug status
The applicant requested orphan drug status in accordance with Article 4 paragraph 1 letter a^{decies} no. 2 TPA.
Orphan drug status was granted on 20 November 2019.

Project Orbis
The applicant requested a marketing authorisation procedure within the framework of Project Orbis. Project Orbis is coordinated by the FDA and provides a framework for concurrent submission and review of oncology products among international partners.

2.2 Indication and dosage

2.2.1 Requested indication

Zepzelca, in combination with atezolizumab, is indicated for the maintenance treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC) without CNS metastases whose disease has not progressed after first-line induction therapy with atezolizumab, carboplatin, and etoposide.

2.2.2 Approved indication

ZEPZELCA, in combination with atezolizumab, is indicated for the maintenance treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC) and with no CNS metastases, whose disease has not progressed after first-line induction therapy with atezolizumab, carboplatin and etoposide (see "Properties/Effects").

2.2.3 Requested dosage

Summary of the requested standard dosage:

The recommended dose as a combination therapy with atezolizumab is 3.2 mg/m^2 by intravenous infusion over 1 hour, repeated every 21 days until disease progression or unacceptable toxicity. When administering ZEPZELCA on the same day, administer atezolizumab first.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	8 May 2025
Formal control completed	9 May 2025

Preliminary decision	25 September 2025
Response to preliminary decision	23 October 2025
Final decision	20 November 2025
Decision	approval

3 Medical context

Small cell lung cancer (SCLC) is the most aggressive form of lung cancer. Although SCLC is characterised by rapid responses to chemotherapy (CTX) and sensitivity to radiotherapy (RT), due to early treatment resistance, prognosis is poor, with median OS of approximately 1 year and 5-year OS of around 10% [1,2].

SCLC is classified as limited stage (LS-) SCLC or extensive stage (ES-) SCLC based on whether the disease is confined to 1 hemithorax encompassed by 1 radiation portal. TNM stages I to III correspond to LS, and stage IV to ES [2]. In addition to ES, poor performance status (PS) 3–4, weight loss, and markers, such as lactate dehydrogenase, associated with bulky disease are the most important adverse prognostic factors. Younger age, good PS, normal creatinine level, normal lactate dehydrogenase, and a single metastatic site are favourable prognostic factors in patients with ES-SCLC [3]. SCLC patients who have never smoked appear to have a better prognosis [2].

Standard therapy for patients newly diagnosed with ES-SCLC consists of chemotherapy with platinum-etoposide and a PD-L1 immune checkpoint inhibitor, based on improved overall survival (OS) compared with chemotherapy alone demonstrated in randomised clinical studies. After initial cytoreduction with chemoimmunotherapy, monthly maintenance therapy with a PD-L1 inhibitor until tumour progression and/or treatment intolerance is recommended to prolong control of tumour growth. However, most patients with ES-SCLC have tumour regrowth after prior tumour shrinkage or development of new metastases on imaging within 3 to 4 months of initiation of maintenance treatment [2]. Hence, there is a substantial medical need for therapies that further improve OS and/or quality of life.

4 Nonclinical aspects

The applicant did not submit new nonclinical studies to support the requested extension of the indication. This was considered acceptable. Based on the ERA, the extension of the indication will not be associated with a significant risk for the environment.

References:

1. Dingemans AMC et al. Small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology 2021;32:839-853.
2. Kim SY et al. Small Cell Lung Cancer. A Review. JAMA 2025;333:1906-1917.
3. NCCN Clinical Practice Guidelines in Oncology. Small Cell Lung Cancer. Version 4.2025 – January 13, 2025.

5 Clinical aspects

5.1 Clinical pharmacology

The pharmacokinetics (PK) and exposure-response relationship of atezolizumab and lurbinectedin were characterised in patients with ES-SCLC in the pivotal IMforte study using sparse PK sampling and an external evaluation of the reference PopPK model. The derived PK parameters were used for the exposure-response analysis. The reference PopPK models were able to adequately describe the PK of atezolizumab and lurbinectedin in the IMforte study.

Thus, the PK of atezolizumab and lurbinectedin are not influenced by the co-administration of each other in ES-SCLC patients and no new covariates were identified. The previously established exposure-efficacy and exposure-safety relationship were confirmed in the exposure-response analyses.

5.2 Dose finding and dose recommendation

No dedicated dose finding has been conducted for the proposed new atezolizumab + lurbinectedin combination treatment. Therefore, it remains unclear if the intended dose regimens, which essentially use dosages previously approved for the respective mono therapies, offer the best benefit-risk balance. In particular, it is uncertain if, due to additive or synergistic effects of the mono components, lower dosages could have achieved similar efficacy at lower toxicity. However, given the overall manageable and acceptable safety profile in an indication with a poor prognosis, including low rates of adverse events leading to treatment discontinuation and death, and overall fewer deaths in the atezolizumab + lurbinectedin treatment arm of the pivotal IMforte study, dose selection is acceptable.

5.3 Efficacy

The results of the pivotal IMforte study were submitted in support of the proposed indication extension. This was a randomised, open-label, multicentre Phase 3 study in 483 patients with ES-SCLC whose disease had not progressed after first-line (1L) induction therapy with atezolizumab, carboplatin, and etoposide. Patients were randomised 1:1 to receive either a combination of atezolizumab + lurbinectedin or atezolizumab alone as maintenance therapy. Patients were required to have an ongoing response or stable disease after completion of 4 cycles of carboplatin, etoposide, and atezolizumab treatment in order to be considered eligible for the maintenance phase of the study.

The primary endpoints for this study were progression-free survival (PFS), as assessed by an independent review facility (IRF), and overall survival (OS). Results as of the data cut-off (DCO) of 29 July 2024 were presented with the initial submission for the final analysis of IRF-PFS and the interim analysis of OS. Additional, updated results data as of the DCO of 12 February 2025 were subsequently submitted for safety (90-day safety update report) and OS (protocol-defined final OS), corresponding to approximately an additional 6.5 months of observation.

At primary PFS analysis as of the DCO of 29 July 2024, the combination of atezolizumab + lurbinectedin demonstrated a statistically significant improvement in median PFS compared to atezolizumab alone, with a stratified hazard ratio (HR) of 0.54 (95%CI 0.43, 0.67). The median PFS was 5.4 months (95%CI 4.2, 5.8) in the atezolizumab + lurbinectedin arm and 2.1 months (95%CI 1.6, 2.7) in the atezolizumab arm.

At the pre-specified OS interim analysis as of the DCO of 29 July 2024, the combination of atezolizumab + lurbinectedin demonstrated a statistically significant improvement in median OS compared to atezolizumab alone, with a stratified HR of 0.73 (95%CI 0.57, 0.95). The median OS was

13.2 months (95%CI 11.9, 16.4) in the atezolizumab + lurbinectedin arm versus 10.6 months (95%CI 9.5, 12.2) in the atezolizumab arm.

At the final OS analysis as of the DCO of 12 February 2025, OS was still in favour of the atezolizumab + lurbinectedin arm. However, as compared to the previous cut-off, the HR increased to 0.81 and an upper boundary of the confidence interval exceeding 1 (95%CI 0.65, 1.01). OS event-free rates for atezolizumab + lurbinectedin vs atezolizumab were 58.3% vs 46.4%, respectively, at 12 months, and 19.7% vs 22.3% months, respectively, at 24 months. In addition, there were uncertainties regarding the OS benefit in young and fit patients, as reflected by the OS HR in pertinent large patient subgroups (40 to 43% of the full analysis set): 1.03 (95%CI 0.73, 1.46) for patients <65 years, and 1.21 (95%CI 0.84, 1.74) and 0.99 (95%CI 0.70, 1.40) for patients with ECOG PS 0 at enrolment and randomisation, respectively. Subsequent anti-cancer therapy was considered adequate, and an impact of subsequent anti-cancer therapy on OS results appeared unlikely. Submission of the final CSR of the IMforte study including updated OS results and OS subgroup analyses based on the database lock at study completion was mandated as a post-approval requirement.

It was noted that more patients in the atezolizumab + lurbinectedin arm underwent follow-up brain RT as compared to the atezolizumab control arm (24.0% vs 14.5%). Similarly, more follow-up surgical procedures of the brain were reported in the investigational arm (5 patients vs none). Although the applicant's assumption that better disease control outside the brain with maintenance atezolizumab + lurbinectedin treatment might have resulted in the brain being the first site of disease progression in a higher proportion of patients in the atezolizumab + lurbinectedin arm compared with atezolizumab sounded plausible and might have contributed – albeit to an unknown extent – to the observed imbalance in follow-up brain disease across treatment arms, uncertainties remained. The applicant was requested to adequately reflect this difference in the Information for healthcare professionals.

Results of secondary health-related quality of life (HRQoL) endpoints, i.e. time to confirmed deterioration from randomisation in patient-reported physical functioning (HR 1.55; 95%CI 1.07, 2.25) and global health status (HR 1.24; 95%CI 0.90, 1.71) as measured by the EORTC QLQC30, were both in favour of the atezolizumab control arm. For physical functioning, the lower boundary of the 95% CI even exceeded 1. In addition, unfavourable results were already observed early on (e.g. Cycle 2, Day 1), when data were still available from substantial proportions of patients.
The open-label conduct was a weakness of the study. Although bias had been mitigated to some extent by using an IRF, knowledge of treatment assignments could still have impacted study outcomes by affecting investigator assessments and decisions (e.g. treatment modifications, subsequent anticancer therapy, etc.) as well as patient reporting (e.g. adverse events, quality of life, etc.) and decisions (e.g. withdrawal).

Eligibility criteria limited the IMforte study population to patients with a good clinical condition, as reflected, among others, by the exclusion of patients with ECOG performance status (PS) >1, or the presence or a history of CNS metastases. However, most recommendations for the therapy of treatment-naïve ES-SCLC with chemoimmunotherapy include patients with ECOG PS 2 and asymptomatic or treated brain metastases [2,3,4]. NCCN guidelines do recommend patients with poor PS (3–4) for systemic therapy if this was due to SCLC [3]. Furthermore, limiting the study population to patients with a good clinical condition might have resulted in overly positive efficacy and safety results (e.g. for medians of time-to-event endpoints, and frequency and severity of adverse events (AEs)). For instance, PS is a prognostic factor in patients with ES-SCLC [3]. Taken together, the study population was only partly representative of the real-world treatment setting, and the applicant was requested to adequately describe the study population in the Information for healthcare professionals. In addition, given the higher rate of subsequent brain disease (see above), non-clinical data pointing to a potential lack of CNS penetration of lurbinectedin, and the 2L indication excluding patients with CNS metastases, the approvable indication was limited to patients without presence or a history of CNS metastases, in line with eligibility for the pivotal IMforte study. For details, see the Information for healthcare professionals.

5.4 Safety

In the randomised phase of the IMforte study, combined atezolizumab + lurbinectedin therapy (N=242) was associated with more toxicity than atezolizumab alone (N=240). As of the DCO of 12 February 2025, more patients receiving atezolizumab + lurbinectedin therapy reported any adverse events (AEs) (97% vs 82%), with the total number of AEs being more than twice as high as in the atezolizumab arm (2081 vs 927 events). AEs of Grade 3-4 (41% vs 25%), AEs of Grade 5 (5% vs 2.5%), serious AEs (34% vs 18%), AEs leading to withdrawal from treatment (7% vs 4%), and AEs leading to any dose modification / interruption (41%vs 16%) were also reported by more patients receiving atezolizumab + lurbinectedin therapy.

The most frequent AEs, for which the difference in proportions was notably higher in the atezolizumab + lurbinectedin arm, included **gastrointestinal disorders** (59.5% vs 27%, with nausea (38% vs 5%) and vomiting (15% vs 2.5%) showing the greatest differences), **fatigue** (21% vs 8%) / **asthenia** (14% vs 7%), **blood and lymphatic system disorders** (44% vs 10%, with anaemia (34% vs 7%) showing the greatest difference), and **infections** (41% vs 27%, with COVID-19 (7% vs 2%) showing the greatest difference).

Although more AEs of Grade 5 were reported for atezolizumab + lurbinectedin therapy (5% vs 2.5%), overall, there were fewer deaths in the investigational arm (66% vs 70%) due to fewer patients who died from progressive disease in the atezolizumab + lurbinectedin arm. Higher proportions of AEs of Grade 5 for atezolizumab + lurbinectedin therapy were due to fatal cardiac disorders (1.7% vs 0%, with 2 deaths due to cardio-respiratory arrest and myocardial infarction, respectively) and neutropenia-related deaths (0.8% vs 0%).

While injection site phlebitis was reported in 1 patient only in the atezolizumab + lurbinectedin arm (under system organ class (SOC) *General disorders and administration site conditions*), there was a notable imbalance in the SOC *Vascular disorders* in disfavour of the atezolizumab + lurbinectedin arm (20% vs 5%). This was mainly due to (**thrombo**)**phlebitis** / **vascular inflammation**: 16.9% in the atezolizumab + lurbinectedin arm vs 0.8% in the IMforte atezolizumab arm (n=240), 2.9% in the atezolizumab monotherapy pool (n=3,178) and 5.8% in the lurbinectedin monotherapy pool (n=554). The majority of all events in the atezolizumab + lurbinectedin arm were considered related to any study drug. Most cases in the atezolizumab + lurbinectedin arm concerned phlebitis and thrombophlebitis not otherwise specified. The majority of all (thrombo)phlebitis / vascular inflammation events in the atezolizumab + lurbinectedin arm were Grade 1 to 2 (absolute 15.7% / relative 93%) and non-serious (15.2% / 90%), and the majority were resolved by the time of DCO (56.1%). The median time to onset was approximately 3 months and median time to resolution from onset was 79 days, but resolution was quicker for the most common cases of phlebitis and thrombophlebitis (approximately 1 to 1.5 months).

Renal and **urinary disorders** were also imbalanced (7% vs 4%), with more patients in the atezolizumab + lurbinectedin arm experiencing renal failure, acute kidney injury, immune-mediated nephritis, and nephropathy / renal disorder / impairment.

Finally, notably higher proportions of patients suffering from potentially life-threatening AEs, immune-mediated **pneumonitis** (any grade 5% vs 2%; Grade 3/4: 1.2% vs 0.4%), and **depression** (3% vs 0%) were reported in the investigational arm.

The safety profile observed for combined atezolizumab + lurbinectedin therapy in the IMforte study was generally consistent with the monotherapy pooled populations for atezolizumab (N=3,178) and lurbinectedin (N=554). AEs in the atezolizumab + lurbinectedin arm of the IMforte study with a notably higher rate than both mono populations included cytopenias and COVID-19. In addition, more patients reported phlebitis on combined atezolizumab + lurbinectedin therapy in the IMforte study than in the monotherapy pooled populations for atezolizumab and lurbinectedin (see above).

The applicant was requested to adequately reflect notable imbalances in AEs between treatment arms observed in the IMforte study in the Information for healthcare professionals, along with

additional information on (thrombo)phlebitis / vascular inflammation events. For details, see the Information for healthcare professionals.

5.5 Final clinical benefit-risk assessment

Combined atezolizumab + lurbinectedin therapy showed statistically significant and clinically meaningful improvements of the primary endpoints IRF-PFS and OS at the analysis as of the DCO of 29 July 2024.

While atezolizumab + lurbinectedin therapy was associated with more toxicity than atezolizumab alone, the combination's safety profile is considered manageable and acceptable in an indication with a poor prognosis, including low rates of AEs leading to treatment discontinuation and death, and overall fewer deaths in the atezolizumab + lurbinectedin treatment arm of the pivotal IMforte study.

Remaining uncertainties were adequately addressed by:

- labelling uncertainties related to efficacy and safety (notable imbalances in AEs) in the respective Information for healthcare professionals (for details see above).
- limiting the approvable indication to patients without CNS metastases, in line with eligibility for the pivotal IMforte study, and including a reference to the "Properties/Effects" section of the Information for healthcare professionals for relevant information on the pivotal study.
- the post-approval requirement to submit the final CSR of the IMforte study by August 2027, including updated OS results and OS subgroup analyses based on the database lock at study completion.

Considering the available evidence and the measures to mitigate remaining uncertainties, the benefit-risk balance was considered positive.

References

1. Dingemans AMC et al. Small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology 2021;32:839-853.
2. Kim SY et al. Small Cell Lung Cancer. A Review. JAMA 2025;333:1906-1917.
3. NCCN Clinical Practice Guidelines in Oncology. Small Cell Lung Cancer. Version 4.2025 – January 13, 2025.
4. Kelly K. UpToDate – Extensive-stage small cell lung cancer: Initial management. Topic last updated: Jun 11, 2025. Literature review current through: May 2025. www.uptodate.com.

6 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.

7 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.

▼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 has temporarily authorised indications, see “Indications/Uses” 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

Temporarily authorised 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.
This indication has been granted temporary authorisation as the documentation was incomplete at the time the application was assessed (Art. 9a Therapeutic Products Act). The temporary authorisation is contingent on the timely fulfilment of conditions. After they have been met, the temporary authorisation can be converted into an authorisation without special conditions.

Indication with non-limited authorisation

ZEPZELCA, in combination with atezolizumab, is indicated for the maintenance treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC) and with no CNS metastases, whose disease has not progressed after first-line induction therapy with atezolizumab, carboplatin and etoposide (see “Properties/Effects”*)*.

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 as monotherapy and as a combination therapy with atezolizumab is 3.2 mg/m^2 by intravenous infusion over 1 hour repeated every 21 days until disease progression or unacceptable toxicity.
When administering ZEPZELCA on the same day, atezolizumab is to be administered first (see “Properties/Effects”). For the recommended dosage of the intravenous or subcutaneous atezolizumab refer to the respective product information.
Patients must meet the following criteria before starting their treatment or re-treatment with Zepzelca:

Treatment criteria - prior to administration of the first cycle

a) Haemoglobin ≥9.0 g/dL, prior red blood cell (RBC) 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 ULN (upper limit of normal)
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 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 withheld 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.
In case atezolizumab is discontinued due to an immune-related severe adverse event, treatment with lurbinectedin may continue at the same dose as a single agent. The evidence for continuation of maintenance therapy with lurbinectedin as monotherapy is limited (2 patients in the pivotal IMforte study). If immune toxicity re-occurs despite discontinuation of atezolizumab, the participant should also discontinue lurbinectedin.

Pre-infusion medication:

The following pre-infusion medication is administered for antiemetic prophylaxis:

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

When using ZEPZELCA with atezolizumab for the maintenance treatment of extensive-stage small cell lung cancer, the administration of primary prophylaxis with granulocyte colony-stimulating factor (G-CSF) (unless contraindicated) can be considered to reduce the risk of febrile neutropenia. If this approach is adopted, the relevant guidelines for the use of G-CSF prophylaxis should be taken into account. There is no comparative evidence for prophylaxis with G-CSF versus as-required G-CSF therapy when using ZEPZELCA + atezolizumab.

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

Dose adjustment in the event of adverse reactions

The recommended dose reductions of ZEPZELCA in case of adverse reactions are listed in Table 1. For recommended measures regarding the dosage of atezolizumab in case of adverse reactions, the specific product information should additionally be consulted.

Table 1: Dose reduction for ZEPZELCA in the event of 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

Dose adjustments for ZEPZELCA for adverse reactions are presented in Table 2.

Table 2: Dose adjustment criteria for ZEPZELCA in the event of adverse reactions

Adverse reaction	Severity[a]	Dose adjustment
Neutropenia[b] *[see "Warnings and Precautions"]*	Grade 4 neutropenia or any grade of febrile neutropenia	• Withhold ZEPZELCA until Grade ≤1 AND • Resume ZEPZELCA at 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
Non haematological toxicity	Grade 2	• Withhold ZEPZELCA until Grade ≤1 AND • Resume ZEPZELCA at same dose

Adverse reaction	Severity[a]	Dose adjustment
	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 discontinue treatment

[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), and who had not received G-CSF as primary prophylaxis, 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 required in patients with mild (CrCl 60-89 mL/min) or moderate (CrCl 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. It must be used with caution and careful monitoring.

ZEPZELCA must not be used in patients with calculated creatinine clearance less than 30 mL/min.

Hepatic impairment

No dose adjustment is required in 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).

Zepzelca must not be used in 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.

Whole blood counts, including differential blood cells and platelet count, must be monitored at baseline and prior to each cycle of ZEPZELCA. Dose adjustments may be required.

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

Neutropenia

In a clinical study in patients with SCLC receiving ZEPZELCA as a single agent, 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 clinical studies of 242 patients with advanced ES-SCLC receiving ZEPZELCA in combination with atezolizumab, 35.7% (lab values) of patients experienced neutropenia (all grades), 17.8% (lab values) experienced Grade 3/4 neutropenia, and 1.7% experienced febrile neutropenia.

In case of febrile neutropenia or neutropenia with a serious infection complication, the use of granulocyte colony-stimulating factors (G-CSF) is recommended.

Hepatotoxicity

In an SCLC cohort of 105 patients receiving ZEPZELCA as a single-agent, ALT increases were reported in 72% of patients (4% ≥Grade 3), while AST increases were reported in 45% of patients (2% ≥Grade 3).

Among the 554 patients treated with ZEPZELCA as a single agent every 21 days, 6% and 3% of patients had Grade 3 elevations of ALT and AST respectively, and 0.4% and 0.5% of patients had Grade 4 elevations of ALT and AST respectively. 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 the absence of initial findings of cholestasis (i.e., no elevation of alkaline phosphatase [ALP] to >2 × ULN) or other reasons explaining the combination of increased ALT and TBL.

In clinical studies of 242 patients with advanced ES-SCLC receiving ZEPZELCA in combination with atezolizumab, ALT increases were reported in 25.3% (lab values) of patients (3.3% ≥Grade 3, lab values), and AST increases were reported in 24.2% (lab values) of patients (2.5% ≥Grade 3, lab values).

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.

Liver function tests, including ALT, AST, and bilirubin, must be monitored. Dose adjustments 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 of extravasation during the ZEPZELCA infusion. If extravasation occurs, immediately discontinue the infusion, remove the infusion catheter, and monitor patients for signs 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 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 known to be associated 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, that is to say 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, co-administration of moderate CYP3A inhibitors (e.g., aprepitant, ciprofloxacin, erythromycin, cyclosporine, fluconazole, grapefruit juice, diltiazem, verapamil) with ZEPZELCA is to be avoided. 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 (e.g., 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, total systemic exposure to lurbinectedin was increased approximately 2.7-fold ($AUC_{0-\infty}$) and total plasma clearance 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 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, co-administration of strong CYP3A inducers (e.g., carbamazepine, phenobarbital, phenytoin, rifampicin, rifabutin, rifapentine, St. John's Wort [*Hypericum perforatum*]) with ZEPZELCA is to be avoided. The use of alternative agents with less CYP3A induction can be considered.

In a drug-drug interaction study (n=8) with bosentan, a moderate CYP3A4 inducer, total systemic exposure to lurbinectedin was decreased by approximately 20% ($AUC_{0-\infty}$) and total plasma clearance increased by 25% when lurbinectedin was given concomitantly with bosentan (125 mg twice daily for 5 days). Given the magnitude of these changes, no clinically relevant effect of co-administration of moderate CYP3A4 inducers (e.g., bosentan, cenobamate, dabrafenib, efavirenz, etravirine, lorlatinib, phenobarbital, primidone, sotorasib) on lurbinectedin exposure is expected 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 on the transfer of lurbinectedin into human milk, the effects on the breast-fed child, or the effect on milk production. Due to the potential of serious adverse effects of ZEPZELCA on the breast-fed child, breast-feeding 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

Use of lurbinectedin as monotherapy

The data described below reflect exposure to ZEPZELCA in 554 patients treated with single-agent therapy. 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. These patients include 105 with SCLC, 230 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 with 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 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 limit of normal (ULN). 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 (lurbinectedin monotherapy)

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	Common
Leukopenia[k]	Very Common (29.6%)
Anaemia[k]	Very Common (17.3%)
Thrombocytopenia[k]	Common
Neutropenia[k]	Very Common (40.6%)
Lymphopenia[k]	Very Common (33.6%)
Metabolism and nutrition disorders	
Decreased appetite	Very common (24.9%)
Dehydration	Common
Psychiatric disorders	
Insomnia	Common
Nervous system disorders	
Peripheral neuropathy[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%)

	Percentage and frequency category
	All patients (n=554)
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
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: maculo-papular rash, urticaria, erythematous skin rash, papular rash and erythema

[f] Merged: generalised pruritus

[g] Merged: back pain, pain in extremity, myalgia, musculoskeletal chest pain and neck pain

[h] Merged: asthenia
[i] Merged: oedema and oedema 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 one patient from the Basket study.

Table 4: Laboratory abnormalities experienced by ≥10% of patients regardless of relationship

Category	Percentage
	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/mm3 (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

Use of lurbinectedin in combination with atezolizumab

The safety of lurbinectedin in combination with atezolizumab was evaluated in IMforte, a randomised, multi-centre, open-label study in which 242 patients with ES-SCLC whose disease had not progressed after first-line induction therapy with atezolizumab, carboplatin, and etoposide received maintenance treatment with lurbinectedin 3.2 mg/m^2 IV and atezolizumab 1200 mg IV on Day 1 of each 21-day cycle until disease progression or unacceptable toxicity.

Among the 242 patients receiving ZEPZELCA with atezolizumab, the median duration of exposure to lurbinectedin was 4.4 months.

The most common adverse reactions, including laboratory abnormalities (≥20%), were lymphopenia (57.3%), thrombocytopenia (54.8%), anaemia (48.5%), leukopenia (38.6%), nausea (37.6%), neutropenia (37.2%), fatigue/asthenia (34.3%), increased alkaline phosphatase (30.7%), decreased

sodium (28.6%), increased alanine aminotransferase (28.2%), decreased calcium (26.1%), increased aspartate aminotransferase (25.8%), increased creatinine (lab: 22.1%), decreased magnesium (20.6%) and decreased albumin (20.1%).

Fatal adverse reactions occurred in 5% of patients receiving ZEPZELCA with atezolizumab. These included cardio-respiratory arrest, myocardial infarction (2 patients each), COVID-19 pneumonia, pneumonia, viral pneumonia, sepsis, neutropenia, vascular device infection, and febrile neutropenia (1 patient each).

Serious adverse reactions occurred in 34.1% of patients receiving ZEPZELCA with atezolizumab. Serious adverse reactions occurring in >2% were pneumonia (2.9%), respiratory tract infection (2.1%), dyspnoea (2.1%), and decreased platelet count (2.1%).

Treatment with ZEPZELCA was permanently discontinued due to adverse reactions in 5.8% of patients who were receiving ZEPZELCA in combination with atezolizumab. The most frequent adverse reactions requiring permanent discontinuation of ZEPZELCA were decreased neutrophil count and anaemia (1.2% each).

Adverse reactions leading to interruption of ZEPZELCA occurred in 28.9% of patients who received ZEPZELCA with atezolizumab; the most common adverse reactions (≥2%) leading to interruption were anaemia (5.04%), fatigue/asthenia (4.6%), decreased neutrophil count (3.3%), decreased platelet count (2.9%), COVID-19 and neutropenia (2.1%, each).

Dose reductions of ZEPZELCA due to an adverse reaction occurred in 16.1% of patients who received ZEPZELCA with atezolizumab. Adverse reactions requiring dosage reductions occurring in ≥2% of patients who received ZEPZELCA with atezolizumab included decreased platelet count (3.3%), fatigue/asthenia (3.1%), nausea (2.1%) and vomiting (2.1%).

In total, 16.9% of all patients in the atezolizumab + lurbinectedin arm (n=242) of the IMforte study experienced any grade (thrombo)phlebitis / vascular inflammation events, as compared with 0.8% in the IMforte atezolizumab arm (n=240), 2.9% in the atezolizumab monotherapy pool (n=3178) and 5.8% in the lurbinectedin monotherapy pool (n=554). The majority of all events in the atezolizumab + lurbinectedin arm were considered related to study drug, especially to lurbinectedin (absolute 9.5% / relative 56%), and required treatment (11.2% / 66%). Most cases in the atezolizumab + lurbinectedin arm concerned phlebitis and thrombophlebitis not otherwise specified. The majority of all (thrombo)phlebitis / vascular inflammation events in the atezolizumab + lurbinectedin arm were of Grade 1 to 2 (absolute 15.7% / relative 93%), non-serious (15.2% / 90%), and the majority were resolved by the time of DCO (56.1%). The median time to onset was approximately 3 months, and median time to resolution from onset was 79 days, but resolution was quicker for the most common cases of phlebitis and thrombophlebitis (approximately 1 to 1.5 months).

Adverse reactions reported in clinical trials are listed by MedDRA system organ class and by frequency in Tables 5 and 6.

Tabulated list of adverse reactions

Frequencies are defined as: 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); "frequency not known (cannot be estimated from available data)". Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 5: Adverse reactions in patients treated with lurbinectedin and atezolizumab in IMforte

System Organ Class Frequency category	**Adverse reaction**
Infections and infestations	
Very common	Upper respiratory tract infection[a] (all grades: 10.3%; Grade 3-4: 0)
Common	COVID-19[b]; respiratory tract infection[c]; pneumonia;urinary tract infection[d]
Blood and lymphatic system disorders	
Very common	Anaemia[e] (all grades: 48.5%; Grade 3-4: 12.0%); Thrombocytopenia[e] (all grades: 54.8%; Grade 3-4: 14.1%); Neutropenia[e] (all grades: 37.2%; Grade 3-4: 17.3%); Leukopenia[e] (all grades: 38.6%; Grade 3-4: 10.4%); Lymphopenia[e] (all grades: 57.3%; Grade 3-4: 18.3%)
Endocrine disorders	
Common	Hypothyroidism
Metabolism and nutrition disorders	
Very common	Decreased appetite (all grades: 18.2%; Grade 3-4: 0.8%); Hypomagnesaemia[e] (all grades: 20.6%; Grade 3-4: 1.3%); Hyponatraemia[e] (all grades: 28.6%; Grade 3-4: 4.1%); Hypocalcaemia[e] (all grades: 26.1%; Grade 3-4: 4.2%)
Common	Weight decreased
Nervous system disorders	
Common	Peripheral neuropathy[f]; dizziness; headache
Vascular disorders	
Very common	Phlebitis[g] (all grades: 16.9%; Grade 3-4: 1.2%)
Respiratory, thoracic and mediastinal disorders	
Very common	Dyspnoea (all grades: 10.7%; Grade 3-4: 2.5%)
Common	Cough; pneumonitis and immune-mediated pneumonitis
Gastrointestinal disorders	
Very common	Nausea (all grades: 37.6%; Grade 3-4: 2.9%); Diarrhoea (all grades: 15.7%; Grade 3-4: 0.4%); Vomiting (all grades:14.9%; Grade 3-4: 0.8%); Constipation (all grades: 12.8%; Grade 3-4: 0)
Common	Abdominal pain[h]
Skin and subcutaneous tissue disorders	
Common	Pruritus; rash
Musculoskeletal and connective tissue disorders	
Very common	Musculoskeletal pain[i] (all grades: 15.7%; Grade 3-4: 0.8%)
Common	Arthralgia
General disorders and administration site conditions	
Very common	Fatigue[j] (all grades: 34.3%; Grade 3-4: 5.0%)
Common	Oedema[k]; pyrexia
Hepatobiliary disorders	
Very common	ALT increased[l] (all grades: 28.2%; Grade 3-4: 3.3%); AST increased[l] (all grades: 25.8%; Grade 3-4: 2.5%);

System Organ Class Frequency category	Adverse reaction
	Blood alkaline phosphatase increased[l] (all grades: 30.7%; grade: 3-4: 1.3%); Immune-mediated hepatitis (diagnosis and lab abnormalities: all grades: 11.2%; Grade 3-4: 3.7%) Albumin decreased (all grades: 20.1%; Grade 3-4: 1.3%)
Common	Gamma-GT increased (3.3%)
Psychiatric disorders	
Common	Depression
Renal and urinary disorders	
Very common	Blood creatinine increased[n] (all grades: 22.1%; Grade 3-4: 2.5%);
Common	Renal failure, acute kidney injury, immune-mediated nephritis, and nephropathy or renal disorder or renal impairment

The frequencies of adverse reactions are based on all-cause adverse event frequencies and on laboratory abnormalities worsening from baseline. AEs occurring in ≥5% of patients and laboratory abnormalities worsening from baseline occurring in ≥20% of patients are included. Several additional PTs were included since the frequency observed with combination of atezolizumab+lurbinectedin was higher than the frequency observed with atezolizumab as a single agent.

[a] Including upper respiratory tract infection, nasopharyngitis, pharyngitis, viral upper respiratory tract infection, and catarrh.
[b] Including COVID-19, COVID-19 pneumonia.
[c] Including respiratory tract infection, bronchitis, influenza, positive respiratory virus tests.
[d] Including urinary tract infection, cystitis.
[e] Laboratory abnormalities worsening from baseline.
[f] Including, hypoaesthesia, peripheral neuropathy, paraesthesia, peripheral sensory neuropathy.
[g] Including phlebitis, injection site phlebitis, thrombophlebitis, thrombosis, arteriosclerosis, deep vein thrombosis, superior vena cava syndrome, chemical phlebitis, intermittent claudication, peripheral arterial occlusive disease, subclavian vein thrombosis.
[h] Including abdominal discomfort, abdominal distension, abdominal pain, upper abdominal pain.
[i] Including back pain, musculoskeletal chest pain, musculoskeletal pain, myalgia, neck pain, pain in extremity.
[j] Including asthenia, fatigue.
[k] Including oedema, peripheral oedema.
[l] Laboratory abnormalities worsening from baseline.

Table 6: Laboratory abnormalities worsening from baseline occurring in ≥20% of patients with extensive-stage SCLC receiving ZEPZELCA with atezolizumab in IMforte

Laboratory abnormality	ZEPZELCA with atezolizumab n=242	
	All grades (%)	Grades 3–4 (%)
Hematology		
Decreased lymphocytes	57.3	18.3
Decreased platelets	54.8	14.1
Decreased haemoglobin	48.5	12
Decreased leukocytes	38.6	10.4
Decreased neutrophils	37.2	17.3
Chemistry		
Increased alkaline phosphatase	30.7	1.3
Decreased sodium	28.6	4.1
Increased ALT	28.2	3.3
Increased AST	25.8	2.5
Decreased calcium	26.1	4.2
Increased creatinine	22.1	2.5
Decreased magnesium	20.6	1.3
Decreased albumin	20.1	1.3
Graded per NCI CTCAE v5.0		

List 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.

Rare cases of tumour lysis syndrome 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 occurring 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 of Grade ≥3 occurring with a frequency >5% were the following: febrile neutropenia (10.8%); sepsis (10.8%); hyponatremia (5.4%); peripheral neuropathy (5.4%) and pneumonia (5.4%).

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

Of the 242 patients with ES-SCLC who received ZEPZELCA and atezolizumab in IMforte, 124 (51%) patients were 65 years of age and older and 29 (12%) were 75 years of age and older.

Table 7: Comparative summary for patients <65 years vs ≥65 years receiving atezolizumab + lurbinectedin

	<65 years (n=118)	**≥65 years (n=124)**
Patients with ≥1 AE	112 (94.9%)	123 (99.2%)
Grade 3–4 AE	38 (32.2%)	62 (50.0%)
Grade 5 AE	7 (5.9%)	5 (4.0%)
Serious AE	34 (28.8%)	49 (39.5%)
AE leading to ZEPZELCA discontinuation.	2 (1.7%)	12 (9.7%)
AE leading to any dose modification/interruption of ZEPZELCA	41 (34.7%)	49 (39.5%)
The frequencies of adverse effects are based on all-cause adverse event frequencies.		

Any grade AEs (all events) reported ≥10% more frequently in elderly patients included anaemia and musculoskeletal pain. Grade ≥3 AEs reported ≥2% more frequently in elderly patients were anaemia,

neutropenia, thrombocytopenia and arthralgia. The SAE reported ≥2% more frequently in elderly patients was neutropenia. The AE leading to treatment discontinuation reported ≥2% more frequently in elderly patients was neutropenia.

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

If an overdose is suspected, the patient must be monitored closely for myelosuppression and hepatic enzymes checked. Supportive-care measures should be instituted 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. These processes interrupt the cell cycle and lead to cell apoptosis.

Lurbinectedin inhibited 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. No marked effects (>10 ms) on the QTc interval were detected with lurbinectedin dosed at 3.2 mg/m² every 21 days.

Clinical efficacy

Metastatic small cell lung cancer (ZEPZELCA as a single agent)

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, and 92% had ECOG PS 0 or 1. 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 one of the following events: disease progression, unacceptable toxicity, treatment delay >21 days from the treatment due date (except in case of clear clinical benefit, upon Sponsor 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 the 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 8.

Table 8: 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)

Parameter	Overall (n=83)
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, OS: overall survival, PFS: progression-free survival

Extensive-stage small cell lung cancer (ZEPZELCA with atezolizumab)

The efficacy of maintenance treatment with ZEPZELCA and atezolizumab was investigated in 483 patients with first-line ES-SCLC in IMforte, a randomised, multicenter, open-label study. Participants were eligible for randomisation if their disease had not progressed after completion of 4 cycles of induction treatment with atezolizumab, carboplatin and etoposide and it they had an ECOG performance status of 0 or 1. Eligible patients were randomised 1:1 to receive maintenance treatment with either ZEPZELCA and atezolizumab or atezolizumab alone. Unless contraindicated, primary prophylaxis with G-CSF was administered in the study protocol for patients assigned to the lurbinectedin and atezolizumab arm, in 84% of patients overall.

The trial excluded patients with ECOG performance status >1, CNS metastases (previous or current), a history of autoimmune disease, or administration of systemic immunosuppressants within 1 weeks prior to enrolment, patients with leptomeningeal disease, inadequate haematologic and end organ function, with planned consolidative chest radiation, uncontrolled pleural or pericardial effusion/ascites, with lesions requiring palliative radiotherapy and patients with clinically significant toxicities from induction therapy Grade >1. Randomisation was stratified by ECOG performance status (0 vs 1), LDH (≤ULN vs >ULN), presence of liver metastases (yes vs no), and prior receipt of prophylactic cranial irradiation (yes vs no).

Patients were randomised to one of the following two treatment arms:

- ZEPZELCA 3.2 mg/m^2 IV with atezolizumab 1200 mg IV once every 3 weeks until disease progression or unacceptable toxicity.
- Atezolizumab 1200 mg IV once every 3 weeks until disease progression or unacceptable toxicity.

Primary efficacy outcome measures were OS and Independent Review Facility (IRF)-assessed PFS per RECIST v1.1 in the randomised population.

A total of 483 patients were randomized, including 242 to the ZEPZELCA and atezolizumab arm and 241 to the atezolizumab arm. The median age was 66 years (range: 35 to 85 years). The majority of patients were White (81.6%); 12.8% were Asian, 6.6% were Hispanic and <1% were Black. Most

patients were male (62.5%) and 97.5% were current or previous smokers. Baseline ECOG performance status was 0 (42.9%) or 1 (57.1%).

At the time of the primary analysis, the median follow-up was 15 months. Treatment with ZEPZELCA in combination with atezolizumab demonstrated a statistically significant improvement in OS (stratified HR: 0.73 [95% CI: 0.57, 0.95]; p = 0.0174, median OS: 13.2 months vs 10.6 months) and IRF-assessed PFS (stratified HR: 0.54 [95% CI:0.43, 0.67]; p <0.0001, median PFS: 5.4 months vs 2.1 months) compared with atezolizumab alone. Efficacy results at the time of the primary analysis are presented in Table 9.

Table 9: Efficacy results from IMforte (primary analysis)

	Lurbinectedin with atezolizumab n=242	**Atezolizumab n=241**
Overall survival[1]		
Deaths (%)	113 (46.7%)	136 (56.4%)
Median, months	13.2	10.6
(95% CI)	(11.9, 16.4)	(9.5, 12.2)
Hazard ratio[2] (95% CI)	0.73 (0.57, 0.95)	
p-value[3, 6]	0.0174	
OS rate at 12 months	56.3%	44.1%
Progression-free survival[1, 4, 6]		
Number of events (%)	174 (71.9%)	202 (83.8%)
Median, months	5.4	2.1
(95% CI)	(4.2, 5.8)	(1.6, 2.7)
Hazard ratio[2] (95% CI)	0.54 (0.43, 0.67)	
p-value[3, 7]	<0.0001	
PFS rate at 6 months	41.2%	18.7%
PFS rate at 12 months	20.5%	12%

[1] Measured from the time of randomisation
[2] Stratified by ECOG performance status, LDH level, presence of liver metastases and prior prophylactic cranial irradiation
[3] Based on the stratified log-rank test
[4] As determined by IRF
[5] Per RECIST v1.1 (Response Evaluation Criteria in Solid Tumors v1.1)
[6] Compared to the allocated alpha of 0.0313 (two-sided) for this interim OS analysis
[7] Compared to the allocated alpha of 0.001 (two- sided) for this final PFS analysis.
CI = confidence interval; PFS = progression-free survival; OS = overall survival

In the descriptive OS analysis, approximately 6.5 months after the primary analysis, the hazard ratio (95% CI) was 0.81 (0.65, 1.01) [deaths: 159 (65.7%) in the lurbinectedin with atezolizumab arm and 169 (70.1%) in the atezolizumab arm]. The results of the exploratory OS subgroup analysis were generally consistent with those from the study population (n=483).

The OS hazard ratio (95% CI) in the subgroup of patients with ECOG PS 0 at induction baseline and at the time of randomisation into the maintenance treatment phase was 1.21 (0.84, 1.74) and 0.99

(0.70, 1.40), respectively, and 1.03 (0.73, 1.46) in patients <65 years [subgroup sizes 40-43% of the study population].

At the time of the primary analysis, more patients in the lurbinectedin with atezolizumab arm of the IMforte study had initial progression in the brain (16.1%) compared to the atezolizumab arm (7.9%). Among patients with the brain as their first site of progression, there was no evidence of faster disease progression in the lurbinectedin with atezolizumab arm. Subsequent radiotherapy of the brain was recorded in 24.0% vs 14.5% of patients in the lurbinectedin with atezolizumab arm compared to the atezolizumab arm and subsequent surgical intervention on the brain in 2.1% vs 0% of patients.

Due to the small number of patients and the exploratory nature of these analyses, no definitive conclusions can be drawn based on these data.

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 administration every 21 days.

Absorption

Non applicable.

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 the faeces (89% of the dose). The most abundant metabolite found in faeces accounted for 1% of the dose, and only traces of unchanged lurbinectedin were detected in the faeces (<0.2% of the dose). Excretion in urine was the minor route (6% of the dose), mainly as unchanged compound (1% of the dose) and one metabolite (up to 1% of the 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 (CrCl 60−89 mL/min) or 73 patients with moderate renal impairment (CrCl 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

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 (corresponding 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 were decreases in body weight/body weight gain and decreased food consumption.

Other information

Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

This medicinal product may be mixed only with those medicinal products listed under “Instructions for handling”.

The diluted ZEPZELCA 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 microns.
- 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 (0.9%) solution for infusion.

Shelf life

Do not use this medicine after the expiry date marked as "EXP" on the pack.

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

Instructions for handling

ZEPZELCA is a cytostatic 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 a 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 a 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

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c/o OBC Suisse AG
Aeschengraben 29
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Manufacturer

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