



Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Lurbinectedin

Proprietary Product Name: Zepzelca

Sponsor: Specialised Therapeutics Pharma Pty
Ltd

March 2022

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- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
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- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
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- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

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List of abbreviations

Abbreviation	Meaning
ACM	Advisory Committee on Medicines
AE	Adverse event
AESI	Adverse events of special interest
ARTG	Australian Register of Therapeutic Goods
BICR	Blinded independent central radiology
CAV	Cyclophosphamide, doxorubicin, and vincristine
CEV	Cyclophosphamide, epirubicin, and vincristine
CMI	Consumer Medicine Information
CNS	Central nervous system
CTFI	Chemotherapy-free interval
CYP3A4	Cytochrome P450 3A4
DNA	Deoxyribonucleic acid
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
ES-SCLC	Extensive-stage small cell lung cancer
FDA	Food and Drug Administration (United States of America)
GI	Gastrointestinal
GMP	Good Manufacturing Practice
IA	Investigator assessment
IC ₅₀	Half-maximal inhibitory concentration
IRC	Independent review committee
ISS	Investigator sponsored study
MDR	Multi-Discipline Review (United States Food and Drug Administration)
NCCN	National Comprehensive Cancer Network (United States of America)

Abbreviation	Meaning
OATP1B1	Organic anion transport protein 1B1
OATP1B3	Organic anion transport protein 1B3
OCT1	Organic cation transporter 1
ORR	Objective response rate
OS	Overall survival
PFS	Progression-free survival
P-gp	P-glycoprotein
PI	Product Information
PK	Pharmacokinetic(s)
PMC	Post-marketing commitments
PMR	Post-marketing requirements
PS	Performance status
PSUR	Periodic Safety Update Report
QTc	Corrected QT interval
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical analysis plan
SCLC	Small cell lung cancer
ULN	Upper limit of normal
US(A)	Unites States (of America)

I. Introduction to product submission

Submission details

<i>Type of submission:</i>	New chemical entity
<i>Product name:</i>	Zepzelca
<i>Active ingredient:</i>	Lurbinectedin
<i>Decision:</i>	Approved for provisional registration
<i>Date of decision:</i>	10 September 2021
<i>Date of entry onto ARTG:</i>	13 September 2021
<i>ARTG number:</i>	335536
<i>, Black Triangle Scheme:¹</i>	Yes. As a provisionally registered product, this medicine will remain in the Black Triangle Scheme for the duration of its provisional registration.
<i>Sponsor's name and address:</i>	Specialised Therapeutics Pharma Pty Ltd Level 2, 17 Cotham Road Kew, Victoria 3101
<i>Dose form:</i>	Powder for solution for infusion
<i>Strength:</i>	4 mg
<i>Container:</i>	Vial
<i>Pack size:</i>	Pack of one vial
<i>Approved therapeutic use:</i>	<i>Zepzelca is indicated for the treatment of patients with metastatic small cell lung cancer (SCLC) that has progressed on or after prior platinum-containing therapy. This indication was approved via the provisional approval pathway, based on objective response rate and duration of response in a single arm trial. Continued approval for this indication depends on verification and description of clinical benefit in a confirmatory trial.</i>
<i>Route of administration:</i>	Intravenous infusion
<i>Dosage:</i>	The recommended dose is 3.2 mg/m ² by intravenous infusion over 60 minutes, repeated once every 21 days until disease progression or unacceptable toxicity.

¹ The **Black Triangle Scheme** provides a simple means for practitioners and patients to identify certain types of new prescription medicines, including those being used in new ways and to encourage the reporting of adverse events associated with their use. The Black Triangle does not denote that there are known safety problems, just that the TGA is encouraging adverse event reporting to help us build up the full picture of a medicine's safety profile.

Only administer Zepzelca to patients with an absolute neutrophil count above $1.5 \times 10^9/L$, and a platelet count above $100 \times 10^9/L$.

For further information refer to the Product Information.

Pregnancy category:

D

Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. This must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your State or Territory.

Product background

This AusPAR describes the application by Specialised Therapeutics Pharma Pty Ltd (the sponsor) to register Zepzelca (lurbinectedin) 4 mg, powder for infusion for the following proposed indication:

For the treatment of patients with small cell lung cancer (SCLC) who have progressed after prior platinum-containing therapy.

Lung cancer is the leading cause of cancer related mortality in Australia² and worldwide.³ Small cell lung cancer (SCLC) is an aggressive neuroendocrine tumour that accounts for approximately 15% of lung cancers.⁴

Limited stage SCLC (tumours confined to the hemithorax of origin, the mediastinum, or the supraclavicular lymph nodes) accounts for 30% of newly diagnosed SCLC. The remainder (majority) of patients with SCLC have extensive stage disease (ES-SCLC) at presentation, which includes tumours that have spread beyond the supraclavicular areas, presence of malignant pleural or pericardial effusion, and metastatic disease.⁵ Standard of care current first line treatment for ES-SCLC in Australia is chemoimmunotherapy consisting of platinum based chemotherapy (platinum plus etoposide), plus either atezolizumab (based on the IMpower133;⁶ trial) or durvalumab (based on CASPIAN;⁷ trial), with continuation of the immunotherapy as maintenance. These regimens are associated with a median

² Australian Institute of Health and Welfare.

³ WHO, GLOBOCAN 2018: Estimated Cancer, Incidence, Mortality and Prevalence Worldwide in 2018.

⁴ Kalemkerian GP et al. *J Natl Compr Canc Netw*; 2013; 1;11(1):78-98.

⁵ Almuish D et al. Multimodality therapy for limited-stage small cell lung cancer. *Journal of Oncology Practice* 2016; 12(2): 111-7.

⁶ IMpower133 is a Phase III, double-blind, placebo-controlled study to evaluate first-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer.

⁷ CASPIAN is a Phase III, randomised, controlled, open-label study to evaluate durvalumab plus platinum-etoposide versus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN).

overall survival (OS) of around 12 to 13 months.^{8,9} Prior to the recent emergence of data supporting the addition of immunotherapy, the standard of care was platinum plus etoposide, based on at least the same efficacy as older regimens (such as cyclophosphamide, doxorubicin, and vincristine (CAV) or cyclophosphamide, epirubicin, and vincristine (CEV)), with less toxicity.¹⁰

The advent of immunotherapy as an add on to the first line standard of care has been fairly recent; TGA approvals of the atezolizumab;¹¹ and durvalumab;¹² indications occurred in July 2019 and November 2020, respectively. As a result, most data supporting the use of second line therapies comes from patients who received first line chemotherapy without immunotherapy.

Selection of second line treatment options and the prognosis of such treatments are dependent on the timing of disease progression relative to first line chemotherapy (the chemotherapy free interval (CTFI)). The literature tends to describe three categories of disease based on CTFI:¹³

'Sensitive, resistant, and refractory. 'Sensitive' refers to patients who have had a tumor response lasting 90 days or longer. These patients are thought to have the greatest potential for benefit from second-line chemotherapy. 'Resistant' refers to patients who have recurred within 90 days of completing primary therapy. 'Refractory' refers to patients with tumors that never responded to first-line therapy or to those who progressed during first-line therapy.'

Chemotherapy resistant or refractory patients (by the above definition) have a less than 10% chance of response to subsequent treatment, whilst sensitive patients are generally thought to have a higher chance of response.^{14, 15}

The National Comprehensive Cancer Network (NCCN)¹⁶ guidelines recommend retreatment with the same chemotherapy regimen for patients with a CTFI of 6 months (about 26 weeks) or longer.¹⁷ The recommendation is based on two small case series conducted in the late eighties. In the first, re-responses were seen in 62% of 37 patients who were re-treated with platinum based chemotherapy after a median CTFI duration of 34 weeks (about 7.8 months) following responses to first line platinum.¹⁸ In the second, re-responses were seen in 50% of 13 patients who had a median CTFI of 30 weeks about

⁸ Liu SV et al. Updated Overall Survival and PD-L1 Subgroup Analysis of Patients with Extensive-Stage Small-Cell Lung Cancer Treated with Atezolizumab, Carboplatin, and Etoposide (IMpower133). *J Clin Oncol*, 2021; 20;39(6):619-630.

⁹ Goldman JW et al. CASPIAN investigators. Durvalumab, with or without tremelimumab, plus platinum-etoposide versus platinum-etoposide alone in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): updated results from a randomised, controlled, open-label, phase 3 trial. *Lancet Oncol*. 2021; 22(1):51-65.

¹⁰ Kelly K. Extensive-stage small cell lung cancer: Initial management. In: UpToDate (Accessed 31 March 2021).

¹¹ Atezolizumab was first registered in the ARTG on 27 July 2017 (ARTG number: 277120).

¹² Durvalumab was first registered in the ARTG on 2 October 2018 (ARTG number: 283215).

¹³ Cheng S et al. Lung Cancer Disease Site Group of Cancer Care Ontario's Program in Evidence-based Care. Chemotherapy for relapsed small cell lung cancer: a systematic review and practice guideline. *J Thorac Oncol*, 2007; 2(4):348-54.

¹⁴ Lara PN, Jr. et al. Relevance of platinum sensitivity status in relapsed/refractory extensive stage small cell lung cancer (ES-SCLC) in the modern era: a patient level analysis of SWOG trials. *Journal of Thoracic Oncology*; 2016; 10(1): 110-115.

¹⁵ Gong J et al. Managing patients with relapsed small-cell lung cancer. *Journal of Oncology Practice*; 2018; 14(6): 359-366.

¹⁶ The National Comprehensive Cancer Network is an alliance of 31 cancer centres in the United States of America, most of which are designated by the United States National Cancer Institute as comprehensive cancer centres.

¹⁷ National Comprehensive Cancer Network Guidelines version 3, 2021. Available from nccn.org.

¹⁸ Postmus PE et al. Retreatment with the induction regimen in small cell lung cancer relapsing after an initial response to short term chemotherapy. *European Journal of Cancer and Clinical Oncology*; 1987; 23: 1409-1411.

6.9 months after responding to and completing first line platinum based chemotherapy.¹⁹ However, the NCCN does not recommend retreatment with the same regimen for patients on maintenance atezolizumab or durvalumab at time of relapse.¹⁵

For patients with disease progression or recurrence within six months following completion of platinum based chemotherapy, and whose performance status remains two or less, treatment options include single agent chemotherapy and palliative radiotherapy. Topotecan is the only agent currently approved by the TGA specifically for the treatment of patients with SCLC with disease progression after first line chemotherapy.²⁰ Other options include the CAV regimen, or single agent chemotherapy options that have been shown to have anti-tumour activity in relapsed SCLC (including paclitaxel,²¹ docetaxel,²² vinorelbine,²³ temozolomide,²⁴ and bendamustine,²⁵ with reported objective response rates (ORR) between 10% and 29%), but these are very rarely used in Australian clinical practice.

All of these second line options (retreatment with a first line platinum based regimen, CAV, topotecan, or other single agent chemotherapy) are associated with inevitable relapse and significant toxicity, and this is an area of significant unmet clinical need.

The approved Australian indication for topotecan is:

For the treatment of small cell lung carcinoma (SCLC) after failure of first line chemotherapy.

The basis for this approval was one randomised trial, published in 1999, conducted in patients who had progressed at least 60 days after initiation of first line chemotherapy, which showed a response rate of 24% (95% confidence interval (CI): 16, 32) with a median duration of response of 3.3 months.²⁶ Supporting data was available from three single arm studies, including for patients with resistant or refractory disease who showed response rates of 2 to 7%:²⁷

'Hycamtin for injection was also studied in three open-label, non-comparative trials (Studies 014, 092 and 053) in a total of 319 patients with recurrent or progressive SCLC after treatment with first-line chemotherapy. In all three trials, patients were stratified as either sensitive (responders who then subsequently progressed greater than or equal to 90 days after completion of first-line therapy) or refractory (no response to first-line chemotherapy or who responded to first-line therapy and then progressed within 90 days of completing first-line therapy). Response rates ranged from 11% to 31% for sensitive patients and 2% to 7% for refractory patients. Median time to progression and median survival were similar in all three trials and the comparative trial.'

¹⁹ Giaccone G et al. Reinduction chemotherapy in small cell lung cancer. *European Journal of Cancer and Clinical Oncology*; 1987; 23: 1697-1699.

²⁰ Australian product information (PI) for topotecan (revision date 29 August 2019).

²¹ Kim SH et al. Paclitaxel as third-line chemotherapy for small cell lung cancer failing both etoposide and camptothecin based chemotherapy. *Medicine (Baltimore)*; 2017; 96(42): e8176.

²² Smyth JF et al. Activity of docetaxel (Taxotere) in small cell lung cancer. The Early Clinical Trials Group of the EORTC. *European Journal of Cancer*; 1994; 30A(8): 1058-60.

²³ Jassem J et al. Phase II study of vinorelbine (Navelbine) in previously treated small cell lung cancer patients. EORTC Lung Cancer Cooperative Group. *European Journal of Cancer*; 1993; 29A(12): 1720-2.

²⁴ Zauderer, M.G. et al. Trial of a 5-day dosing regimen of temozolomide in patients with relapsed small cell lung cancers with assessment of methylguanine-DNA methyltransferase. *Lung Cancer*; 2014; 86(2): 237-240.

²⁵ Lammers PE et al. Phase II study of bendamustine in relapsed chemotherapy sensitive or resistant small-cell lung cancer. *Journal of Thoracic Oncology*; 2014; 9(4): 559-562.

²⁶ von Pawel J et al. Topotecan versus cyclophosphamide, doxorubicin, and vincristine for the treatment of recurrent small-cell lung cancer. *J Clin Oncol*; 1999 Feb;17(2):658-67.

²⁷ FDA Prescribing Information for HYCAMTIN (topotecan) for injection, for intravenous use. Available from the FDA website.

A second, later dataset for topotecan is available from a randomised trial published in 2014, which compared topotecan with amrubicin, a third generation topoisomerase inhibitor, and failed to show superiority of amrubicin;²⁸ (also see Table 7 in Safety section for further information).

There are no products registered in Australia, provisionally or otherwise, for treatment of SCLC in the third line or beyond.

This evaluation was facilitated through Project Orbis,²⁹ an initiative of the United States (US) Food and Drug Administration (FDA) Oncology Center of Excellence (OCE). Under this project, the FDA and the TGA collaboratively reviewed the application. This innovative evaluation process provided a framework for process alignment and management of evaluation issues in real-time across jurisdictions.

Each regulator agency maintained its regulatory process to make independent decisions about the approval (market authorisation).

Regulatory status

This product is considered a new chemical entity for Australian regulatory purposes.

At the time the TGA considered this application, a similar application had been approved in the United States of America (USA).

Table 1: International regulatory status

Region	Submission date	Status	Approved indications
United States of America	December 2019	Approved on 15 June 2020	<i>Zepzelca (lurbinectedin) is indicated for the treatment of patients with SCLC who have progressed after prior platinum containing therapy.</i>

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <<https://www.tga.gov.au/product-information-pi>>.

²⁸ 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; 32(35):4012-9.

²⁹ **Project Orbis** seeks to increase collaboration among international regulators, which may in turn allow patients with cancer to receive earlier access to products in other countries where there may be significant delays in regulatory submissions, regardless of whether the product has received approval. Pivotal clinical trials in oncology are commonly conducted internationally and these global trials are increasingly important for investigating the safety and effectiveness of cancer drugs for approval across jurisdictions. Future drug development may benefit by establishing a greater uniformity of new global standards of treatment, leading to the optimal design of these important trials. For further information visit: <https://www.fda.gov/about-fda/oncology-center-excellence/project-orbis>

II. Registration timeline

The following table captures the key steps and dates for this application and which are detailed and discussed in this AusPAR.

Table 2: Timeline for Submission PM-2020-02181-1-4

Description	Date
Designation; Orphan; ³⁰	17 February 2020
Determination; Provisional; ³¹	29 April 2020
Submission dossier accepted and first round evaluation commenced	28 May 2020
First round evaluation completed	2 November 2020
Sponsor provides responses on questions raised in first round evaluation	21 December 2020
Second round evaluation completed	12 February 2021
Delegate's Overall benefit-risk assessment	8 September 2021
Sponsor's pre-Advisory Committee response	Not applicable
Advisory Committee meeting	Not applicable
Registration decision (Outcome)	10 September 2021
Completion of administrative activities and registration on the ARTG	13 September 2021
Number of working days from submission dossier acceptance to registration decision*	153

*Statutory timeframe for standard applications is 255 working days

³⁰ 'Orphan drugs' are often developed to treat small and very specific patient populations who suffer from rare diseases and conditions. In order to facilitate orphan drug access to the Australian marketplace and help offset orphan drug development costs the TGA waives application and evaluation fees for prescription medicine registration applications if a related **orphan designation** is in force. A medicine may be eligible for orphan drug designation if all orphan criteria set by the TGA are met. The orphan designation application precedes the registration application and the designation is specific to the sponsor, orphan indication for which designation was granted and dosage form of the medicine.

³¹ As part of the **provisional approval pathway**, the provisional registration process will allow certain medicines to be provisionally registered in the Australian Register of Therapeutic Goods (ARTG) for a limited duration. These medicines are registered on the basis of preliminary clinical data, where there is the potential for a substantial benefit to Australian patients. The TGA will re-assess risks related to the absence of evidence through data provided at a later stage, as part of the confirmatory data. Confirmatory data should confirm the relationship between outcomes predicted by the surrogate endpoint, or other preliminary data, and the clinical benefit as demonstrated by direct clinical outcomes.

The sponsor may apply to transition to full registration at any time up until the provisional registration lapse date, once they have completed the obligations outlined for the provisional registration period and complete confirmatory data on safety and efficacy are available.

III. Submission overview and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations.

This section is a TGA summary of wording used in TGA's evaluation report, which discussed numerous aspects of overseas evaluation reports and included some information that was commercial-in-confidence.

Quality

The quality evaluator concluded that the proposed trade name is acceptable. The proposed drug substance specification imposed by the drug product manufacturer is acceptable. The drug product specifications are acceptable.

A shelf life of 5 years, when stored at 2 to 8°C with the conditions 'Refrigerate. Do not freeze.' has been assigned. The products are packed in cartons containing one vial. The container closure system is West Pharma Daikyo Fluorotec closure (V10-F597W RSV) 20 mm lyo stopper D777-1 RB2 coating.

The proposed PI is acceptable.

Final mockup labels have been provided. The labels are acceptable.

Reviews of microbiological/sterility aspects and of bacterial endotoxin testing found these aspects to be acceptable, including that sterility testing is adequate, and product information (PI) text is acceptable, having been amended to reflect microbiological safety with regard to immediacy of usage and storage limitations after preparation. Bacterial endotoxin testing is adequate, with an endotoxin specification of not more than 10 Endotoxin unit/mg.

Acceptable manufacturing and quality control have been demonstrated for lurbinectedin, and there are no outstanding issues with the chemistry and quality aspects of Zepzelca.

Nonclinical

The nonclinical evaluator noted that lurbinectedin is small molecule alkylating drug that binds covalently to guanine-cytosine (GC)-rich DNA sequences, resulting in adduct formation, DNA binding, eventually double strand breaks, and ultimately cell death. Lurbinectedin inhibits transcription through binding to GC-rich sequences of DNA located around promoter regions, the eviction of transcription factors from their binding sites, and stalling the elongating RNA polymerase II on promoters. Consistent with its mechanism of action, lurbinectedin had antiproliferative and cytotoxic activity in multiple tumour cell lines. Consistent with its mechanism of action, lurbinectedin is genotoxic.

Administration of lurbinectedin to athymic mice implanted with various human tumour cell lines (including SCLC) inhibited tumour growth. Enhanced anti-tumour activity was seen with doxorubicin in combination with lurbinectedin compared to either drug alone, which led to the design of the Phase III ATLANTIS trial.

Toxicological findings included:

- Injection site findings (including haemorrhage, oedema, inflammation, thrombosis, and necrosis)
- Bone marrow effects leading to transient leukopenia and mild anaemia with decreased bone marrow cellularity
- Gastrointestinal toxicity

- Male reproductive toxicity (testicular atrophy and hypospermia)
- Hepatic toxicity

Based on the half life of 51 hours, the nonclinical evaluator recommended six and four months of effective contraception for females and males, respectively, and not to breastfeed during treatment with lurbinectedin and for two weeks after the final dose.

In vivo exposure levels in monkeys appeared to be lower for both major human metabolites and, as animals tolerated lower lurbinectedin doses than the 3.2 mg/m² human dose. There is not full toxicological coverage of these metabolites. However, given that each of these main metabolites represent less than 15% of the parent compound and toxicity profiles in humans are similar to those in animals, the disparity in metabolite exposure does not represent a significant safety concern for the intended patient population.

The nonclinical evaluator concluded the pharmacology studies support the proposed indication. The safety pharmacology studies raise no obvious concerns notwithstanding the subclinical exposure. Toxicity findings in repeat dose studies are typical of cytotoxic drugs. Effects on the gastrointestinal tract, bone marrow, liver bile duct, kidneys, male reproductive organs, injection site were observed in animal species at subclinical exposures.

Lurbinectedin is expected to be genotoxic.

Given the nature of lurbinectedin (cytotoxic and mutagenic), it is expected to be teratogenic and should not be used during pregnancy. It caused 100% embryo lethality in rats. Pregnancy category D;³² is considered appropriate; this is consistent with the category for other cytotoxic antineoplastic agents.

Lurbinectedin is highly toxic in all animal species tested in the nonclinical program. Exposures (plasma maximum concentration and area under the curve achieved in animal safety pharmacology and toxicity studies were significantly below the clinical exposure.

Since the product is for the treatment of advanced cancer, the proposed clinical use may be approved only if adverse effects in patients are manageable and the benefit outweighs the risk based on clinical data.

Clinical

The clinical dossier consisted of the following studies:

- nine Phase I clinical trials
- seven Phase II clinical trials
- three Phase III clinical trials

Pharmacology

The pharmacology characteristics of lurbinectedin were studied in a first in human study (Study A-001), mass balance study (Study A-005), safety and efficacy study supporting the proposed indication (Study B-005), and supportive study in patients with ovarian cancer (Study C-004). A population pharmacokinetics (PK) analysis was conducted to identify the effect of intrinsic factors (age, body weight, sex, renal function, and hepatic function) and extrinsic factors (concomitant medications) on the PK of lurbinectedin. Exposure response

³² Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

analyses for safety and efficacy to support the proposed dosage regimen as well as the potential for lurbinededin to prolong the corrected QT interval (QTc);³³ were also included in the submission.

Lurbinededin is metabolised by cytochrome P450;³⁴ 3A4 (CYP3A4). No dedicated clinical drug interaction studies with modulators of CYP3A4 were conducted. The co-administration of drugs that are known to be strong or moderate CYP3A4 inhibitors and strong or moderate CYP3A4 inducers with lurbinededin should be avoided. If the co-administration of moderate CYP3A4 inhibitors cannot be avoided, dose reductions should be implemented based on adverse events (AE) (neutropenia, thrombocytopenia, and hepatotoxicity) as clinically indicated. This recommendation is supported by the safety analysis of 39 patients who received concomitant medications that are known to be moderate CYP3A4 inhibitors which suggested similar frequency and severity of AEs in comparison to the overall patient population.

In vitro, lurbinededin is an inhibitor of P-glycoprotein (P-gp) (alf-maximal inhibitory concentration (IC₅₀);³⁵ = 3.85 µM and inhibitory concentration total/IC₅₀ = 0.04 and inhibitory concentration free/IC₅₀ = 0.0004), organic anion transport protein 1B1, organic anion transport protein 1B3, and organic cation transporter 1. A value for the IC₅₀ could not be calculated in the case of the latter three transporters with maximum inhibition reaching 37%, 26%, and 20%, respectively. Collectively, the potential for clinical drug interaction is low.

The clinical evaluator noted that there are post marketing requirements and post-marketing commitments relevant to CYP3A4 in the FDA evaluation of lurbinededin:³⁶

- lurbinededin requires a clinical study to characterise the effect of itraconazole (a strong CYP3A4 inhibitor, and an inhibitor of P-gp) on lurbinededin PK.
- lurbinededin requires a physiologically based PK modelling study to characterise the expected effect of co-administration of a moderate CYP3A4 inhibitor on lurbinededin exposure.
- notes commitment to a clinical study to evaluate the effect of repeat doses of a moderate CYP3A inducer on the single dose PK of lurbinededin.

A study with a strong inducer of CYP3A4 was not recommended given the likelihood of a substantial reduction in lurbinededin exposure, and attendant risk of compromised efficacy, whilst dose increase recommendations may not be possible given the narrow safety margin of lurbinededin.

The mass balance study with radioactive lurbinededin demonstrated that lurbinededin is primarily eliminated in the faeces (89% of radioactivity), mainly as metabolites. Population PK analysis did not identify a clinically meaningful change in lurbinededin

³³ Corrects the QT interval for heart rate extremes using Bazett, Fridericia, Framingham, or Hodges formulas.

³⁴ Cytochrome P450 (CYP) enzymes: CYPs are the major enzymes involved in drug metabolism, accounting for large part of the total metabolism. Most drugs undergo deactivation by CYPs, either directly or by facilitated excretion from the body. Also, many substances are bioactivated by CYPs to form their active compounds. Many drugs may increase or decrease the activity of various CYP isozymes either by inducing the biosynthesis of an isozyme (enzyme induction) or by directly inhibiting the activity of the CYP (enzyme inhibition). This is a major source of adverse drug interactions, since changes in CYP enzyme activity may affect the metabolism and clearance of various drugs. Such drug interactions are especially important to take into account when using drugs of vital importance to the patient, drugs with important side-effects and drugs with small therapeutic windows, but any drug may be subject to an altered plasma concentration due to altered drug metabolism.

³⁵ Half-maximal inhibitory concentration (IC₅₀) is a measure of the effectiveness of a compound in inhibiting biological/biochemical function.

³⁶ FDA, Center for Drug Evaluation and Research, Approval package for Zepzelca, lurbinededin, 15 June 2020. Available from the FDA website.

exposure in patients with mild hepatic impairment (total bilirubin > 1 x upper limit of normal (ULN) to 1.5 x ULN) compared to patients with normal liver function, and no dose adjustment is necessary for this population. The effects of moderate or severe hepatic impairment on lurbinectedin exposure have not been studied and no dosing recommendation can be made. FDA approval of lurbinectedin requires a clinical study to characterise the PK of lurbinectedin in patients with varying degrees of hepatic impairment.³⁶

Renal excretion represents 6% of lurbinectedin elimination (1% as unchanged lurbinectedin). Population PK analysis did not identify a clinically meaningful difference in lurbinectedin exposure in patients with mild or moderate renal impairment compared to patients with normal renal function. The effects of severe renal impairment on lurbinectedin exposure have not been studied. No dose adjustment based on renal function is recommended, based on the minimal renal excretion.

Exposure response analyses identified a positive relationship for efficacy with higher probability of objective response rate (ORR) at higher lurbinectedin exposure. Similarly, the higher exposure correlated with higher probability of AEs (Grade 4 neutropenia and Grade 3/4 thrombocytopenia). Clinical utility index, which compared the probability of achieving response relative to the probability of AEs, indicated that the proposed dosing regimen of 3.2 mg/m² every three weeks achieves an acceptable balance of safety and efficacy.

Efficacy

Study B-005 design

Study B-005, was an open label, non-randomised, multicentre, exploratory Phase II study of lurbinectedin (also known as Study PM01183) in selected advanced solid tumours.

Patients were enrolled between October 2015 and October 2018, and the submitted clinical study report data with a data cut off date of 15 January 2019.

Patients were enrolled in nine single arm cohorts based on tumour type: pre-treated advanced SCLC, head and neck carcinoma, neuroendocrine tumours, biliary tract carcinoma, endometrial carcinoma, breast cancer gene 1/2-associated metastatic breast cancer, carcinoma of unknown primary site, germ cell tumours, and Ewing's family of tumours.

To be eligible for inclusion in the SCLC cohort, patients had pathologically confirmed SCLC, measurable disease per RECIST v1.1,³⁷ Eastern Cooperative Oncology Group (ECOG) performance status (PS);³⁸ 0 or 1 and had received only one prior chemotherapy-

³⁷ The Response Evaluation Criteria In Solid Tumours (RECIST) is a voluntary international standard with unified and easily applicable criteria to define when a patient's tumour has improved ('respond'), stayed the same ('stabilise'), or worsened ('progress') during treatment. The criteria were published in February 2000 by an international collaboration including the European Organisation for Research and Treatment of Cancer (EORTC), National Cancer Institute (NCI) of the United States, and the National Cancer Institute of Canada Clinical Trials Group. Today, the majority of clinical trials evaluating cancer treatments for objective response in solid tumours use RECIST. These criteria were developed and published in February 2000, and subsequently updated in 2009.

³⁸ ECOG Performance Status: The Eastern Cooperative Oncology Group (ECOG) has developed criteria used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis. The following are used:

0 - Fully active, able to carry on all pre-disease performance without restriction
1 - Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work
2 - Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours

containing line of therapy (not counting other therapies such as immunotherapy). Patients with central nervous system involvement were excluded.

Patients in the SCLC cohort received lurbinectedin monotherapy at a dose of 3.2 mg/m² (capped at 6.4 mg) as a 60 minute intravenous infusion every three weeks (on Day 1 of each 21 day treatment cycle), until disease progression or unacceptable toxicity.

Dose reduction was permitted for any Grade 3 or higher non-haematological toxicity, Grade 3 or 4 thrombocytopenia with Grade 3 or higher bleeding, Grade 4 neutropenia, any grade febrile neutropenia, or neutropenia associated with infection/sepsis, or frequent or prolonged (> 1 week) dose delays due to treatment related adverse events.

Up to two dose reductions (first reduction: 2.6 mg/m², second reduction: 2 mg/m²) were allowed per patient, and re-escalation of dose was not permitted.

Patients who experienced Grade 3 to 4 hypersensitivity reactions were discontinued from study treatment.

The primary endpoint was confirmed ORR per RECIST v1.1,³⁷ by investigator assessment in the all treated patients population set. The ORR was estimated using an exact binomial distribution and its 95% -two sided exact confidence interval using the Clopper-Pearson method.³⁹ The sponsor proposed a hypothesis test of excluding an ORR of 15% based on historical data for topotecan and cyclophosphamide, doxorubicin, and vincristine (CAV) regimen (Table 5).

Secondary endpoints included:

- Objective response rate (ORR) by an independent review committee (IRC) per RECIST v1.1;³⁷
- Duration of response (DOR) by investigator assessment and IRC.

Time to event endpoints were also reported but cannot be reliably interpreted in the absence of an internal comparator (that is in the single arm setting).⁴⁰

Protocol changes

The size of the intended SCLC cohort was increased twice: first to 50 patients, based on emerging data from a different trial of lurbinectedin in combination with doxorubicin (response rate: 50%; 95% CI: 34 to 66%), then to 100 patients, based on the preliminary evidence of monotherapy activity that had been seen in Study B-005 at that time.

The statistical analysis plan (SAP) was amended (to version 2.0) accordingly 'to update the sequential test methodology and to provide further details on the control of type I and II error probability (alpha and beta), taking into account the two planned interim analysis performed at 15 and 25 patients.'

Blinded independent central radiology (BICR) review of imaging and CTFI-based subgroup analyses were also added after protocol amendment 5. Sensitive disease was defined as a CTFI of ≥ 90 days, and resistant disease as CTFI < 90 days.

Enrolled population (SCLC cohort)

The all treated patients population consisted of 105 patients who received therapy (out of 110 enrolled). Selected population demographics and baseline disease characteristics are summarised in Table 3 with a median CTFI of 106 days (range: 0 to 491) in the population

3 - Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours

4 - Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair

5 - Dead

³⁹ A method for obtaining a confidence interval for an unknown binomial probability, p.

⁴⁰ FDA. Clinical trial endpoints for the approval of cancer drugs and biologics: guidance for industry, December 2018. Available from the FDA website.

overall, 43% of patients had resistant disease (this included 21 patients with a CTFI less than 30 days) and 57% had sensitive disease at Baseline (this included 20 patients who had a CTFI of longer than 180 days).

Table 3: Study B-005 Population characteristics in all treated small cell lung cancer patients, and in subgroups based on chemotherapy-free interval (data cut off 15 January 2019)

Characteristic		All treated SCLC n = 105	Sensitive (CTFI ≥ 90 days) n = 60	Resistant (CTFI < 90 days) n = 45
Male, n (%)		63 (60%)	35 (58%)	28 (62%)
Median age, years (min, max)		60 (40, 83)	59 (44, 79)	66 (40, 83)
Age < 65 years, n (%)		68 (65%)	46 (77%)	22 (49%)
Region: Europe		94 (90%)	56 (93%)	38 (84%)
ECOG performance status, n (%)	0	38 (36%)	27 (45%)	11 (24%)
	1	59 (56%)	30 (50%)	29 (64%)
	2	8 (8%)	3 (5%)	5 (11%)
Current/former smoker, n (%)		97 (92%)	54 (90%)	43 (96%)
Extensive stage SCLC at diagnosis, n (%)		73 (70%)	35 (58%)	38 (84%)
2 prior lines of therapy, n (%)		7 (7%)	3 (5%)	4 (9%)
Prior radiotherapy, n (%)		76 (72%)	57 (95%)	19 (42%)
Prophylactic cranial irradiation, n (%)		61 (58%)	47 (78%)	14 (31%)
Prior immunotherapy, n (%)		8 (8%)	3 (5%)	5 (11%)

Disposition

Patient disposition for Study B-005 is given in Table 4, below.

Table 4: Study B-005 Patient disposition (data cut-off 15 January 2019)

Patient disposition, n (%)	All treated SCLC (n = 105)
Discontinued treatment	94 (90%)
Progressive Disease	84 (80%)
Treatment Related Adverse Event	2 (2%)
Death	2 (2%)
Investigator's Decision	4 (4%)

Patient disposition, n (%)	All treated SCLC (n = 105)
Patient Refusal	2 (2%)
Ongoing at cut-off	11 (10%)

Efficacy results

Results for ORR and DOR according to both investigator and BICR assessment are summarised in Table 5.

Table 5: Study B-005 Results in the all treated patients set, and in subgroups based on chemotherapy-free interval (data cut off 15 January 2019)

		All Treated SCLC n = 105	Sensitive (CTFI ≥ 90 days) n = 60	Resistant (CTFI < 90 days) n = 45
Investigator assessment				
ORR	ORR, % (95% CI)	35% (26, 45)	45% (32, 58)	22% (11, 37)
	CR, n	0	0	0
	PR, n	37	27	10
DOR	Median, months (95% CI)	5.3 (4.1, 6.4)	6.2 (3.5, 7.3)	4.7 (2.6, 5.6)
	% lasting ≥ 6 months	35%	44%	10%
BICR assessment				
ORR	ORR, % (95% CI)	30% (22, 40)	43% (31, 57)	13% (5, 27)
	CR, n	0	0	0
	PR, n	32	26	6
DOR	Median, months (95% CI)	5.1 (4.9, 6.4)	5.3 (4.9, 7.0)	4.8 (2.4, 5.3)
	% lasting ≥6 months	25%	31%	0

Abbreviation: BICR = blinded independent central review; chemotherapy-free treatment interval (CTFI); CI = confidence interval; CR = complete response; DOR = duration of response; ORR = objective response rate per RECIST (Response Evaluation Criteria in Solid Tumours) v1.1; PR = partial response.

*Exploratory subgroup analyses***Table 6: Study B-005 Objective response rates in subgroups of the all treated patients.**

		<i>BICR-assessed ORR</i>				<i>Investigator-assessed ORR</i>			
Category	Subgroup	N	n	ORR	95% CI	N	n	ORR	95% CI
Sex	Female	42	10	24%	(12, 39)	42	13	31%	(18, 47)
	Male	63	22	35%	(23, 48)	63	24	38%	(26, 51)
Age group	<65	68	22	32%	(22, 45)	68	22	32%	(22, 45)
	≥65	37	10	27%	(14, 44)	37	10	27%	(14, 44)
CTFI category	Resistant	45	6	13%	(5, 27)	45	10	22%	(11, 37)
	Sensitive	60	26	42%	(29, 55)	60	27	47%	(34, 60)
Stage at diagnosis	ES-SCLC	73	15	21%	(12, 32)	73	19	26%	(16, 38)
	LS-SCLC	32	17	53%	(35, 71)	32	18	56%	(38, 74)
Prior immunotherapy		8	5	63%	(24, 91)	8	5	63%	(24, 91)

Abbreviation: BICR = blinded independent central review; chemotherapy-free treatment interval (CTFI); CI = confidence interval; ES-SCLC = extended-stage small cell lung cancer; LS-SCLC = limited-stage small cell lung cancer; N = total patients in subgroup; n = number of responders in subgroup; ORR = objective response rate per RECIST (Response Evaluation Criteria in Solid Tumours) v1.1.

Interpretation of these subgroup analyses is limited by their exploratory nature and small group sizes. In particular, although partial responses were seen in 5 of out 8 patients who had received add on immunotherapy with prior platinum regimens, the very small subgroup size renders the efficacy of lurbinectedin in this setting unclear. This is one of the key uncertainties expected to be addressed by confirmatory data.

Safety**Study B-005**

Amongst the 105 SCLC patients, dose interruptions, reductions and discontinuations occurred in 30%, 25% and 2% of patients respectively. Neutropenia (17%) was the most common event resulting in dose reduction, myelosuppression (18%) was the most common event resulting in dose delay. The AEs leading to discontinuation were worsened peripheral neuropathy (in a patient who had peripheral neuropathy at Baseline), and myelosuppression in a different patient.

The clinical evaluator agreed with the following safety assessment:

‘The safety profile of lurbinectedin is most notable for myelosuppression, fatigue, musculoskeletal pain, gastrointestinal AEs (nausea, vomiting, diarrhea) and respiratory AEs (dyspnea, cough). Significant and serious adverse reactions such as myelosuppression and aminotransferase laboratory elevation are addressed in the Warnings and Precautions section of the label with recommendations to withhold, dose reduce or permanently discontinue as necessary depending on the severity of toxicity. Additionally, G-CSF prophylaxis is recommended for severe neutropenia.

In Study B-005, the following findings were specific to the SCLC cohort:

- *There were no deaths on or within 30 days of study drug discontinuation that were attributable to lurbinectedin.*
- *Treatment-emergent SAEs were reported in 34% of patient. Pneumonia, dyspnea, upper respiratory tract infections, febrile neutropenia and myelosuppression were identified as the most commonly observed serious adverse events (SAEs).*
- *Dose reductions occurred in 25% of patients with neutropenia (17%) representing the most common AE resulting dose reduction.*
- *Dose delays occurred in 31% of patients, most frequently due to myelosuppression.*
- *Drug discontinuation was infrequent (n=2).*

The overall the safety profile of lurbinectedin is acceptable when assessed in the context of the treatment of a life-threatening disease, and in the context of current available therapies.'

Small cell lung cancer cohort

The Delegate agreed with the FDA label containing the following additional detail on safety information from the SCLC cohort of Study B-005:⁴¹

'The safety of Zepzelca was evaluated in a cohort of 105 patients with previously treated SCLC in Study B-005. Patients received Zepzelca 3.2 mg/m² intravenously every 21 days. All patients in this study received a pre-specified anti-emetic regimen consisting of a corticosteroid and serotonin antagonist. Patients could receive Granulocyte colony-stimulating factor (G-CSF) for secondary prophylaxis (i.e., after patients had an initial decrease in white blood cells (WBC)), but not primary prophylaxis. Among patients who received Zepzelca, 29% were exposed for 6 months or longer and 6% were exposed for greater than one year.

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

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

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

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

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

⁴¹ Approved FDA label for lurbinectedin. Accessed 16 July 2021.

Table 7: Study B-005 Adverse reactions (greater than or equal to ten percent) in patients with small cell lung cancer who received Zepzelca

Adverse Reaction	Zepzelca ^a (n = 105)	
	All Grades ^{a,b} (%)	Grades 3 to4 (%)
General disorders		
Fatigue	77	12
Pyrexia	13	0
Chest pain	10	0
Gastrointestinal disorders		
Nausea	37	0
Constipation	31	0
Vomiting	22	0
Diarrhea	20	4
Abdominal pain ^c	11	1
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain ^d	33	4
Metabolism and nutrition disorders		
Decreased appetite	33	1
Respiratory, thoracic and mediastinal disorders		
Dyspnea	31	6
Cough ^e	20	0
Infections and infestations		
Respiratory tract infection ^f	18	5
Pneumonia ^g	10	7
Nervous system disorders		
Peripheral neuropathy ^h	11	1
Headache	10	1

^a Graded per NCI CTCAE 4.0. ^b No grade 5 adverse reactions were reported. ^c Includes abdominal pain, abdominal pain upper and abdominal discomfort. ^d Includes musculoskeletal pain, back pain, arthralgia, pain in extremity, musculoskeletal chest pain, neck pain, bonepain and myalgia. ^e Includes cough and productive cough. ^f Includes upper respiratory tract infection, viral upper respiratory tract infection,

respiratory tract infection and bronchitis. ^gIncludes pneumonia and lung infection. ^hIncludes neuropathy peripheral, neuralgia, paresthesia, peripheral sensory neuropathy, hypoesthesia, and hyperesthesia.

Clinically relevant adverse reactions in less than 10% of patients who received Zepzelca included dysgeusia, febrile neutropenia and pneumonitis (see Table 7).

Table 8: Study B-005 Select laboratory abnormalities (greater than or equal to twenty percent) worsening from Baseline in patients with small cell lung cancer who received Zepzelca

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

^aThe denominator used to calculate the rate varied from 95 to 105 based on the number of patients with a baseline value and at least one post-treatment value. ^bGraded per NCI CTCAE 4.0.

Corrected QT interval substudy

The clinical dossier included a report from a sub-study of 39 patients with advanced solid tumours was conducted within Study B-005 to assess the potential for QTc prolongation with lurbinectedin treatment. The Delegate noted that there was no large mean effect on the QTc was detected and a maximum increase in heart rate of 18.3 beats per minute was observed at three hour post end of infusion.

Supporting safety data

The primary safety data from the SCLC cohort of Study B-005 (n = 105) was supported by safety data from a further 449 patients with advanced solid tumours other than SCLC who received lurbinectedin at the proposed dose (3.2 mg/m² intravenously (IV) every 21 days): either in Study B-005, or in Study C-004 (CORAIL trial). The CORAIL trial was an

open label randomised control trial (RCT) of lurbinectedin versus pegylated liposomal doxorubicin or topotecan in patients with platinum resistant ovarian cancer.

Serious Adverse Event (SAEs) and adverse events of special interest (AESI) from across the clinical development program (19 clinical trials) were also submitted. The median duration of exposure was 3.1 months for the overall safety population (n = 554) and 3.3 months in the SCLC cohort of Study B-005.

Toxicity in the larger safety population was broadly similar to that seen in the SCLC cohort. Respiratory signs and symptoms were reported more commonly in SCLC patients, and the large safety cohort reported higher rates of abdominal pain and intestinal obstruction, in keeping with the large cohort of included patients with ovarian cancer.

Seven deaths occurred in the overall safety population due to infection in the context of myelosuppression (five within 30 days of treatment discontinuation) that were attributed by the reviewer to lurbinectedin.

Myelosuppression and hepatotoxicity were the most significant adverse events and have been included as warnings/precautions in the approved FDA label. **Error! Bookmark not defined.**

Confirmatory data plan

It was initially intended that the ATLANTIS trial would provide data to confirm the clinical benefit of the proposed provisional indication. The ATLANTIS trial (n = 613) was a randomised, multicentre, international study comparing lurbinectedin (at a lower dose than in Study B-005: 2 mg/m²) in combination with doxorubicin against physician's choice of control (topotecan, or CAV) for the second line treatment of advanced SCLC after failure of one prior platinum based therapy.⁴² Patients with a CTFI of less than 30 days were excluded.

The ATLANTIS trial failed to demonstrate superiority of overall survival with doxorubicin plus lurbinectedin compared to the control arm in the intent to treat population (the primary endpoint), and based on the study design, no additional hypotheses were formally tested.⁴³ The study is therefore unable to provide statistically robust data to confirm clinical benefit of the proposed provisional monotherapy indication. Despite the failure of the primary endpoint, the point estimate for the primary endpoint did not raise concerns that survival was poorer with the lurbinectedin /doxorubicin combination.

Interpretation of the ATLANTIS trial's relevance to the proposed provisional indication would have been complex even if it had demonstrated a positive primary endpoint, as it did not directly study lurbinectedin as monotherapy nor at the same dosage studied in Study B-005.

In replacement of the Atlantis trial as a confirmatory study, the sponsor proposes a new, three arm, randomised, controlled trial, with a protocol numbered PM1183-C-008-21. This study is referred to below as Study C-008 for brevity. The proposed study design is summarised in Table 9.

⁴² Farago AF et al. ATLANTIS: a Phase III study of lurbinectedin/doxorubicin versus topotecan or cyclophosphamide/doxorubicin/vincristine in patients with small-cell lung cancer who have failed one prior platinum-containing line. *Future Oncol*; 2019; 15(3):231-239.

⁴³ PharmaMar and Jazz Pharmaceuticals announcement of results of the ATLANTIS phase III study with lurbinectedin, 2020. Available from pharmamar.com.

Table 9: Study C-008 Study design of the study

Study design component	Details
Administrative	<p>Title: A Randomized, Multicenter, Open-label, Phase III Study of Lurbinectedin Single-Agent or Lurbinectedin in Combination with Irinotecan versus Investigator's Choice (Topotecan or Irinotecan) in Relapsed Small Cell Lung Cancer (SCLC) Patients.</p> <p>Locations: greater than 100 sites planned worldwide</p> <p>Timing: enrolment to commence quarter four of 2021; enrolment period expected to last about 29 months; end of study clinical cut-off planned for approximately 10 months after last patient randomised. Total duration of study estimated to be 39 months.</p>
Design	<p>Open label, three arm (each of about 705 patients), randomised (1:1:1), active controlled trial.</p> <p>Randomisation to be stratified by:</p> <p>Chemotherapy-free interval after first line (greater than or equal to 90 days (sensitive) versus less than 90 days (resistant))</p> <p>Prior anti-PD-(L)1 therapy (Yes versus No)</p> <p>Enrolment of patients who have not received previous anti-PD-(L)1 therapy will be limited to 30%</p> <p>Baseline central nervous system involvement (Yes versus. No)</p> <p>Lactate dehydrogenase value (greater than upper limit of normal versus. less than or equal to upper limit of normal)</p> <p>Investigator's choice of comparator (topotecan versus. irinotecan)</p>
Population	<p>Adult patients with ECOG PS;³⁸ less than or equal to 2 who have advanced small cell lung cancer that has progressed after one prior line of platinum-containing therapy with a chemotherapy-free interval of at least 30 days and controlled, asymptomatic central nervous system disease, if present.</p>
Interventions	<p>Arm A (lurbinectedin monotherapy):</p> <p>Lurbinectedin 3.2 mg/m² IV as a 60 minute infusion on Day 1 of each 21 day cycle</p> <p>Arm B (lurbinectedin plus irinotecan):</p> <p>Irinotecan 75 mg/m² IV as a 90 minute infusion on Day 1 and Day 8 of each 21 day cycle, plus</p> <p>Lurbinectedin 2.0 mg/m² IV as a 60-min infusion on Day 1 of each 21 day cycle</p> <p>Granulocyte colony-stimulating factor on Day 1 of each 21 day cycle</p>
Comparator	<p>Arm C (single agent chemotherapy):</p> <p>Investigator's choice of topotecan or irinotecan, both at standard doses.</p>

Study design component	Details
Outcomes	<p>Primary: overall survival (A versus C) and (B versus C)</p> <p>Secondary: progression-free survival, objective response rate, duration of response comparison of chemotherapy-free interval based subgroups, safety, patient-reported outcomes.</p> <p>Exploratory: compare Arm A and Arm B to subgroups of Arm C based on choice of control therapy (topotecan or irinotecan), compare Arm A and Arm B to each other, pharmacokinetics and pharmacogenomics.</p> <p>The study plans to produce anonymised copies of tumour response assessment imaging for potential blinded independent radiological review.</p>
Statistical plan	<p>Comparison of overall survival (primary endpoint) will be done by log rank test, using a fallback testing procedure with loop back alpha passing, and an uneven split of alpha:</p> <p>Alpha = 0.04 for the first comparison of A versus C.</p> <p>Alpha = 0.01 for the second comparison of B versus C.</p> <p>An independent data monitoring committee will have oversight of the study.</p> <p>An interim analysis is planned at 70% of the anticipated 555 death events. Lan DeMets implementation of the O'Brien-Fleming alpha spending function will be used to calculate the significance levels and boundaries at the interim and final overall survival analyses and preserve the type-1 error level control.</p> <p>If both primary endpoints are positive, secondary endpoints will be tested using a gatekeeping strategy: first progression free survival then objective response rate.</p> <p>Stratification factor(s) will be removed from the stratified log-rank test if there is risk of over-stratification.</p>

In addition to the randomised trial, Study C-008, the Delegate notes an investigator-sponsored study (ISS) has been underway in Australia since April 2020. Participants are patients who have enrolled in the sponsor's 'co-pay' access scheme, and who had chemo-immunotherapy as their first line of therapy in the ES-SCLC setting. The ISS is described by the sponsor as 'a retrospective multicentre study to evaluate the efficacy and safety of lurbinectedin as second line treatment for patients with SCLC in a real-world setting'. The primary endpoint is ORR, and key secondary endpoints include overall survival and safety. Results from the ISS are not yet available, but as Study B-005 contained a limited number of patients treated post immuno-chemotherapy, the data from the ISS may provide some further single arm support for the proposed provisional indication, when results become available. Topline results of the ISS should be made a condition of registration if provisional approval is granted.

Risk management plan

Specialised Therapeutics Pharma Pty Ltd has submitted Core-risk management plan (RMP) version 0.2 (15 January 2020; data lock point (DLP) 17 April 2020) and Australia specific annex (ASA) version 0.1 (April 2020) in support of this application. In response to TGA's questions, the sponsor has provided ASA version 0.2 (dated Dec 2020) in

association with Core-RMP version 0.2 (15 January 2020; DLP 17 April 2020). At the request of the TGA, the sponsor has provided updated version 0.3 (Sept 2021) in association with Core-RMP version 0.2 to support the decision on provisional registration.

The summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised in Table 10.⁴⁴

Table 10: Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Myelosuppression	Ü	-	Ü	-
	Liver enzyme increase	Ü	-	Ü	-
Important potential risks	None	-	-	-	-
Missing information	Use during pregnancy, including reproductive and development toxicity	Ü ¹	-	Ü	-
	Use in patients with hepatic impairment	Ü	Ü ²	Ü	-
	Drug interaction with potent CYP3A4 inhibitors or inducers	Ü	Ü ³	Ü	-

¹Pregnancy Follow-Up form, ²Clinical trial – PM1183-A-017-20, ³Clinical trial – PM1183-A-018-20 and PM1183-A-019-20

In the Australian context, management of SCLC is through tertiary treatment centres by medical oncologists with expertise in the treatment of lung cancers. Lurbinectedin is a one hour IV infusion which may be administered in the day unit of a cancer treatment centre.

⁴⁴ Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.

Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labelling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

The summary of safety concerns is considered acceptable from an RMP perspective. Should the Delegate raise any issues that impact on the safety specification, the sponsor may be required to address these issues in a revised RMP.

Routine pharmacovigilance activities have been proposed for all safety concerns and sponsor commits to implementation of a 'Pregnancy follow up form' for use in Australia, as stated in the ASA. Three additional planned pharmacovigilance activities have been proposed to further characterise the missing information: 'Use in patients with hepatic impairment' and 'Drug interaction with potent CYP3A4 inhibitors and inducers'. There is a single Phase III confirmatory study (PM1183-C-008-21) proposed in the ASA version 0.3 clinical study plan to support provisional registration. Subject to Delegate's decision on final acceptability of the clinical study plan, the pharmacovigilance plan is considered acceptable.

Only routine risk minimisation activities are proposed for all safety concerns. This is considered acceptable given the context of use by oncology specialists who are familiar with and experienced in the management of such concerns. The proposed Consumer Medicine Information (CMI) and PI are updated to inform of Zepzelca's inclusion in the Black Triangle Scheme for additional monitoring when medicine is in usage. Pending Delegate's decision on acceptability of sponsor's proposed PI statement explaining the medicine is provisional, the risk minimisation plan is considered acceptable.

Risk-benefit analysis

Delegate's considerations

For patients with SCLC, second line treatment options are very limited. Topotecan is the most commonly used agent and the only one specifically registered for second line treatment of SCLC in Australia, and its use is based on data which was gathered prior to a recent change in standard-of-care.

In Study B-005, lurbinectedin administered in the second line setting to patients with advanced SCLC demonstrated activity, including in patients with platinum resistant disease. It is unclear whether the responses in this single arm study will translate into a benefit in survival or progression free survival compared to topotecan. A cross trial comparison between the results per BICR in Study B-005 and historical controls treated with topotecan or a CAV (chemotherapy) regimen is presented in Table 10.

Table 11: Cross-trial comparison of efficacy by blinded independent review (objective response rate and duration of response)

	CAV* Von Pawel et al. 1999 Error! Bookmark not defined. (n=104)	Topotecan Von Pawel et al. 1999 Error! Bookmark not defined. (n=107)	Topotecan Von Pawel et al. 2014Error! Bookmark not defined. (n=213)	Lurbinectedin B-005-14 2020 (n=105)
ORR (95% CI)	18.3% (10.8-25.7)	24.3% (16.2-32.4)	16.9% (12.1-22.6)	30.5% (21.9-40.2)
DOR, months (95% CI)	3.5 (1.9-16.1)	3.3 (NR) range 2.2-11.5	4.2 (NR)	5.1 (4.9-6.4)
<i>ORR (95% CI) by CTFI subgroups:</i>				
CTFI <90 days (platinum resistant)	NR	NR	9.4% (3.0-15.0)	13.3% (5.1-26.8)
CTFI >90 days (platinum)	NR	NR	23.1% (15-31)	43.4% (30.6-56.8)

CAV* Von Pawel et al. 1999 Error! Bookmark not defined. (n=104)	Topotecan Von Pawel et al. 1999 Error! Bookmark not defined. (n=107)	Topotecan Von Pawel et al. 2014Error! Bookmark not defined. (n=213)	Lurbinectedin B-005-14 2020 (n=105)
sensitive)			

NR = not reported. * Cyclophosphamide, doxorubicin and vincristine

The response rate appears to be descriptively higher in Study B-005 than in the other trials: both in the entire patient group and in patients with platinum sensitive disease, although the lack of separation of confidence intervals is noted. The other trials are also notably older than Study B-005. However, the Study B-005 population included patients with a poorer prognosis and a lower likelihood of response than the other populations included in Table 3.

Although there are a number of existing second line treatment options for treatment of SCLC, they are very limited in terms of efficacy, but also in terms of quality and age of supporting data. Topotecan is the only treatment option for which there is Phase III supporting data that is not more than two decades old, in which it demonstrated benefit over CAV. Re-treatment with first line platinum has shown larger response rates, but in very old, single arm datasets. All existing options are associated with uncertain effectiveness in the post-immunotherapy setting that is posed by the recent approvals of add-on durvalumab and atezolizumab in the first line, as well as with inevitable relapse and significant toxicity.

Proposed action

Advanced SCLC is a life threatening disease with very limited existing therapeutic options.

Pivotal Study B-005 provides evidence of activity of lurbinectedin in the second line treatment of advanced SCLC, because in the absence of therapy, the natural history of the disease is that tumours grow or remain stable rather than shrink.

It is unclear whether the demonstrated responses in this single arm study will translate into improved time to event endpoints (such as PFS or OS) compared to the only existing registered therapy, topotecan. It is noted that amrubicin showed promising early data, including in platinum resistant and refractory patients, which did not translate into a survival benefit when compared to standard of care (topotecan or CAV) in a subsequent Phase III trial. **Error! Bookmark not defined.**

Whilst Study B-005 was conducted prior to the emergence of first line immunochemotherapy and contained very few patients who had received it, data from the available small cohort does not indicate an absence of responses, and comprehensive representation is expected amongst the confirmatory trial population. There is a similar lack of data to support the use of topotecan (or other chemotherapy) after first line immunochemotherapy.

The safety profile of lurbinectedin monotherapy in SCLC appears to be acceptable, given the life threatening nature of the disease.

The proposed confirmatory study is Study C-008, with overall survival as the primary endpoint. Study report availability is expected to be early 2026. This is expected to be available within the limitations of Australian provisional registration (maximum 6 years, including two x 2-year extensions).

The benefit-risk balance of provisional registration of lurbinectedin for the proposed usage is positive, and the remaining uncertainties are expected to be addressed by the pending confirmatory dataset.

Advisory Committee considerations

The Delegate did not refer this application to the Advisory Committee on Medicines (ACM) for advice.

Outcome

Based on a review of quality, safety and efficacy, the TGA approved the registration of Zepzelca (lurbinectedin) 4 mg, powder for injection, container.

Zepzelca is indicated for the treatment of patients with metastatic small cell lung cancer (SCLC) that has progressed on or after prior platinum-containing therapy. This indication was approved via the provisional approval pathway, based on objective response rate and duration of response in a single arm trial. Continued approval for this indication depends on verification and description of clinical benefit in a confirmatory trial.

Specific conditions of registration applying to these goods

- Zepzelca (lurbinectedin) is to be included in the Black Triangle Scheme. The Product Information (PI) and Consumer Medicines Information (CMI) for Zepzelca must include the black triangle symbol and mandatory accompanying text for the products entire period of provisional registration.
- The lurbinectedin core European Union (EU)-risk management plan (RMP) (version 0.2, dated 15 January 2020, data lock point 17 April 2020), with Australian specific annex (ASA) (version 0.3, dated September 2021), included with submission PM-2020-02181-1-4, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of the approval letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of the approval letter, or the entire period of provisional registration, whichever is longer.

The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on Good Pharmacovigilance Practices (GVP) Module VII-Periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.

- Confirmatory trial data (as identified in the sponsor's plan to submit comprehensive clinical data on the safety and efficacy of the medicine before the end of the 6 years that would start on the day that registration would commence) must be provided.

Specifically, the sponsor must conduct studies as described in the clinical study plan in version 0.3 (September 2021) of the ASA. The following study report(s) should be submitted to TGA:

- PM1183-C-008-21, by first quarter of 2026
- The sponsor should submit results for the primary endpoint from the Investigator-Sponsored Study led by authors at the Peter MacCallum Cancer Centre, titled 'Retrospective multicentre study of the efficacy and safety of lurbinectedin as second line treatment for patients with small cell lung cancer (SCLC),' when available.
- For all injectable products the PI must be included with the product as a package insert.

Attachment 1. Product Information

The PI for Zepzelca approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <<https://www.tga.gov.au/product-information-pi>>.

This medicinal product is subject to additional monitoring in Australia due to provisional approval. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION

ZEPZELCA (LURBINECTEDIN) POWDER FOR SOLUTION FOR INFUSION

NAME OF THE MEDICINE

ZEPZELCA 4 mg powder for solution for infusion.

QUALITATIVE AND QUANTITATIVE COMPOSITION

For the full list of excipients, see section 6.1 *List of excipients*.

PHARMACEUTICAL FORM

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

CLINICAL PARTICULARS

THERAPEUTIC INDICATIONS

ZEPZELCA is indicated for the treatment of patients with metastatic small cell lung cancer (SCLC) that has progressed on or after prior platinum-containing therapy. This indication was approved via the **provisional approval** pathway, based on objective response rate and duration of response in a single arm trial. Continued approval for this indication depends on verification and description of clinical benefit in a confirmatory trial.

DOSE AND METHOD OF ADMINISTRATION

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

Recommended dose and schedule

The recommended dose is 3.2 mg/m² by intravenous infusion over 60 minutes, repeated once every 21 days until disease progression or unacceptable toxicity.

Only administer ZEPZELCA to patients with an absolute neutrophil count above 1.5 x 10⁹/L, and a platelet count above 100 x 10⁹/L.

Dose modifications for adverse reactions

The recommended dose reduction levels for adverse reactions are listed in [Table 1](#). Dosage modifications for ZEPZELCA for adverse reactions are presented in [Table 2](#). Permanently discontinue ZEPZELCA in patients who are unable to tolerate 2.0 mg/m² or require a dose delay greater than two weeks.

Table 12: ZEPZELCA dose reduction schedule

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

Table 13: Dosage modifications for ZEPZELCA for adverse reactions

• Adverse reaction	• Severity*	• Dosage modification
• Neutropenia • [see 4.4 <i>Special warnings and precautions for use</i>]	• Grade 4** • or • Any grade febrile neutropenia	• Withhold ZEPZELCA until Grade ≤ 1 • Resume ZEPZELCA at a reduced dose
• Thrombocytopenia • [see 4.4 <i>Special warnings and precautions for use</i>]	• Grade 3 with bleeding • or • Grade 4	• Withhold ZEPZELCA until platelet ≥ 100 x 10 ⁹ /L • Resume ZEPZELCA at a reduced dose
• Hepatotoxicity • [see 4.4 <i>Special warnings and precautions for use</i>], or other adverse reactions	• Grade 2	• Withhold ZEPZELCA until Grade ≤ 1 • Resume ZEPZELCA at a reduced dose
	• Grade ≥ 3	• Withhold ZEPZELCA until Grade ≤ 1 • Resume ZEPZELCA at a reduced dose

* National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0.

** Patients with isolated Grade 4 neutropenia (neutrophil count less than 0.5 x 10⁹/L) may receive G-CSF prophylaxis rather than undergo lurbinectedin dose reduction.

Premedication

Pre-infusion, consider prophylactic administration of the following antiemetic medications:

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

Preparation and administration

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

The ZEPZELCA vial is for single use (in one patient on one occasion) only. Discard any residue.

Prepare the solution for infusion using aseptic technique as follows:

- Inject 8 mL of Sterile Water for Injection USP into the vial, yielding a reconstituted solution containing 0.5 mg/ml lurbinectedin. Shake the vial until dissolution is complete.

- Visually inspect the reconstituted solution for particulate matter and discoloration. It should be clear, colourless or slightly yellowish, and free of visible particles.
- Calculate the required volume of reconstituted solution as follows:

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

$$0.5 \text{ mg/mL}$$

- For administration through a central venous line, withdraw the required volume of reconstituted solution from the vial and add to an infusion container containing at least 100 mL of diluent (0.9% Sodium Chloride Injection USP or 5% Glucose Injection).
- For administration through a peripheral venous line, withdraw the required volume of reconstituted solution from the vial and add to an infusion container containing at least 250 mL of diluent (0.9% Sodium Chloride Injection USP or 5% Glucose Injection).

Use as soon as practicable after reconstitution and dilution. If necessary, the solution can be stored prior to administration, either at room temperature/in ambient light or, ideally, under refrigerated (2° to 8° C) conditions, for a maximum of 24 hours following reconstitution (including infusion time).

Dose modification for hepatic impairment

Dose adjustment is not required for patients with mild hepatic impairment (total bilirubin $\leq 1.5 \times \text{ULN}$ and $\text{AST} \leq 3 \times \text{ULN}$). The effect of moderate or severe hepatic impairment (total bilirubin $> 1.5 \times \text{ULN}$) on the pharmacokinetics of lurbinectedin is unknown [see 5.2 *Pharmacokinetic properties*].

Dose modification for renal impairment

Dose adjustment is not required in patients with mild to moderate ($\text{CL}_{\text{CR}} 30\text{-}89 \text{ mL/min}$) renal impairment. The effect of severe renal impairment ($\text{CL}_{\text{CR}} < 30 \text{ mL/min}$) on the pharmacokinetics of lurbinectedin is unknown [see 5.2 *Pharmacokinetic properties*].

CONTRAINDICATIONS

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

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Myelosuppression

ZEPZELCA can cause myelosuppression.

In clinical studies of 554 patients with advanced solid tumours receiving ZEPZELCA [see 4.8 *Adverse effects (undesirable effects)*], Grade 3 or 4 neutropenia occurred in 41% of patients, with a median time to onset of 15 days and a median duration of 7 days. Febrile neutropenia occurred in 7% of patients. Sepsis occurred in 2% of patients and was fatal in 1% (all cases occurred in patients with solid tumours other than SCLC). Grade 3 or 4 thrombocytopenia occurred in 10%, with a median time to onset of 10 days and a median duration of 7 days. Grade 3 or 4 anaemia occurred in 17% of patients.

Administer ZEPZELCA only to patients with baseline neutrophil count of at least $1.5 \times 10^9/L$ and platelet count of at least $100 \times 10^9/L$.

Monitor blood counts including neutrophil count and platelet count prior to each administration. For neutrophil count less than $0.5 \times 10^9/L$ or any value less than lower limit of normal, the use of G-CSF is recommended. Withhold, reduce the dose, or permanently discontinue ZEPZELCA based on severity [see 4.2 *Dose and method of administration*].

Hepatotoxicity

ZEPZELCA can cause hepatotoxicity.

In clinical studies of 554 patients with advanced solid tumours receiving ZEPZELCA [see 4.8 *Adverse effects (undesirable effects)*], Grade 3 elevations of ALT and AST were observed in 6% and 3% of patients, respectively, and Grade 4 elevations of ALT and AST were observed in 0.4% and 0.5% of patients, respectively. The median time to onset of Grade ≥ 3 elevation in transaminases was 8 days (range: 3 to 49), with a median duration of 7 days.

Monitor liver function tests prior to initiating ZEPZELCA, periodically during treatment, and as clinically indicated. Withhold, reduce the dose, or permanently discontinue ZEPZELCA based on severity [see 4.2 *Dose and method of administration*].

Use in hepatic impairment

ZEPZELCA has not been studied in patients with AST $>3 \times \text{ULN}$, or in patients with moderate or severe hepatic impairment (bilirubin $>1.5 \times \text{ULN}$).

Use in renal impairment

ZEPZELCA has not been studied in patients with severe renal impairment ($\text{CL}_{\text{CR}} < 30 \text{ mL/min}$) or end-stage renal disease.

Embryo-fetal toxicity

Based on animal data and its mechanism of action, ZEPZELCA can cause fetal harm when administered during pregnancy [see 4.6 *Fertility, pregnancy and lactation*].

Test to verify the pregnancy status of females of reproductive potential prior to initiating ZEPZELCA. Advise patients who are pregnant of the potential risk to the fetus. Advise female patients of reproductive potential to use effective contraception during treatment with ZEPZELCA and for 6 months after the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with ZEPZELCA and for 4 months after the last dose.

Use in the elderly

Of the 105 patients with SCLC who received ZEPZELCA in clinical studies, 35% were ≥ 65 years of age, and 9% were ≥ 75 years of age. No overall difference in effectiveness was observed between patients who were ≥ 65 years of age compared to those who were < 65 years of age.

There was a higher incidence of serious adverse reactions in patients who were ≥ 65 years of age compared to those who were < 65 years of age (49% vs. 26%, respectively). The serious adverse reactions most frequently reported in patients ≥ 65 years of age were related to myelosuppression and consisted of febrile neutropenia (11%), neutropenia (11%), thrombocytopenia (8%), and anaemia (8%) [see 4.8 *Adverse effects (undesirable effects)*].

Paediatric use

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

Effects on laboratory tests

See 4.8 *Adverse Effects (undesirable effects)*.

INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Strong and moderate CYP3A inhibitors

Coadministration with a strong or a moderate CYP3A inhibitor is expected to increase lurbinectedin systemic exposure [see 5.2 *Pharmacokinetic properties*] and may increase the incidence and severity of adverse reactions to ZEPZELCA.

Avoid coadministration of ZEPZELCA with strong CYP3A inhibitors (e.g. itraconazole, ketoconazole, posaconazole, voriconazole, or grapefruit) or moderate CYP3A inhibitors (e.g. aprepitant, ciprofloxacin, diltiazem, erythromycin, fluconazole, fluvoxamine, imatinib, or verapamil). For moderate CYP3A4 inhibitors, if coadministration with ZEPZELCA cannot be avoided, consider dose reduction of ZEPZELCA, based on individual tolerability as clinically indicated [see 4.2 *Dose and method of administration*].

Strong and moderate CYP3A inducers

Coadministration with a strong CYP3A inducer is expected to decrease lurbinectedin systemic exposure [see 5.2 *Pharmacokinetic properties*] and may reduce ZEPZELCA efficacy. Avoid coadministration of ZEPZELCA with strong CYP3A inducers (e.g. carbamazepine, phenytoin, rifampicin, or St. John's wort) or moderate CYP3A inducers (e.g. bosentan, phenobarbital, or primidone).

FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

ZEPZELCA can cause embryoletality at doses lower than the human dose of 3.2 mg/m² [see 4.6 *Fertility, pregnancy and lactation - Use in pregnancy*].

No dedicated fertility studies were conducted in animal species. Testicular atrophy and hypospermia were observed in rats and dogs at doses below the recommended clinical dose.

- Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to initiating ZEPZELCA.

- Contraception

Females

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

Males

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

Use in pregnancy – Pregnancy Category D

Based on animal data and its mechanism of action [see 5.1 *Pharmacodynamic properties*], lurbinectedin can cause fetal harm when administered during pregnancy. There are no available clinical data to inform the risk of ZEPZELCA use during human pregnancy. Intravenous administration of a single lurbinectedin dose (approximately 0.2 times the 3.2 mg/m² clinical dose) to pregnant rats during the period of organogenesis caused 100% embryolethality.

Advise patients who are pregnant and females of reproductive potential of the potential risk to a fetus.

Use in lactation

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

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of lurbinectedin on a person's ability to drive and use machines have not been formally assessed.

ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The following clinically significant adverse reactions are described in detail in other sections of the prescribing information:

- *Myelosuppression [see Special Warnings and Precautions (4.4)]*
- *Hepatotoxicity [see Special Warnings and Precautions (4.4)]*

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

The pooled safety population described in 4.4 *Special warnings and precautions for use* reflects exposure to ZEPZELCA as a single agent at a dose of 3.2 mg/m² intravenously every 21 days in 554 patients with advanced solid tumours. Among 554 patients who received ZEPZELCA, including 105 patients with small cell lung cancer (SCLC) in PM1183-B-005-14 (Study B-005), 24% were exposed for 6 months or longer and 5% were exposed for greater than one year.

Small Cell Lung Cancer (SCLC)

The safety of ZEPZELCA was evaluated in a cohort of 105 patients with previously treated SCLC in Study B-005 [see 5.1 *Pharmacodynamic properties- Clinical studies*]. Patients received ZEPZELCA 3.2 mg/m² intravenously every 21 days. All patients in this study received a pre-specified anti-emetic regimen consisting of a corticosteroid and serotonin antagonist. Patients could receive G-CSF for secondary prophylaxis (i.e., after patients had a first adverse event of leukopenia), but not primary prophylaxis (i.e. prior to any occurrence of leukopenia). Among patients who received ZEPZELCA, 29% were exposed for 6 months or longer and 6% were exposed for greater than one year.

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

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

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

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

The most common adverse reactions, including laboratory abnormalities, ($\geq 20\%$) were leukopenia, lymphopenia, fatigue, anaemia, neutropenia, increased creatinine, increased alanine aminotransferase, increased glucose, thrombocytopenia, nausea, decreased appetite, musculoskeletal pain, decreased albumin, constipation, dyspnoea, decreased sodium, increased aspartate aminotransferase, vomiting, cough, decreased magnesium and diarrhoea.

The most common adverse reactions, and selected laboratory abnormalities that occurred in the SCLC cohort of Study B-005 are summarised in [Table 3](#) and [Table 4](#), respectively.

Table 14: Adverse reactions that occurred in at least 10% of patients with SCLC who received ZEPZELCA in Study B-005

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

^a Graded per NCI CTCAE 4.0.

^b No grade 5 adverse reactions were reported.

^c Includes abdominal pain, abdominal pain upper and abdominal discomfort.

^d Includes musculoskeletal pain, back pain, arthralgia, pain in extremity, musculoskeletal chest pain, neck pain, bone pain and myalgia.

^e Includes cough and productive cough.

^f Includes upper respiratory tract infection, viral upper respiratory tract infection, respiratory tract infection and bronchitis.

^g Includes pneumonia and lung infection.

^h Includes neuropathy peripheral, neuralgia, paraesthesia, peripheral sensory neuropathy, hypoesthesia, and hyperaesthesia.

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

Table 15: Selected laboratory abnormalities that worsened from baseline in at least 20% of patients with SCLC who received ZEPZELCA in Study B-005

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

^a The denominator used to calculate the rate varied from 95 to 105 based on the number of patients with a baseline value and at least one post-treatment value.

^b Graded per NCI CTCAE 4.0.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems and drugsafety-STA@stbiopharma.com.

OVERDOSE

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

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

There is no known antidote for overdosage with ZEPZELCA.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

PHARMACOLOGICAL PROPERTIES

PHARMACODYNAMIC PROPERTIES

Mechanism of action

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

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

Pharmacodynamics

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

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

Cardiac electrophysiology

The potential for QT prolongation with lurbinectedin was evaluated in a sub-study of 39 patients with advanced cancer who received lurbinectedin 3.2 mg/m² every 3 weeks in Study B-005. No large mean increase in QTcF (>20 ms) was detected. The maximum mean QTcF change from baseline was 5.4 ms (upper bound of 90% CI: 9.6 ms).

Clinical trials

Study B-005

Study B-005 (PM1183-B-005-14) was an open-label, multicentre, single-arm study evaluating ZEPZELCA as a single agent in patients with advanced or metastatic solid tumours, including a cohort of patients with small cell lung cancer (SCLC) whose disease had progressed on or after platinum-based chemotherapy. Patients received 3.2 mg/m² ZEPZELCA, administered as a 60-minute IV infusion once every 21 days (one cycle). Patients received a median of 4 cycles of ZEPZELCA (range 1 to 24 cycles). The trial excluded patients with central nervous system (CNS) involvement, grade \geq 3 dyspnoea, daily intermittent oxygen requirement, hepatitis or cirrhosis, and immunocompromised patients. Tumour assessments were conducted every 6 weeks for the first 18 weeks and every 9 weeks thereafter. The primary efficacy outcome measure was confirmed, investigator-assessed, overall response rate (ORR), using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Additional efficacy outcome measures included investigator-assessed duration of response (DOR), as well as ORR and DOR assessed by an Independent Review Committee (IRC).

A total of 105 patients with SCLC who progressed on or after platinum-based chemotherapy were enrolled. The median age was 60 years (range, 40-83 years) and 35% were at least 65 years old. The majority of patients were male (60%) and white (75%); ethnicity was not reported for 23%. Baseline ECOG performance status was 0 or 1 for 92% of patients, and 92% were current/former smokers. All patients had received at least one line of platinum-based chemotherapy for advanced disease (range 1-2 lines), and prior radiotherapy had been administered to 71% of patients. and prior radiotherapy had been administered to 71% of patients. Eight patients (8%) had prior immunotherapy in addition to platinum-based

chemotherapy. Sixty patients (57%) had platinum-sensitive SCLC, defined as recurrence or progression ≥ 90 days after the last dose of platinum-containing therapy (chemotherapy free interval [CTFI] ≥ 90 days). The remaining 45 patients had platinum-resistant SCLC, defined as recurrence or progression < 90 days after the last dose of platinum-containing therapy (CTFI < 90 days).

Table 5 summarises investigator-assessed and IRC- assessed key efficacy measures in all patients and in platinum-resistant and platinum-sensitive subgroups.

Table 16: Efficacy results in the SCLC cohort of Study B-005

	• ZEPZELCA (n=105)		
	• All SCLC • (n=105)	• CTFI <90 days • (n=45)	• CTFI ≥ 90 days • (n=60)
• Investigator-assessed responses			
• ORR (95% CI)	• 35% (26%, 45%)	• 22% (11%, 37%)	• 45% (32%, 58%)
• Complete response rate	• 0%	• 0%	• 0%
• Partial response rate	• 35%	• 22%	• 45%
• Median DOR, months (95% CI)	• 5.3 (4.1, 6.4)	• 4.7 (2.6, 5.6)	• 6.2 (3.5, 7.3)
• % with DOR ≥ 6 months*	• 35%	• 10%	• 44%
• IRC-assessed responses			
• ORR (95% CI)	• 30% (22%, 40%)	• 13% (5%, 27%)	• 43% (31%, 57%)
• Complete response rate	• 0%	• 0%	• 0%
• Partial response rate	• 30%	• 13%	• 43%
• Median DOR, months (95% CI)	• 5.1 (4.9, 6.4)	• 4.8 (2.4, 5.3)	• 5.3 (4.9, 7.0)
• % with DOR ≥ 6 months*	• 25%	• 0%	• 31%

CI: confidence interval, CTFI: chemotherapy-free interval, DOR: duration of response, IRC: Independent Review Committee, ORR: (confirmed) overall response rate

* Based on observed duration of response.

PHARMACOKINETIC PROPERTIES

After a 3.2 mg/m² lurbinectedin dose administered as a 1-hour IV infusion, geometric means (CV%) of total plasma C_{max} and AUC_{0-inf} were 107 µg/L (79%) and 551 µg·h/L (94%), respectively. No accumulation of lurbinectedin in plasma is observed upon repeated administrations every 3 weeks.

Distribution

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

Metabolism

Lurbinectedin is metabolised by CYP3A4 *in vitro*.

Excretion

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

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

Drug interaction studies

Lurbinectedin is metabolised by CYP3A4 *in vitro*, and interactions with strong and moderate CYP3A inhibitors and inducers are anticipated. Dedicated clinical drug-drug interaction studies with CYP3A modulators have not been completed.

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

In vitro data

Cytochrome P450 (CYP) enzymes:

- Lurbinectedin is metabolised by CYP3A4.
- At clinically relevant concentrations, lurbinectedin is not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4.
- Lurbinectedin is not an inducer of CYP1A2 or CYP3A4.

Transporter systems:

- Lurbinectedin is a substrate of MDR1 (P-gp), but is not a substrate of OATB1P1, OATP1B3, OCT1, or MATE1.
- Lurbinectedin inhibits MDR1 (P-gp), OATP1B1, OATP1B3, and OCT1 but not BCRP, BSEP, MATE1, OAT1, OAT3, or OCT2.

Pharmacokinetics in specific populations

No clinically significant differences in the pharmacokinetics of lurbinectedin were identified based on age (range: 18-85 years), sex, body weight (range: 39-154 kg), mild to moderate renal impairment (CL_{CR} 30 to 89 mL/min) or mild hepatic impairment (total bilirubin \leq ULN and AST $>$ ULN, or total bilirubin between 1.0-1.5 \times ULN and any AST). The effects of severe renal impairment ($CL_{cr} < 30$ mL/min) and moderate or severe hepatic impairment (total bilirubin $> 1.5 \times$ ULN and any AST) on the pharmacokinetics of lurbinectedin have not been studied.

PRECLINICAL SAFETY DATA

Genotoxicity

Lurbinectedin is genotoxic to mammalian cells in the presence and absence of metabolic activation, and was positive in the mouse lymphoma cell assay. Lurbinectedin was not mutagenic *in vitro* in a bacterial reverse mutation (Ames) assay.

Carcinogenicity

Carcinogenicity testing of lurbinectedin has not been performed.

PHARMACEUTICAL PARTICULARS

LIST OF EXCIPIENTS

(S)-lactic acid

Sucrose

Sodium Hydroxide

INCOMPATIBILITIES

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

SHELF LIFE

Unopened vials: 60 months [see 6.4 *Special precautions for storage*].

After reconstitution or dilution: 24 hours, including infusion time. Use immediately if possible [see 6.4 *Special precautions for storage*].

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

SPECIAL PRECAUTIONS FOR STORAGE

Unopened vials: refrigerate (2° to 8°C). Refrigerate. Do not freeze.

After reconstitution or dilution: stable at room temperature with exposure to ambient light for up to 24 hours. However, microbiological hazard is minimized by immediate use, or refrigeration (2° to 8°C) if storage is necessary. Do not store for longer than 24 hours, including infusion time. Do not freeze.

NATURE AND CONTENTS OF CONTAINER

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

SPECIAL PRECAUTIONS FOR DISPOSAL

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

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

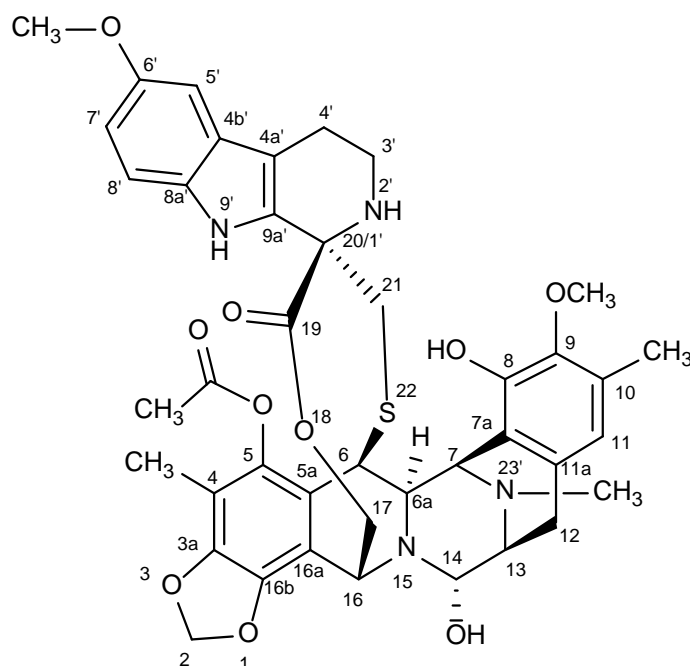
PHYSICOCHEMICAL PROPERTIES

ZEPZELCA is a synthetic molecule, which binds to the minor groove of DNA and is a selective inhibitor of oncogenic transcription. The chemical name of ZEPZELCA (lurbinctedin) is (1'R,6R,6aR,7R,13S,14S,16R)-8,14-dihydroxy-6',9-dimethoxy-4,10,23-trimethyl-19-oxo-2',3',4',6,7,9',12,13,14,16-decahydro-6aH-spiro[7,13-azano-6,16-(epithiopropanooxymethano)[1,3]dioxolo[7,8]isoquinolino[3,2-b][3]benzazocine-20,1'-pyrido[3,4-b]indol]-5-yl acetate.

Molecular formula: C₄₁H₄₄N₄O₁₀S.

Molecular weight: 784.87 g/mol.

Chemical structure:



CAS number

497871-47-3

MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine (S4)

Attachment AusPAR - Zepzelca – lurbinectedin- Specialised Therapeutics Pharma Pty Ltd - PM-2020-02181-1-4 FINAL 1 April 2022. This is the Product Information that was approved with the submission described in this AusPAR. It may have been superseded. For the most recent PI, please refer to the TGA website at <<https://www.tga.gov.au/product-information-pi>>

SPONSOR

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DATE OF FIRST APPROVAL

10 September 2021

DATE OF REVISION

N/A

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information

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