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CADTH Reimbursement Recommendation

Lurbinectedin (Zepzelca)

Indication: For the treatment of adult patients with stage III or metastatic small cell lung cancer who have progressed on or after platinum-containing therapy

Sponsor: Jazz Pharmaceuticals Inc.

Final recommendation: Do not reimburse

CADTH

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Redactions: Confidential information in this document may be redacted at the request of the sponsor in accordance with the *CADTH Drug Reimbursement Review Confidentiality Guidelines.*

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Summary

CADTH

What Is the CADTH Reimbursement Recommendation for Zepzelca?

CADTH recommends that Zepzelca not be reimbursed by public drug plans for the treatment of stage III or metastatic small cell lung cancer (SCLC).

Why Did CADTH Make This Recommendation?

- While evidence from a clinical trial demonstrated that some patients had disease that responded during treatment with Zepzelca, without a control group there is uncertainty in how much the observed responses were due to Zepzelca treatment rather than chance.
- There was too much uncertainty in the reviewed evidence to determine how Zepzelca compares to other treatments used in Canada in terms of delaying disease progression, improving survival, and minimizing side effects.
- It is unclear whether Zepzelca meets any of the needs identified by patients: improving survival, delaying disease progression, relieving cancer symptoms, minimizing side effects, and maintaining or improving quality of life.

Additional Information

What Is SCLC?

SCLC accounts for 10% to 15% of lung cancer cases, with approximately two-thirds of patients with SCLC diagnosed with metastatic disease and approximately one-quarter diagnosed with stage III disease. Most patients with metastatic SCLC survive for less than 1 year.

Unmet Needs in SCLC

Although most patients with stage III or metastatic SCLC respond to first-line treatment with chemotherapy, most patients relapse within months. Many patients are not well enough to receive second-line chemotherapy after relapse, and those who are do not experience much benefit.

How Much Does Zepzelca Cost?

Treatment with Zepzelca is expected to cost approximately $12,940 per patient per 21-day cycle.

Recommendation

The CADTH pan-Canadian Oncology Drug Review Expert Review Committee (pERC) recommends that lurbinectedin not be reimbursed for the treatment of adult patients with stage III or metastatic SCLC who have progressed on or after platinum-containing therapy.

Rationale for the Recommendation

The efficacy and safety of lurbinectedin was evaluated in a cohort of patients with SCLC who had received 1 prior line of platinum-containing chemotherapy (N = 105) within a phase II, open-label, single-arm basket trial (Study B-005) in patients with advanced solid tumours. The primary end point for the SCLC cohort, objective response rate (ORR) per investigator assessment (IA), was 35.2% (95% confidence interval [CI], 26.2% to 45.2%) with lurbinectedin treatment. The lack of a control group limited the interpretation of the results and led to uncertainty in the magnitude of any clinical benefit with lurbinectedin. Although indirect treatment comparisons (ITCs) were submitted that compared lurbinectedin versus IV topotecan, carboplatin plus etoposide, and a mixture of post-platinum systemic therapies in a Canadian setting, numerous limitations in the analyses meant that conclusions could not be drawn on the efficacy and safety of lurbinectedin versus relevant comparators in this setting. Health-related quality of life (HRQoL), an outcome that is important to patients, was not assessed in Study B-005 and it is unknown how HRQoL with lurbinectedin treatment compares with other available treatments. Patients identified a need for treatments that improve survival, delay disease progression, relieve cancer symptoms, minimize side effects, and maintain or improve quality of life, but pERC could not conclude from the trial and ITC evidence that lurbinectedin meets any of these needs.

Discussion Points

- The sponsor requested a reconsideration of the initial draft recommendation to not reimburse lurbinectedin for the treatment of adult patients with stage III or metastatic SCLC who have progressed on or after platinum-containing therapy. pERC discussed each of the issues identified by the sponsor in their request for reconsideration.
- pERC noted that the lack of a control group in Study B-005 particularly limited the interpretation of the overall survival (OS) and progression-free survival (PFS) results and no conclusions could be drawn regarding OS and PFS. In addition, there was no adjustment for multiple outcomes and hypothesis testing was conducted only for ORR per IA.
- There were limitations in all 3 ITCs that meant conclusions could not be drawn for any of them. Potential residual confounding was a limitation of all the ITCs. In addition, the selection of the comparator trial for the simulated treatment comparison (STC) was not transparent. For the combined matching adjusted indirect comparisons (MAICs) and network meta-analyses (NMAs), the validity of the approach of combining these analyses is unknown and the MAICs were limited by imprecision and poor overlap of the study populations.

- During the initial and reconsideration meetings, pERC considered the high unmet need for treatments to delay disease progression, improve HRQoL, and minimize adverse effects. pERC noted that there are other treatment options in this setting (e.g., carboplatin or cisplatin plus etoposide, topotecan, irinotecan with or without cisplatin or carboplatin, and cyclophosphamide plus doxorubicin plus vincristine [CAV]). Input from patient and clinician groups noted that lurbinectedin may be better tolerated than these options, but there is insufficient clinical evidence that lurbinectedin offers benefits in HRQoL or adverse effects over any of these options.
- pERC noted that the Health Canada Notice of Compliance for lurbinectedin is conditional on the results of trials to verify its clinical benefit and that it is currently being studied in a phase III randomized trial. The LAGOON study is a randomized open-label trial comparing lurbinectedin monotherapy, lurbinectedin plus irinotecan, and investigator's choice of irinotecan or topotecan in patients with SCLC who have failed 1 line of platinum-containing chemotherapy. Results for the LAGOON study, when they become available, will provide a direct comparison of efficacy and safety for lurbinectedin versus an active comparator.
- The phase III ATLANTIS trial (N = 613) was a randomized open-label trial of lurbinectedin plus doxorubicin versus investigator's choice of CAV or topotecan in patients with SCLC who failed 1 prior line of platinum-containing chemotherapy. The study did not meet its primary end point and there was no OS benefit with lurbinectedin plus doxorubicin. The ATLANTIS trial used a lower dosage of lurbinectedin than the Health Canada–approved dosage and was not included in the CADTH review, but pERC noted that it demonstrates the feasibility of conducting a phase III trial for the second-line treatment of SCLC.
- pERC did not consider the new information provided by the sponsor in their request for reconsideration to support the synthetic control arm (SCA) analysis sufficient to allow for a conclusion of clinical benefit with lurbinectedin over the currently available treatment options.
- During the reconsideration meeting, pERC also discussed the feedback from patient groups and the clinical experts who emphasized their experience of better tolerability with lurbinectedin over other treatment options. Improving survival, delaying disease progression, managing cancer symptoms, ease of use, and maintaining HRQoL while minimizing side effects were all identified by patients as important outcomes. However, pERC maintained its position that given the limitations with the trial and ITC evidence, there is insufficient clinical evidence to conclude that lurbinectedin offers benefit in HRQoL or adverse effects over the other available treatment options. Given the uncertain comparative efficacy of lurbinectedin versus relevant comparators, pERC could not conclude that there is an overall clinical benefit with lurbinectedin even when considering the potential for improved tolerability.

Background

SCLC accounts for 10% to 15% of all lung cancers and is classically staged into limited-stage (LS) or extensive-stage (ES) disease; approximately two-thirds of patients present with metastatic ES disease, while approximately one-quarter have stage III LS disease at diagnosis. The initial symptoms of SCLC are nonspecific and include cough, chest pain, trouble breathing, wheezing, hoarseness, loss of appetite, weight loss, and fatigue. For

patients with metastatic ES disease, median OS is less than 1 year and the 5-year survival rate is approximately 5%. In Canada, the standard first-line systemic therapy for patients with both LS (stage III or earlier) or ES (metastatic) SCLC is a platinum-based drug (cisplatin or carboplatin) plus etoposide for 4 to 6 cycles. Starting in 2021, standard first-line therapy for patients with ES disease includes platinum doublet therapy plus durvalumab. Second-line treatment options available to both patients with ES and LS disease include rechallenge with platinum plus etoposide (if progression occurs after an appropriate interval), topotecan, and CAV. Third-line treatment options include topotecan, CAV, and irinotecan with or without a platinum-based drug.

Lurbinectedin is an alkylating agent that is indicated for the treatment of adult patients with stage III or metastatic SCLC who have progressed on or after platinum-containing therapy. The drug is supplied as a 4 mg vial and administered at a dose of 3.2 mg per m^2 by IV infusion over 60 minutes repeated every 21 days. The sponsor estimated that there would be 521 patients per year (as of 2022) in Canada (outside of Quebec) who would be eligible to receive lurbinectedin.

Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information:

- a review of 1 phase II, multicenter, open-label, single-arm basket trial (Study B-005) in patients with advanced solid tumours, including a cohort of patients with SCLC who had received 1 prior line of platinum-containing chemotherapy (N = 105)
- patients' perspectives gathered by 2 patient groups, Lung Cancer Canada (LCC) and the Lung Health Foundation (LHF) (previously known as the Ontario Lung Association)
- input from the public drug plans and cancer agencies that participate in the CADTH review process
- 2 clinical specialists with expertise diagnosing and treating patients with stage III or metastatic SCLC
- input from 2 clinician groups, the LCC Medical Advisory Committee and the Ontario Health-Cancer Care Ontario Lung Cancer Drug Advisory Committee
- a review of the pharmacoeconomic model and report submitted by the sponsor
- information submitted as part of the sponsor's request for reconsideration (described in the following).

Stakeholder Perspectives

The information in this section is a summary of input provided by the patient groups that responded to CADTH's call for patient input and from the clinical experts consulted by CADTH for the purpose of this review.

Patient Input

Two patient groups provided input for this review: LCC and the LHF (previously known as the Ontario Lung Association). LCC conducted phone interviews with 2 patients from Canada with SCLC (1 localized and 1 metastatic) and environmental scans with 1 patient and 2 caregivers of patients with metastatic SCLC from the US in March 2022; all had experience with lurbinectedin. LHF conducted an online survey (2 respondents, no demographic or disease information collected) and phone interviews (3 patients from Canada with lung cancer; type and stage not reported) from September 2021 to December 2021 and collected input from 2 additional individuals (one registered nurse and 1 certified respiratory educator); none had experience with lurbinectedin. Patients highlighted the nonspecific early symptoms of SCLC and the resulting delays in diagnosis, as well as the physical (e.g., shortness of breath, cough, fatigue, pain), emotional, and social toll of a SCLC diagnosis. Patients acknowledged that while existing treatments for SCLC (e.g., surgery, radiation, chemotherapy, targeted therapy, immunotherapy) prolonged survival and delayed disease progression, the side effects of currently available second- and third-line chemotherapies for metastatic SCLC (e.g., nausea, fatigue, weight, and hair loss) were sometimes severe and negatively impacted HRQoL, employment, and ability to perform activities of daily living. Patients identified an unmet need for additional second-line treatment options for metastatic SCLC that can prolong survival, delay disease progression, manage cancer symptoms, and maintain HRQoL while having minimal side effects. Patients emphasized that stopping or delaying disease progression was the most important factor in choosing treatments and that they were more receptive to the potential side effects of efficacious therapies. Patients who had experience with lurbinectedin felt that the drug had reduced or stabilized tumour size, delayed disease progression, helped them continue or resume activities of daily living, including employment, and had more manageable side effects and a shorter recovery time compared with other SCLC therapies they had received.

Clinician Input

Input From the Clinical Experts Consulted by CADTH

Two clinical specialists with expertise in the diagnosis and management of stage III and metastatic SCLC provided input for this review. According to the clinical experts, patients with stage III or metastatic SCLC manifest rapid responses to first-line chemotherapy but these are not sustained. Currently available second-line chemotherapy options (e.g., topotecan, CAV, irinotecan) have significant drawbacks, such as toxicity and inconvenience (e.g., topotecan has a dosage regimen of 5 consecutive days of IV treatment every 3 weeks). The clinical experts stated that lurbinectedin would be used for second- or third-line therapy of stage III or metastatic SCLC following first-line platinum plus etoposide therapy and potential rechallenge; if disease progression following first-line therapy occurred after a relatively long interval (e.g., 6 to 12 months), many clinicians would rechallenge with platinum plus etoposide as second-line therapy before using lurbinectedin. The clinical experts emphasized that all patients with ES SCLC need additional treatment options to prolong survival and maintain HRQoL. According to the clinical experts, the patient population best suited to treatment with lurbinectedin would be patients with ES SCLC who progress following treatment with platinum plus etoposide with or without durvalumab, while patients with poor performance status (e.g., Eastern Cooperative Oncology Group [ECOG] performance status [PS] of 3 or greater) or limited organ function would be least suitable for treatment with lurbinectedin. According to the clinical experts, response to lurbinectedin would be assessed based on imaging scans (approximately every 3 months), clinical improvement, and laboratory markers. Clinically

meaningful responses to treatment would be manifested by improvement in symptoms and improvement or stabilization of HRQoL. The clinical experts stated that lurbinectedin should be discontinued in patients when disease progression or unacceptable toxicities occur, or by patient choice. They also noted that lurbinectedin would be given in an outpatient setting and would be ordered by a medical oncologist.

Clinician Group Input

Two clinician groups, the LCC Medical Advisory Committee (10 medical oncologists, 2 respirologists, 1 thoracic surgeon, and 1 pathologist) and the Ontario Health-Cancer Care Ontario Lung Cancer Drug Advisory Committee (5 medical oncologists) provided input for this review. No major contrary views were presented. Clinician groups echoed the high unmet need for additional efficacious second-line treatment options for stage III and metastatic SCLC that have fewer side effects and are more convenient to administer. The clinician groups noted that some clinicians would perform imaging evaluations slightly more frequently (every 2 to 3 cycles or 6 to 9 weeks versus every 3 months) and that in addition to improvement or stabilization of symptoms and HRQoL, clinically meaningful responses to lurbinectedin would be manifested through tumour shrinkage observed on imaging scans. In addition, the clinician groups noted that it was not yet clear if re-treatment with platinum plus etoposide would be the preferred option in patients with platinum-sensitive disease who have treatment-free periods beyond some cut-off (e.g., 6 months).

Drug Program Input

Input was obtained from the drug programs that participate in the CADTH reimbursement review process. The following were identified as key factors that could potentially impact the implementation of a CADTH recommendation for lurbinectedin:

- considerations for initiation of therapy
- considerations for prescribing of therapy
- care provision issues
- system and economic issues
- potential need for a provisional funding algorithm.

The clinical experts consulted by CADTH provided advice on the potential implementation issues raised by the drug programs.

Clinical Evidence

Pivotal Studies and Protocol Selected Studies

Description of Studies

One phase II, multicenter, open-label basket trial (Study B-005) designed to evaluate the efficacy and safety of lurbinectedin in previously treated patients with advanced solid tumours provided evidence for this review; only data for the SCLC cohort (N = 105) are described in this report. The primary objective of the study was to assess the ORR per IA of lurbinectedin in patients with advanced SCLC who had received 1 prior line of systemic therapy. Secondary objectives included ORR per independent review committee (IRC), duration of response

(DOR) per IA and IRC, clinical benefit rate per IA and IRC, PFS per IA and IRC, and OS. Adult patients (age 18 years and older) with SCLC who had received 1 previous line of systemic therapy for advanced disease and met the eligibility criteria were enrolled at 26 sites primarily in Europe (predominantly Spain; no sites in Canada). Patients were treated with lurbinectedin (3.2 mg per m^2 on day 1 of a 21-day treatment cycle) until disease progression or unacceptable toxicity.

Adult patients (age 18 years and older) with SCLC, ECOG PS 2 or lower, and measurable disease who had received 1 prior line of systemic therapy for advanced disease were eligible if they did not have known central nervous system involvement by CT or MRI, did not have serious comorbidities, and had not received chemotherapy within 3 weeks. The median age at study entry was 60 years. Most patients (56.2%) had an ECOG PS of 1, while roughly one-third (36.2%) had an ECOG PS of 0; only 8 patients (7.6%) had an ECOG of PS 2. Most patients (93.3%) had ES disease at study entry and only 2 patients (1.9%) had non-metastatic disease at study entry. Nearly all patients (93.3%) had received 1 line of prior systemic therapy (platinum-based regimen = 100.0%; etoposide = 99.0%) while only 7.6% of patients had received prior immunotherapy. Based on their chemotherapy treatment-free intervals (CTFIs), 42.9% of patients had platinum-resistant disease (CTFI shorter than 90 days, including both refractory disease [20.0%, CTFI shorter than 30 days] and resistant disease [22.9%, CTFI 30 to 89 days]) while 57.1% of patients had platinum-sensitive disease (CTFI 90 days or longer, including both sensitive disease [38.1%, CTFI 90 to 179 days] and very sensitive disease [19.0%, CTFI 180 days or longer]).

Lurbinectedin (3.2 mg per m^2) was administered as a 1-hour IV infusion on day 1 of a 3-week treatment cycle. The dose was capped at a body surface area of 2.0 m^2 (6.4 mg). Treatment was continued until disease progression (per IA), unacceptable toxicity, treatment delay of 3 weeks or longer (except in the case of clear clinical benefit with sponsor's approval), requirement for more than 2 dose reductions, intercurrent illness of sufficient magnitude to preclude safe continuation of the study, major protocol deviation that may affect the risk to benefit ratio for the participating patient, investigator decision, noncompliance with study requirements, or patient refusal. During the treatment period, tumour response was evaluated for all original sites of disease involvement at baseline every 2 cycles until cycle 6, and then every 3 cycles thereafter.

Efficacy Results

Overall Survival

Median OS was 9.3 months overall (95% CI, 6.3 to 11.8 months). Median OS among patients with CTFI shorter than 90 days and 90 days or longer was 5.0 months (95% CI, 4.1 to 6.3 months) and 11.9 months (95% CI, 9.7 to 16.2 months), respectively.

Progression-Free Survival

Median PFS per IA was 3.5 months overall (95% CI, 2.6 to 4.3 months). Median PFS per IA among patients with CTFI shorter than 90 days and 90 days or longer was 2.6 months (95% CI, 1.3 to 3.9 months) and 4.6 months (95% CI, 2.8 to 6.5 months), respectively.

Median PFS per IRC was 3.5 months overall (95% CI, 2.6 to 4.2 months). Median PFS per IRC among patients with CTFI shorter than 90 days and 90 days or longer was 1.4 months (95% CI, 1.3 to 3.5 months) and 4.3 months (95% CI, 3.0 to 6.3 months), respectively.

Objective Response Rate

The ORR per IA was 35.2% overall (95% CI, 26.2% to 45.2%). The ORR per IA among patients with CTFI shorter than 90 days and 90 days or longer was 22.2% (95% CI, 11.2% to 37.1%) and 45.0% (95% CI, 32.1%, 58.4%), respectively.

The ORR per IRC was 30.5% overall (95% CI, 21.9%, 40.2%). The ORR per IRC among patients with CTFI shorter than 90 days and 90 days or longer was 13.3% (95% CI, 5.1%, 26.8%) and 43.3% (95% CI, 30.6%, 56.8%), respectively.

Duration of Response

Median DOR per IA in patients who had a confirmed complete response or partial response as best overall response was 5.3 months overall (95% CI, 4.1 to 6.4 months). Median DOR per IA among patients with CTFI shorter than 90 days and 90 days or longer was 4.7 months (95% CI, 2.6 to 5.6 months) and 6.2 months (95% CI, 3.5 to 7.3 months), respectively.

Median DOR per IRC in patients who had a confirmed complete response or partial response as best overall response was 5.1 months overall (95% CI, 4.9 to 6.4 months). Median DOR per IRC among patients with CTFI shorter than 90 days and 90 days or longer was 4.8 months (95% CI, 2.4 to 5.3 months) and 5.3 months (95% CI, 4.9 to 7.0 months), respectively.

Harms Results

Adverse events (AEs) occurred in most patients (98.1%), serious AEs occurred in 32.4% of patients, AEs leading to dose reduction occurred in 26.3% of patients, and withdrawals due to AEs occurred in 3.8% of patients. Sixty-six patients (62.9%) died during the study, all due to progressive disease. Among CADTH protocol-defined notable harms, the most common myelosuppression-associated AEs in Study B-005 were anemia (95.2%), lymphopenia (85.7%), leukopenia (79.0%), neutropenia (71.4%), and thrombocytopenia (43.8%). Febrile neutropenia occurred in 4.8% of patients. The most common hepatotoxicity-associated AEs were increased alanine aminotransferase (71.8%), increased gamma glutamyltransferase (65.0%), increased asparagine aminotransferase (A44.7%), and increased alkaline phosphatase (33.0%). Peripheral neuropathy and peripheral sensory neuropathy occurred in 2 patients (1.9%).

Critical Appraisal

The major limitations of Study B-005 were its single-arm, non-comparative design and relatively small sample size with associated uncertainty in estimation of effect sizes. Other potential internal validity concerns included potential for bias in outcome assessment (e.g., tumour response) in a single-arm open-label study, the descriptive nature of efficacy analyses, and the absence of formal statistical hypothesis testing (other than ORR per IA).

The clinical experts consulted by CADTH for this review considered the demographic and disease characteristics of the patients in Study B-005 to be broadly reflective of adult patients with advanced SCLC who have received prior platinum doublet therapy in Canada. However, as with any trial population, the clinical experts felt that the patients in Study B-005 were slightly younger, in better health, and more treatment-seeking than the general population of patients with SCLC. Patients with central nervous system involvement, who would be expected to have worse prognoses, were excluded from Study B-005; however, patients with short CTFI, who are excluded from many trials due to their poor prognoses, were included. Although the study assessed lurbinectedin in the second-line treatment setting, the clinical experts felt that the study results could be generalized to the third-line treatment setting

as well. Stabilization of HRQoL and cancer symptoms, which were identified as important outcomes to patients, as well as goals of treatment by the clinical experts consulted by CADTH for this review, were not assessed in Study B-005.

Indirect Comparisons

Description of Studies

Three sponsor-submitted ITCs are included in this CADTH report. First, a study evaluating the treatment landscape and comparative efficacy of lurbinectedin in the treatment of patients with advanced SCLC following exposure to platinum therapy in Alberta, Canada, who were diagnosed with SCLC (any stage) and who initiated a post-platinum systemic therapy, building an SCA to evaluate aggregate trial-level data for comparison to the phase II B-005 study.

The second ITC is an STC facilitating the indirect comparison of lurbinectedin (using individual patient data from the B-005 trial) to topotecan IV (using aggregated data from the von Pawel 2014 RCT) in patients with relapsed or refractory SCLC.

The third ITC is a MAIC created to be used with an NMA to evaluate the comparative efficacy and safety of lurbinectedin versus competing interventions (including topotecan IV and carboplatin plus etoposide) among patients with SCLC receiving second-line treatment with respect to ORR, DOR, OS, and PFS, as well as hematological grade 3 or 4 AEs (including anemia, thrombocytopenia, neutropenia, and febrile neutropenia).

Efficacy Results

The first ITC, the SCA analysis, is descriptive in nature but also provides a comparison of lurbinectedin (Study B-005) against the SCA stratified by CTFI and stage at initial diagnosis. The median OS in this adjusted population analysis of the SCA reached 5.8 months (95 CI, 5.1 to 6.9 months) while the median OS in the B-005 trial was 9.3 months (95% CI, 6.3 to 11.8). The unadjusted OS reached a median of 6.58 months (95% CI, 5.75 to 7.46 months). The SCA was subsequently updated to align more closely with the B-005 trial population by excluding patients who developed brain metastasis post-diagnosis but before initiating post-platinum therapy. In the updated SCA, the median OS in this adjusted population analysis of the SCA reached 6.1 months (95% CI, 5.4 to 7.7 months) while the unadjusted OS reached a median of 6.7 months (95% CI, 6.0 to 7.7 months).

In the second ITC, the STC evaluated OS and PFS. Adjusted estimates showed the median OS was 10.0 months (95% CI, 8.5 to 11.6 months) and 7.8 months (95% CI, 6.6 to 8.5 months) in the lurbinectedin and topotecan trials, respectively, with a mean difference of 2 months (95% CI, 0.4 to 4.0 months). For PFS, adjusted estimates were obtained, with a median PFS of 3.4 months (95% CI, 3.0 to 3.9 months) and 3.5 months (95% CI, 2.9 to 4.2 months) in the lurbinectedin and topotecan trials, respectively, with a mean difference of −0.10 months (95% CI, −0.89 to 0.69 months).

The third ITC showed the results of a MAIC and an NMA that evaluated OS, PFS, ORR, DOR, and harms.

For OS, from the MAIC evaluation, the hazard ratio (HR) for lurbinectedin versus carboplatin plus etoposide was 0.42 (95% CI, 0.2 to 0.65). In the base-case NMA for OS, lurbinectedin had an HR of 0.43 (95% credible interval [CrI], 0.26 to 0.70) against IV topotecan, and 0.42 (95% CrI, 0.30 to 0.58) against carboplatin plus etoposide.

[redacted].

For ORR, when assessing the MAIC base case, no evidence of difference was detected between lurbinectedin versus carboplatin plus etoposide ([redacted]). While in the NMA, no evidence of difference was detected between lurbinectedin versus IV topotecan (odds ratio [OR] = 2.36; 95% CrI, 0.89 to 6.23) or against carboplatin plus etoposide (OR = 0.85; 95% CrI, 0.40 to 1.83).

[redacted]

[redacted]

Harms Results

Harms were only directly evaluated in the third ITC (MAIC and NMA).

Grade 3 or 4 anemia in MAIC estimates had lower odds in the lurbinectedin arm compared to the carboplatin plus etoposide arm ([redacted]). The NMA estimates also showed lower odds for lurbinectedin when compared to carboplatin plus etoposide (OR = 0.22; 95% CrI, 0.08, 0.61) and against IV topotecan (OR = 0.21; 95% CrI, 0.06, 0.74) with consistent results in the sensitivity analyses.

MAIC estimates for grade 3 or 4 thrombocytopenia also showed lower odds for lurbinectedin versus carboplatin plus etoposide ([redacted]) and it was similar across sensitivity analyses. Similarly, in the NMA assessing grade 3 or 4 thrombocytopenia, the base-case analysis showed lower odds (OR = 0.23; 95% CrI, 0.08 to 0.69) and was consistent with the sensitivity analyses.

However, lurbinectedin in the MAIC had increased odds of grade 3 or 4 neutropenia ([redacted]) when compared to carboplatin plus etoposide, but this effect was the opposite when evaluating against IV topotecan in the group of patients with any platinum sensitivity (in the sensitivity analysis) ([redacted]) and when observing the patients with sensitive disease and CTFI larger than 90 days ([redacted]). In the NMA, the results were similar, with increased odds for lurbinectedin when compared to carboplatin plus etoposide (OR = 7.05; 95% CrI, 3.09 to 16.11) but not against IV topotecan (OR = 1.19; 95% CrI, 0.45 to 3.17). The reason for these differences in neutropenia rates were deemed to be explained by differences in the requirements for prophylaxis with granulocyte colony stimulating factor across studies.

Critical Appraisal

The results from all ITCs have uncertainty due to imprecision in effect estimates, risk of confounding, and risk of bias in the body of evidence (e.g., violation of proportional hazards, intransitivity, poor overlap of covariates in the MAIC weighting process, use of observational data from a single-arm non-randomized trial connected through a MAIC into each NMA), with sparsity of the formed network used for the NMAs. The ORR and DOR were also uncertain, with no evidence of better ORR odds for lurbinectedin when compared to carboplatin plus etoposide or topotecan IV, and incomplete evidence for evaluating the DOR. The maturity of data for evaluating long-term outcomes was also uncertain.

Some generalizability issues arose because some arms included in the third ITC evaluated drugs not used in Canada (e.g., oral topotecan) and some of the variables considered important by the clinical experts could not be included.

Other Relevant Evidence

No other relevant evidence was identified for this review.

Economic Evidence

Table 1: Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis PSM

Target population	• B-005 trial population: adults with SCLC who have received 1 prior chemotherapy-containing line of therapy
	• Two subgroup analyses provided, based on prior response to platinum-based treatment
	  ◦ platinum-sensitive
	  ◦ platinum-refractory

Treatment	Lurbinectedin 3.2 mg/m^2 by IV infusion once every 21 days until disease progression or unacceptable toxicity
Submitted price	Lurbinectedin, 4 mg vial: $6,470.00 per vial
Treatment cost	$12,940 per 21-day cycle

Comparators	• B-005 trial population:
	  ◦ Topotecan
	  ◦ CAV
	  ◦ RWE: basket comprised of CAV, topotecan, etoposide, carboplatin + etoposide, cisplatin + etoposide, "other platinum regimens," and "other regimens"
	  ◦ SYNTH: basket comprised of CAV, etoposide, carboplatin + etoposide, cisplatin + etoposide, and "other regimens"
	• Platinum-sensitive subgroup: topotecan, carboplatin + etoposide, cisplatin + etoposide, carboplatin + irinotecan
	• Platinum-refractory subgroup: topotecan, CAV

Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (25 years)
Key data source	Single-arm phase II basket trial (PM1183-B-005-14); naive comparisons to comparators
Key limitations	• The comparative effects of lurbinectedin on PFS and OS is unknown due to lack of head-to-head or comparative evidence for lurbinectedin to currently available treatments. The sponsor's use of naive comparisons to inform the pharmacoeconomic model introduces unresolvable uncertainty.

Component	Description
	• The full Health Canada–approved population was not modelled. The sponsor assessed the cost-effectiveness of lurbinectedin as a second-line treatment; the cost-effectiveness of lurbinectedin as a third-line treatment is unknown. • The sponsor's model predicts an OS benefit with lurbinectedin that is not supported by clinical data. The predicted gains in PFS exceed those observed in the B-005 trial, and the sponsor's model predicts that the majority of the incremental benefits with lurbinectedin treatment will be realized after patients have discontinued lurbinectedin. • The sponsor assumes that all patients will receive lurbinectedin for four 21-day cycles, regardless of disease progression, which is inconsistent with the monograph-recommended dosing (i.e., until disease progression or unacceptable toxicity). Drug acquisition costs are likely underestimated, biasing the results in favour of lurbinectedin.
CADTH reanalysis results	• Due to the identified limitations regarding the lack of comparative clinical effectiveness, as well as issues with the submitted model, the comparative clinical effectiveness, and as a result, the cost-effectiveness, of lurbinectedin relative to currently available treatments is unknown. • CADTH conducted an exploratory analysis and adopted alternative extrapolation curves for PFS and OS. Sequential analyses are not presented due to the lack of comparability among patient populations. Both the sponsor's analysis and the CADTH exploratory reanalysis address the cost-effectiveness of lurbinectedin as a second-line treatment; the cost-effectiveness of lurbinectedin in the third-line setting is unknown because of a lack of clinical data. • In the CADTH exploratory reanalysis, the ICER for lurbinectedin was $307,232 per QALY compared with SYNTH, a synthetic control arm constructed from real-world data. Based on the CADTH reanalysis, an 83% price reduction would be required for lurbinectedin to be considered cost-effective at a willingness-to-pay threshold of $50,000 per QALY compared with expected usual care (i.e., SYNTH). • The results of the reanalysis should be viewed only as exploratory given the previously noted limitations and the extensive uncertainty associated with the comparative clinical effectiveness and underestimated lurbinectedin acquisition costs. As such, a higher price reduction for lurbinectedin may be warranted.

CAV = cyclophosphamide plus doxorubicin plus vincristine; ICER = incremental cost-effectiveness ratio; LY = life-year; OS = overall survival; PFS = progression-free survival; PSM = partitioned survival model; QALY = quality-adjusted life-year; RWE = real-world evidence; SCLC = small cell lung cancer; SYNTH = synthetic arm evidence.

Budget Impact

CADTH identified the following key limitations with the sponsor's analysis: the number of patients eligible for lurbinectedin is uncertain and may be underestimated; all relevant comparators were not considered and may depend on disease stage, line of therapy, and platinum sensitivity; the uptake of lurbinectedin is uncertain; the duration of lurbinectedin treatment is likely underestimated, which underestimates drug acquisition costs; and costs associated with subsequent treatment were not considered. CADTH revised the sponsor's base case by including irinotecan-based regimens as a relevant comparator. In the CADTH base case, the budget impact of reimbursing lurbinectedin is expected to be $9,582,252 in year 1, $11,052,096 in year 2, and $12,257,895 in year 3, with a 3-year total of $32,892,244. This estimate is highly sensitive to the duration of lurbinectedin treatment.

Request for Reconsideration

The sponsor filed a request for reconsideration for the draft recommendation for lurbinectedin (Zepzelca) for the treatment of adult patients with stage III or metastatic SCLC who have progressed on or after platinum-containing therapy. In their request, the sponsor identified the following issues:

- pERC's assessment of the 3 submitted ITCs. New analyses to support the original SCA analysis were included in the request for reconsideration under this issue.
- The sponsor is of the view that lurbinectedin is associated with low levels of treatment-related AEs, a widely accepted proxy for quality of life improvement.
- The sponsor described 5 additional analyses to support the results of Study B-005. These constituted new information that was not accepted by CADTH for the reconsideration in accordance with the Procedures for CADTH Reimbursement Reviews at the time the request for reconsideration was submitted. As outlined in Section 9.5.5 of the procedures, the new information failed to meet 1 or both of the following considerations: the new information has been provided to try and address an important clear gap in the evidence that has been identified by pERC; and the new information was not available during the review phase of the CADTH reimbursement review process.
- Results from the LAGOON phase III study will not be available until approximately May 2025. The sponsor is of the view that CADTH has made a recent positive recommendation based on an incomplete phase I and II study with a similar degree of uncertainty and important therapeutic need.

In the meeting to discuss the sponsor's request for reconsideration, pERC considered the following information:

- feedback on the draft recommendation from the sponsor
- information from the initial submission relating to the issues identified by the sponsor
- new information provided by the sponsor to address an important clear gap in the evidence identified by pERC
- feedback from 2 clinical specialists with expertise in diagnosing and treating SCLC
- feedback on the draft recommendation from 2 patient groups: LCC and the LHF
- feedback on the draft recommendation from 2 clinician groups: the Ontario Health-Cancer Care Ontario Lung Cancer Drug Advisory Committee and the LCC clinician group
- feedback on the draft recommendation from the public drug plans.

Clinical Evidence for the Reconsideration

In the request for reconsideration, the sponsor provided the following additional supportive analyses of the SCA: a formal comparison with trial results, a quantitative bias assessment (QBA), an E-value analysis, and a survivorship analysis. At the time the request for reconsideration was submitted, new information for standard reviews was considered by CADTH for inclusion in the reconsideration under the *Procedures for CADTH Reimbursement Reviews*.

In the formal comparison, individual-level CTFI-specific data from the B-005 trial were extracted from the CTFI-specific OS curves reported in the trial, and both unadjusted and CTFI-adjusted (using outcome regression and hard matching) HRs were calculated from a

Cox proportional hazards model. Matched individuals were randomly selected within each CTFI stratum for comparison between the SCA and the B-005 trial. The unadjusted HR for OS comparing lurbinectedin in the B-005 trial to the SCA was 0.72 (95% CI, 0.54 to 0.97), the CTFI-adjusted HR was 0.61 (95% CI, 0.45 to 0.82), and the matched HR was 0.63 (95% CI, 0.45 to 0.90).

In the QBA, the HR for OS was re-estimated to assess the impact of residual confounding by stage at initial diagnosis (outcome regression only). The QBA was conducted using the estimated prevalence of ES disease in the B-005 trial (69.5%) and the SCA (57.5%). A CTFI-adjusted HR comparing ES versus LS disease was estimated in the SCA and used to conduct the QBA (HR = 1.30; 95% CI, 0.94 to 1.79). After adjusting for stage at initial diagnosis in the QBA, the HR was 0.59 (95% CI, 0.44 to 0.79).

In the E-value analysis, E-values were calculated to further assess the impact of residual confounding on the comparison of OS between the SCA and B-005 trial populations. The E-value is defined as "the minimum strength of association, on the risk ratio scale, that an unmeasured confounder would need to have with both the treatment and the outcome to fully explain away a specific treatment-outcome association, conditional on the measured covariates." According to the sponsor-submitted report, the observed CTFI-adjusted HR for OS of 0.61 (95% CI, 0.45 to 0.82) would be entirely explained away by residual confounding if there was a single uncontrolled confounder where the risk ratio for death was 2.16 and the ratio comparing the prevalence of the covariate in the B-005 trial versus the SCA was 2.16, after adjusting for CTFI. Disease stage at initial diagnosis was weakly associated with the outcome after adjusting for CTFI in the SCA (HR = 1.30; 95% CI, 0.94 to 1.79), which was below the estimated E-value of 2.16. The ratio of the prevalence of ES disease at initial diagnosis between the trial versus the SCA was 1.21, also below the estimated E-value of 2.16.

In the survivorship analysis, comparison of 6-, 12-, and 24-month survival favoured lurbinectedin in the B-005 trial versus the SCA. The 1-year survival for the SCA by outcome regression was 27% (95% CI, 21% to 35%) compared to 34% (95% CI, 25% to 47%) in the B-005 study. By hard matching, 1-year survival for the SCA was 29% (95% CI, 21% to 40%) compared to 40% (95% CI, 29% to 54%) in the B-005 study.

A formal analysis adjusted for CTFI was conducted, and several supportive analyses were performed with the goal of addressing residual confounding by stage at initial diagnosis (QBA and E-value analysis). However, none of the additional analyses provided as part of the request for reconsideration addressed the possibility that contributions from multiple confounders or other sources of biases could have impacted the results. The E-value analysis did not account for imprecision in the effect estimate and relied upon an approximate conversion of the HR to a risk ratio that contributed to imprecision in the calculated E-value.

pERC Information

Members of the Committee

Dr. Maureen Trudeau (Chair), Mr. Daryl Bell, Dr. Jennifer Bell, Dr. Matthew Cheung; Dr. Winson Cheung, Dr. Michael Crump, Dr. Leela John, Dr. Christian Kollmannsberger, Mr. Cameron Lane,

Dr. Christopher Longo, Dr. Catherine Moltzan, Ms. Amy Peasgood, Dr. Anca Prica, Dr. Adam Raymakers, Dr. Patricia Tang, Dr. Marianne Taylor, and Dr. W. Dominika Wranik.

Initial Meeting Date: July 13, 2022

Regrets: One expert committee member did not attend.

Conflicts of interest: None

Reconsideration Meeting Date: December 7, 2022

Regrets: None

Conflicts of interest: None